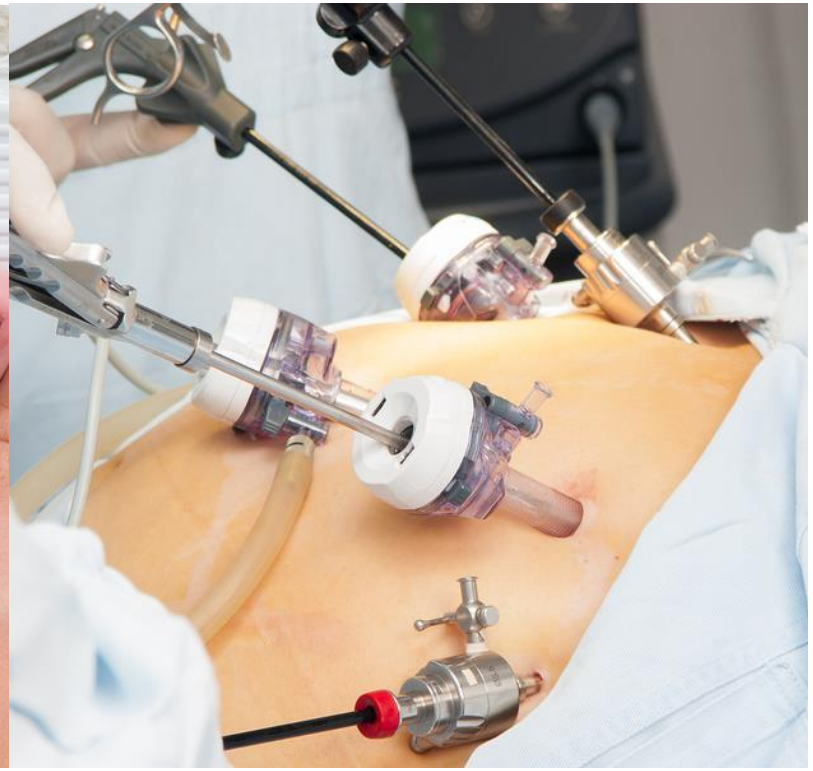
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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

BARIATRIC SURGERY: AN HTA REPORT ON THE EFFICACY, SAFETY AND COST-EFFECTIVENESS





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HEALTH TECHNOLOGY ASSESSMENT

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BARIATRIC SURGERY: AN HTA REPORT ON THE EFFICACY, SAFETY AND COST-EFFECTIVENESS

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Effect
AR	Absolute Risk
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical Classification
(L)AGB	Laparoscopic adjustable gastric banding
ACS-NSQIP	American College of Surgeons National Surgical Quality Improvement Program
ASMBS	American Society for Metabolic and Bariatric Surgery
AUD	Alcohol Use Disorder
BMI	Body Mass Index, calculated as weight in kg devided by height in meters squared (kg/m^2)
BPD-(DS)	Biliopancreatic diversion (with duodenal switch)
BS	Bariatric surgery
Calcium	Ca
CEA	Cost-effectiveness analysis
CPAP	Continuous Positive Airway Pressure
Cu	Copper
CUA	Cost-utility analysis
CV	Cardiovascluar
CVD	Cardiovascular Disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (version 5)
EASO	European Association for the Study of Obesity
EB	Eating behaviour

ED	Eating disorder
EMA	European Medicines Agency
EOSS	Edmonton Obesity Staging System
EPR	Entitled to Preferential Reimbursement *(Dutch: recht op Verhoogde tegemoetkoming (VT), French: Bénéficiaire d'intervention majoré (BIM))*
EWL	Excess Weight Loss / %-EWL : percentage excess weight loss
FDA	Food and Drug Administration (US)
Fe	Iron
FU	Follow-up
GB	Gastric bypass
GI	Gastrointestinal
GL	(Practice) Guideline
GOR(D)	Gastro-Oesophagal Reflux (Disease)
HAS	Haute Autoritié de Santé (France)
HbA1c	glycated hemoglobin
HR / adjHR	Hazard Rate / adjusted HR
HR-Qol	Health-Related Quality of Life
HTA	Health Technology Assessment
ICD 9 - CM	International Classification of Diseases Ninth Revision, Clinical Modification
ICER	Incremental cost-effectiveness ratio
ICQ	Interquartile range (difference between Q1 (= P25) en Q3 (= P75))
ICU	Intensive Care Unit

IFSO	International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)
IH	Internal Hernia
IMA	Intermutualistic Agency
INAMI	Institut national d'assurance maladie-invalidité
IQR	Interquartile range
LAGB	Laparoscopic adjustable gastric banding
LOS	Length of stay
LT	Long-term
LGA	Large-for-gestational-age (infants)
LYG	Life years gained
MBS	Metabolic and bariatric surgery
MDD	Major Depressive Disorder
MDT	Multi-Disciplinary team
MGB-OAGB	Mini gastric bypass-one anastomosis gastric bypass
MS	Metabolic surgery
MZG - RHM	Minimal Hospital Data (Dutch: Minimale Ziekenhuisgegevens (MZG), French: Résumé Hospitalier Minimum (RHM))
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steato-Hepatitis
NICE	The National Institute for Health and Care Excellence
NIHDI	National Institute for Health and Disability Insurance
NNB	Number neeeded to benefit

NNH	Number needed to harm
NNT	Number neeeded to treat
NSAID	Nonsteroidal anti-inflammatory drugs
OAGB	One anastomosis gastric bypass
OR	Odds ratio
OSAS	Obstructive sleep apnea syndrome
PoA	Points of (clinical) attention
PHGRS	Post-prandial hypoglycaemic reactive syndrome
PICO	Patient intervention comparator outcome
PK	Pharmacokinetics
PPI	Proton pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PY	Patient-years or person-years (of exposure or of follow-up)
QALY	Quality-adjusted life years
QoL	Quality of Life
RCT	Randomized Clinical Trial
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering
RoB	Risk of Bias
RR	Relative Risk
RRR	Relative Risk Reduction
RYGB (lap-RYG)	Roux-en-Y gastric bypass (laparoscopic RYGB); when not specifically stipulated, RYGB refers in general to lap-RYGB
SD	Standard deviation

Se	Selenium
SG (lap-SG or LSG)	Sleeve Gastrectomy (laparoscopic SG); when not specifically stipulated, SG refers in general to lap-SG
SGA	Small-for-gestational-age (infants)
SIGN	Scottish Intercollegiate Guidelines Network
SOS study	Swedish Obese Subjects study
SR	Systematic Review
SR-MA	Systematic Review and Meta-analysis
ST	Short-term
SUD	Substance use disorder
T2DM	Type 2 diabetes mellitus
TCT	Technical cell
US(A)	United States (of America)
Vit.	Vitamin(s)
WLS	Weight loss surgery
WTP	Willingness to pay
Zn	Zinc

SCIENTIFIC REPORT

1 AIMS

The present report is a Health Technology Assessment (HTA) of bariatric surgery. The topic of bariatric surgery has been initially introduced as a Topic Proposal to the KCE by the Flemish “Kenniscentrum voor Eet- en Gewichtsproblemen”. The initial context of the questions resided in the willingness and aim to improve the clinical care trajectory and management of bariatric patients, both as to what concerns the preoperative care and evaluation, as well as to what relates to the life-long postoperative care. Furthermore and in parallel to this initial question, the Chronic Disease Observatory of the RIZIV – INAMI formulated in its final report on March 23-2017[1] some recommendations deserving particular attention, namely on whether or not it is desirable to extent the current reimbursed indications to 1) adolescents and 2) patient with type 2 diabetes but with a lower BMI threshold of 30-34.9 kg/m² (which is lower than the current reimbursement threshold of BMI ≥35 for patients with type 2 diabetes).

Therefore KCE took the decision to 1st perform an HTA on bariatric surgery in general, and to have some specific focus on the above mentioned sub-populations allowing a potential reconsideration of the reimbursement criteria, and 2nd to start subsequently a Health Service Research (HSR) project taking into account some specific attention points that came out from this HTA research, with the final aim to improve and optimize the clinical care for bariatric patients, and patients that are potential candidates for bariatric surgery. Both the “Kenniscentrum voor Eet- en Gewichtsproblemen” and the “Chronic Disease Observatory” stressed the need for a holistic approach of patients with obesity, including a pre- and postoperative multidisciplinary follow-up. These aspects will be further elaborated in the HSR report. This report present the HTA part.

Reimbursement of bariatric surgery is currently restricted with inclusion criteria dating from 2010. Meanwhile new scientific evidence has emerged, making these criteria potentially obsolete. This report provides an up-to-date evaluation of the clinical effectiveness, safety and cost-effectiveness of bariatric surgery. For reasons quoted in this document, this HTA-evaluation evaluates the nowadays most commonly used and best documented techniques which are the Roux-en-Y Gastric Bypass (RYGB), and the

Sleeve Gastrectomy (SG), while some data and medical discussion also refer to a much lesser extent to laparoscopic adjustable gastric banding (LAGB), an intervention that was frequently performed untill some time ago, and which now largely is being abandoned, mainly for safety and tolerance reasons. Many historic RCT data on bariatric sugery also refer to, or do include data from patients who underwent LAGB, explaining why some of the data discussed relate to the LAGB procedure.

Note that not in scope of this report are: other historic batriatric interventions,[a] variants of the RYGB, more recent but less established interventions (such as the One Anastomosis Gastric Bypass[b] (OAGB, or so-called 'mini-gastric bypass), nor are the new less established (gastroscopic) techniques such as the gastric balloons, the 'endo-barrier', and the transoral endoscopic gastroplication. Many of these techniques need more in depth, larger and longer evaluations in clinical trials, before firm conclusions can be made regarding their mid- and long-term clinical outcomes.

Therefore the conclusions of this report essentially relate and apply to the RYGB- and the SG-interventions.

The report will focus on three questions:

1. Are the current reimbursement indications appropriate?
2. Should the reimbursement be expanded to adolescent?
3. Should the reimbursement be expanded to type 2 diabetics with a BMI 30-34.9?

At present there is no reimbursement for bariatric surgery in patients below the age of 18, nor for diabetic patients with a BMI below 35. The report will pay special attention to these populations with regard to a recommendation formulated by the Chronic Disease Observatory (Workgroup Obesity surgery).[1] Formal recommendations with regard to these two particular points are made in the synthesis report of this HTA.

Within the context of the current HTA report, the following important or critical domains will be analysed (chapter 4):

- effect on weight loss (important outcome as the weight related parameters were primary endpoints for the RCT)
- long-term effect on mortality risk, for bariatric surgery in general
- effect on quality of life (QoL), for bariatric surgery in general

Besides also short/long-term safety of bariatric surgery will be evaluated (chapter 5). Where relevant the identified safety issues will be subject of further consideration in a subsequent and ongoing Health Service Research (HSR) project on metabolic and bariatric surgery (MBS) that will aim to optimize and improve the organisation of pre- and post-operative care for metabolic and bariatric surgery in Belgium. For both the efficacy and safety question a review of the literature is performed. The specific criteria appropriate to each section are explained at the beginning of every chapter.

In the efficacy/effectiveness chapter, a concise quality appraisal of the evidence on long-term effects on mortality that is based on SR-MA found in literature is done in accordance with the GRADE principles. The same is done for QoL of bariatric surgery in general, and bariatric surgery in patients with type 2 diabetes with a BMI 30-34.9, and bariatric surgery in adolescents. Effect on weight is important but less critical as an outcome than the effect on mortality and/or QoL.

For all other clinical efficacy and safety outcomes, no formal grading based on GRADE has been applied since the coverage of these topics was very vast and diverse.

[a] The Biliopancreatic diversion with duodenal switch (BPD-DS) is another nowadays unfrequently used intervention that still might have a very limited place in the treatment of super-obese patients or as a possible technique for revisional bariatric surgery in some patients.

[b] We note that the OAGB is subject of an ongoing specific HTA evaluation made by the French Authorities (Haute Autoritié de Santé, France - HAS).

In 2006, the KCE published already a report on pharmacological and surgical treatment of obesity, and of residential care for severely obese children in Belgium.[2] At that time, specific billing codes and conditions for refunding bariatric interventions did not yet exist within the Belgian social security system. Nevertheless, it was estimated that more than 9000 bills with codes assumed to be used for bariatric surgery were paid by the INAMI/RIZIV in 2004. Hospitalisation for bariatric surgery, excluding re-hospitalisations for complications, was estimated to cost the social security at least 15 million Euros in 2003. This report will also include an update on the Belgian practice (chapter 7). It will provide demographic and longitudinal reimbursement related data, delivered by the Intermutualistic Agency (IMA/AIM) from patients that underwent bariatric surgery between 2007 and 2016. It will also discuss longitudinal clinical data obtained from the RIZIV – INAMI's Technical Cell (TCT) related to patients hospitalised between 2008 and 2014.

Finally, based on a systematic review of economic literature, the cost-effectiveness of bariatric surgery will be evaluated (chapter 8).

Aims of this report

- **Evaluate the clinical effectiveness and safety of bariatric surgery (with specific focus on adolescents and patients with type 2 diabetes and a BMI of 30-34.9 kg/m2).**
- **Describe the Belgian practice.**
- **Evaluate the cost-effectiveness of bariatric surgery.**

We remark that:

- **The clinical conclusions of the HTA report will essentially relate to RYGB- and the SG-interventions.**
- **Pre- and postoperative follow-up issues and formal recommendations with regard to this will be considered in a separate Health Services Research (HSR) KCE report.**

2 BACKGROUND

2.1 Epidemiology

2.1.1 Definitions

Obesity is a condition in which fat accumulates in the body to a point where it may impair health. Obesity occurs when caloric uptake exceeds caloric expenditure. The pathophysiology of obesity encompasses environmental factors (excess caloric intake and sedentary life style) often combined with some degree of genetic predisposition, pointing to a possible interplay between genetic predisposition and an obesogenic environment. Nevertheless, obesity is considered as a preventable condition, given that even with a genetic predisposition (apart from some rare monogenic diseases) a healthy lifestyle (healthy diet and physical activity) can prevent obesity. Severe obesity often is a chronic condition that may have adverse effects, entailing an increased morbidity and mortality.[3-5]

The Body Mass Index (BMI) is used as a proxy to identify overweight and obesity. It is calculated as weight in kilogram (kg) divided by height in meters squared (m^2). The World Health Organization (WHO) defines a BMI of 25 to 29.9 kg/m^2 as overweight, and a BMI ≥30 kg/m^2 as obese. It further distinguishes obesity in obesity class I (BMI 30 to <35 kg/m^2), class II (BMI 35 to <40 kg/m^2, or severe obesity) and class III (BMI ≥40 kg/m^2, or morbid obesity).[6] In scientific literature a BMI ≥50 is in often referred to as super-obesity.

For children and adolescents in the age group between 5-19 years, WHO defines obesity as a BMI value which is greater than 2 standard deviations (SD) above the WHO Growth Reference median (= a BMI-for-age value of +2 Z-scores, in other words >2 SD from the median BMI for that age).[6]

From a population point of view, obesity and overweight categories have been defined by examining longitudinal data that associate a given weight with future health effects or risks.[4, 5]

BMI is a surrogate measure for evaluating obesity as it neither takes into account body composition (relative amounts of fat mass/muscle/bone/fluid content etc.) nor does it provide insight in the type of obesity (adiposity) and the underlying fat distribution (e.g. visceral or abdominal adiposity which encompasses a higher health risk than general or gynoid adiposity which implies a lesser risk).The BMI is a suitable measure to screen for obesity at the population level (for Western countries) since it is easy to measure and does not show clinical meaningful differences in the prediction of adverse outcomes compared to other measures. [7, 8] Nevertheless, the above mentioned BMI categories do not apply for all ethnic groups, and BMI has limited diagnostic performance at the individual level (e.g. it does not take into account the type of obesity and underlying fat distribution).[9]

Besides BMI, other measures or indicators can be useful in the evaluation of visceral obesity, such as measures and categories of waist circumference. In addition, phenotypic characteristics of the metabolic syndrome (= insulin resistance syndrome) like the presence of (pre-)diabetes, hypertension, a low HDL-cholesterol, high triglycerides, and/or a high waist-circumference might indicate a higher associated risk, as is also the presence of non-alcoholic steato-hepatitis. Insulin resistance and metabolic syndrome are more prevalent in people with visceral adiposity.

Obesity clearly does imply risks, may lead to physical and psychological symptoms, can cause functional limitation, the development of co-morbidities and complications, and cause psycho-social problems. Therefore and in addition to the above mentioned WHO-defined categories, other staging tools like the EOSS or Edmonton Obesity Staging System are also being proposed.[10, 11] The EOSS distinguishes 4 stages of obesity and takes into account 1) risk-factors, comorbidities and possible end-organ damage, 2) physical symptoms, 3) psychological symptoms, and 4) functional limitations & quality of life.

2.1.2 Chronic conditions associated with obesity

Obesity is associated with considerable morbidity including type 2 diabetes mellitus (T2DM), cardiovascular disease (such as stroke and coronary artery disease), obstructive sleep apnoea, osteoarthritis, obesity related cancers and depression.[3, 6] The risk for these co-morbidities increases with increasing BMI. Especially people with obesity category II (BMI 35 to <40 kg/m²) and morbid obesity (BMI ≥40 kg/m²) are at increased risk.[4, 5, 12] Approximately 85% of patients with T2DM have a BMI categorising them as overweight (BMI 25.0 to 29.9 kg/m²) or obese (BMI >30.0 kg/m²).[13]

The increased prevalence of comorbidities results in a reduction of life expectancy, and thus a higher early mortality risk.[4, 5] In a recent epidemiologic study, overweight participants lost 1 disease-free year, the mildly obese 3 to 4 years, and the severely obese 7 to 8 years compared with normal-weight participants.[12]

A non-exhaustive overview of the possible comorbidities and complications of obesity can be found in Table 1

Table 1 – Possible comorbidities and complications of obesity (non-exhaustive list)

Risk factors-conditions	Outcomes
'Metabolic syndrome'	Coronary heart disease
Type 2 diabetes (pre-diabetes)	Coronary heart disease, stroke, peripheral arterial disease, nephropathy, neuropathy, retinopathy
Hypertension	Chronic kidney disease
Hyperlipidaemia	Peripheral artery disease
	Other diabetes complications
Gastrointestinal	Gastro-oesophagal reflux
	Gallstones
	Liver fat accumulation and Non-alcoholic steatohepatitis

	Cirrhosis – hepatocellular carcinoma
Restricted ventilation	Exertional dyspnoe; asthma
	Obstructive sleep apnoe
	Obesity hypoventilation syndrome (Pickwick syndrome)
Mechanical effects of weight	SGastro oesophagal reflux
	Urinary incontinence
	Osteoarthritis
	Varicose veins
Increased peripheral steroid interconversion in adipose tissue	Hormone-dependent cancers (breast, uterus)
	Male hypogonadism
	Influence on polycystic ovarian syndrome or PCOS (infertility, hirsutism)
Others	Psychological morbidity / psychosocial impact (low self-esteem, body image disorder, depression, social isolation and stigmatisation)
	Socioeconomic disadvantage (lower income, un-employment, less likely to be promoted, increased sick-leave)
	Overall increased cancer risk, especially cancers of the oesophagus, stomach, colorectum, liver, uterus, ovaries, kidneys
	Skin infections (groin and submammary candidiasis; hidradenitis)

Source material: Shang et al.[14] and Perreault et al.[15]

2.1.3 The global burden of obesity

According to the OECD (Organisation for Economic Co-operation and Development), 54% of the population is overweight, including 19% who have obesity (on average 20% of women and 19% of men are obese).[16] A study in 20 European countries found an overall prevalence rate of overweight and obesity of 53% with the highest prevalence rates in Eastern European countries. For obesity (BMI ≥30 kg/m²), Slovenia (20.8%), Estonia (19.7%) and the UK (19.2%) had the highest rates.[17] While the increase in some countries plateaus (at a high level), there is still a general increase in the prevalence of obesity observed around the globe, even in countries with historically low prevalence rates.[6, 16, 18]

The burden of obesity is not only health-related but has also an economic impact. It imposes a high economic burden on individuals, household budgets and nations.[19] Besides the excess healthcare expenditure there are also costs associated with loss of productivity (lower productivity at work, loss of work days, permanent disability – see part 1.1.1).

Belgian data based on the 2014 National food consumption poll (Sciensano; former WIV-ISP) gives the following picture for Belgium in 2014:

- mean BMI = 26.3 (age 18-64 y)
- 45% of the population is either overweight or obese (29% overweight & 16% obese): age group 3-64 y.

One in 7 adults in Belgium is obese (BMI ≥30). This is similar to the data presented for Belgium by the European Social Survey (2014): 13.8% obese and 33.0% overweight.[17]

Considering the infant & adolescent group (3-17 y), 11 to 15% is overweight, and 3-5 % is obese.[20]

Key points

- **The World Health Organization (WHO) defines a BMI of 25 to 29.9 kg/m² as overweight, and a BMI ≥30 kg/m² as obese. It further distinguishes obesity in obesity class I (BMI 30 to <35 kg/m²), class II (BMI 35 to <40 kg/m², or severe obesity) and class III (BMI ≥40 kg/m², or morbid obesity).[6] In scientific literature a BMI ≥50 is in often referred to as super-obesity.**
- **Obesity is associated with considerable morbidity including type 2 diabetes mellitus (T2DM), cardiovascular disease (such as stroke and coronary artery disease), obstructive sleep apnoea, osteoarthritis, some sorts of cancer (e.g. oesophageal adenocarcinoma) and depression.[3, 6] The risk for these co-morbidities increases with increasing BMI. Especially people with obesity category II (BMI 35 to <40 kg/m²) and morbid obesity (BMI ≥40 kg/m²) are at increased risk.[4, 5, 12]**
- **In Belgium, 45% of the population is either overweight or obese (29% overweight & 16% obese). Considering the infant & adolescent group (3-17 y), 11 to 15% is overweight, and 3-5 % is obese.[20]**

2.2 Management of obesity

Regarding the management of the obesity problem and pandemic, and referring back to its pathophysiology with the very important role of lifestyle factors, primary prevention remains of paramount importance. Obesity and overweight are considered conditions that are for the largest part preventable through following a healthy diet and maintaining physical activity.

Once confronted with overweight or obesity, losing weight might not be easy, and maintaining the obtained weight loss often even is a bigger challenge.

Although the health risks of obesity (if not longstanding) are largely reversible in many cases, obesity is increasingly considered a chronic (complex) disorder (disease), for which long-term follow-up and management is or might be necessary.[3] Often, this is best accomplished by a multi-facet approach, and for many people/patients even a multidisciplinary (para-)medical management may be advisable/needed.

The obese phenotype is complex. Although BMI is a good surrogate for adiposity at the group level, each patient's risk may be different and can be stratified on the basis of a personal and family medical history, a psychiatric history, blood analysis, as well as a behavioural history that includes information about physical activity, nutrition and eating behaviour.[3]

Management and specific treatments for obesity have to be aligned with the severity of overweight/obesity, the medical risk factors, associated coexisting diseases, and functional limitations.

The main treatment options for obesity are lifestyle interventions, pharmacotherapy and bariatric surgery.

2.2.1 Lifestyle intervention

Lifestyle interventions are often referred to as the conservative treatment option for obesity and include changing eating behaviour and increasing physical activity. They are advised as the first option for weight management. They are a first line option for several reasons: 1) they are and do remain the basis and mainstay of each therapy, 2) they are relatively low-cost, and 3) they have a limited inherent direct risks of complications.

Lifestyle interventions are designed to modify eating habits and increase physical activity with the aim to improve health and quality of life by achieving and maintaining moderate weight loss. In general literature indicate that high-intensity behavioural counselling is needed for most of the patients/individuals, and this during a period of at least 6 months. Behavioural therapy (individual and/or in group), the core of lifestyle counselling, aims to provide patients with techniques for adopting dietary and activity recommendations. Less-intensive lifestyle counselling is an option for preventing additional weight gain in patients at low risk for disease/complications or who choose not to participate in a high-intensity program.[3]

In general the implementation of lifestyle changes aim at body weight reductions of 7-10%, though losing already 5-7% of weight results in health gains.

Weight regain is common after a patient completes a lifestyle intervention program. The most effective behavioural method for preventing weight regain is continued but less intensive support on a regular basis. Although this long-term behavioural counselling can be effective, it is not widely available. Moreover when this approach fails to produce the weight loss that patients desire, it is often difficult to convince them to remain in counselling to maintain the smaller weight loss they achieved.[3]

More information can be found in literature, like e.g. in the recent overview article by Heymsfield et al.[3]

2.2.2 Pharmacotherapy

Pharmacotherapy for the treatment of obesity might be indicated as an adjunct to lifestyle interventions, e.g. when weight reduction is not obtained (or insufficient) via lifestyle interventions alone, or because of increasing health risks.

However for a number of reasons, in clinical practice, the current role of pharmacotherapy in the management of obesity is limited. Among these reasons are:

1. The obtained weight loss is often limited and at maximum moderate. Not all patients respond.
2. In order for the achieved weight loss to be maintained, long-term (chronic) use of weight loss medications often will be necessary.
3. Safety and/or tolerance issues may exist. In the past several weight loss medications have been withdrawn from the market for safety reasons. Currently a limited number of drugs are registered in the US for use in the treatment of obesity, though because of lingering concerns about long-term medication safety, FDA mandated cardiovascular disease trials. The number of registered medications in the EU is even more limited.
4. Cost is often substantial, and mostly at the expense of the patient.

The only three weight loss medications approved for this indication in Europe are:

- Xenical®/Orlistat® – active substance orlistat: orlistat inhibits and lowers the absorption of fat from the small intestine by inhibiting the lipase enzyme leading to increased fat loss via the faeces (fat malabsorption); main limitations are limited clinical efficacy, gastrointestinal intolerance (steatorrhoea or 'fatty' diarrhoea, oily spotting and flatus with discharge), and involves out-of-pocket cost
- Mysimba® – active substance combination: naltrexone and bupropion: combination of an opioid antagonist and a dual neurotransmitter uptake inhibitor; main limitations are moderate efficacy and gastrointestinal

adverse events, dizziness and insomnia (currently not commercialized in Belgium)

- Saxenda® – active substance liraglutide (Saxenda is the higher dose version of Victoza® a drug which is registered for type 2 diabetes): efficacy moderate; main limitations are: gastrointestinal intolerance especially at beginning of therapy, and involves important out-of-pocket cost

The only two medications approved for weight-loss that are on the Belgian market are Xenical®/Orlistat® (orlistat) and Saxenda® (liraglutide).

2.2.3 *Bariatric surgery (Metabolic and bariatric surgery)*

Bariatric surgery (BS) is generally only advised as a treatment option for patients with morbid obesity (BMI ≥40) or with class 2 obesity (BMI ≥35) in combination with certain co-morbidities.[3, 21, 22] BS or MBS (metabolic and bariatric surgery) can be considered as a treatment option for the treatment of severe obesity when important repetitive efforts to obtain durable weight loss through lifestyle modifications were unsuccessful.

Bariatric surgery (surgical treatment for weight loss) has been performed since several decades, and these procedures are increasing in popularity. Several types of bariatric surgeries exist, with some procedures being abandoned for reasons of tolerance, safety, and/or limited long-term efficacy while others are gaining momentum and becoming established like for instance the more recent laparoscopic Gastric Sleeve (Sleeve Gastrectomy or SG) beside the well-established laparoscopic Roux-en-Y Gastric Bypass (RYGB). Currently the SG and the RYGB are the two most commonly performed bariatric surgical interventions. The development of laparoscopic approaches since the mid-1990s, has significantly reduced rates of perioperative morbidity and mortality, so that nowadays almost all bariatric surgery is performed laparoscopically.

Overall one distinguishes three main categories of bariatric surgeries: restrictive, malabsorptive, and those that have a mixed restrictive and malabsorption component.

The 4 most important used bariatric interventions are Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), laparoscopic adjustable gastric band (LAGB), and biliopancreatic diversion with duodenal switch (BPD-DS, often also briefly referred to as 'duodenal switch'). A schematic drawing of these interventions can be found in Figure 1. Unless explicitly mentioned otherwise, the terms RYBG, SG and LAGB in this report refer to the laparoscopically performed approach of these interventions.

- **Laparoscopic adjustable gastric banding (LAGB)** involves the placement of an inflatable silicone band around the upper part of the stomach. This creates a gastric pouch of approximately 30 mL which restricts the amount of food that a stomach can receive (increasing satiety mainly after ingestion of solid food). It allegedly does not cause anatomical changes and is considered reversible. LAGB does not reduce the absorption of calories and nutrients.
  LAGB is an example of a purely restrictive intervention; very often performed until about 5-10 years ago; initially meant to be a minimally invasive, 'fully' reversible intervention with low short-term post-operative risk and complications;[22] however lower efficacy than RYGB or SG, and many problems of intolerance and/or complications on the mid- and long-term; this explains why this procedure has been largely abandoned in most countries (as is also the case in Belgium – see chapter 7), and in fact nowadays there are more gastric bands being removed than placed[23, 24].

- **Roux-en-Y gastric bypass (RYGB)** restricts food intake by creating a small pouch (<50 ml) at the top of the stomach. This pouch is the only part of the stomach that receives food, which greatly limits the amount of food a patient can comfortably eat and drink at one time. It is anastomosed to the Roux limb of jejunum. Food bypasses 95% of the stomach and the duodenum and part of the jejunum. As a consequence, fewer nutrients and calories are absorbed. Apart from its mixed restrictive-malabsorptive nature, it is clear that this intervention also causes beneficial metabolic effects through changes in GI-tract hormones (e.g. GLP-1, influencing satiety, and improving glucose metabolism). It is more complex to reverse compared with LAGB. In theory the RYGB can be reversed, though in practice it might be

challenging to restore gastric function completely towards the pre-surgery status.
RYGB is an example of a mixed restrictive-malabsorptive intervention and is nowadays often considered as 'gold standard'[c].[24]

- **Vertical sleeve gastrectomy or "sleeve gastrectomy" (SG)** involves the removal of approximately 70% of the stomach and is thus irreversible. The remaining section of the stomach is formed into a tube-like structure which cannot hold a great amount of food, causing acceleration of gastric emptying (rapid nutrient passage). It also leads to a decrease in the production of the appetite-regulating hormone ghrelin (a hormonal effect), lessening the desire to eat. Sleeve gastrectomy does not directly affect the absorption of calories and nutrients in the intestines.
  SG is an example of a purely restrictive intervention and is used increasingly and since recently even surpassing the RYGB in many countries. Since recently SG at the international level now overtakes RYGB in numbers.[26, 27]

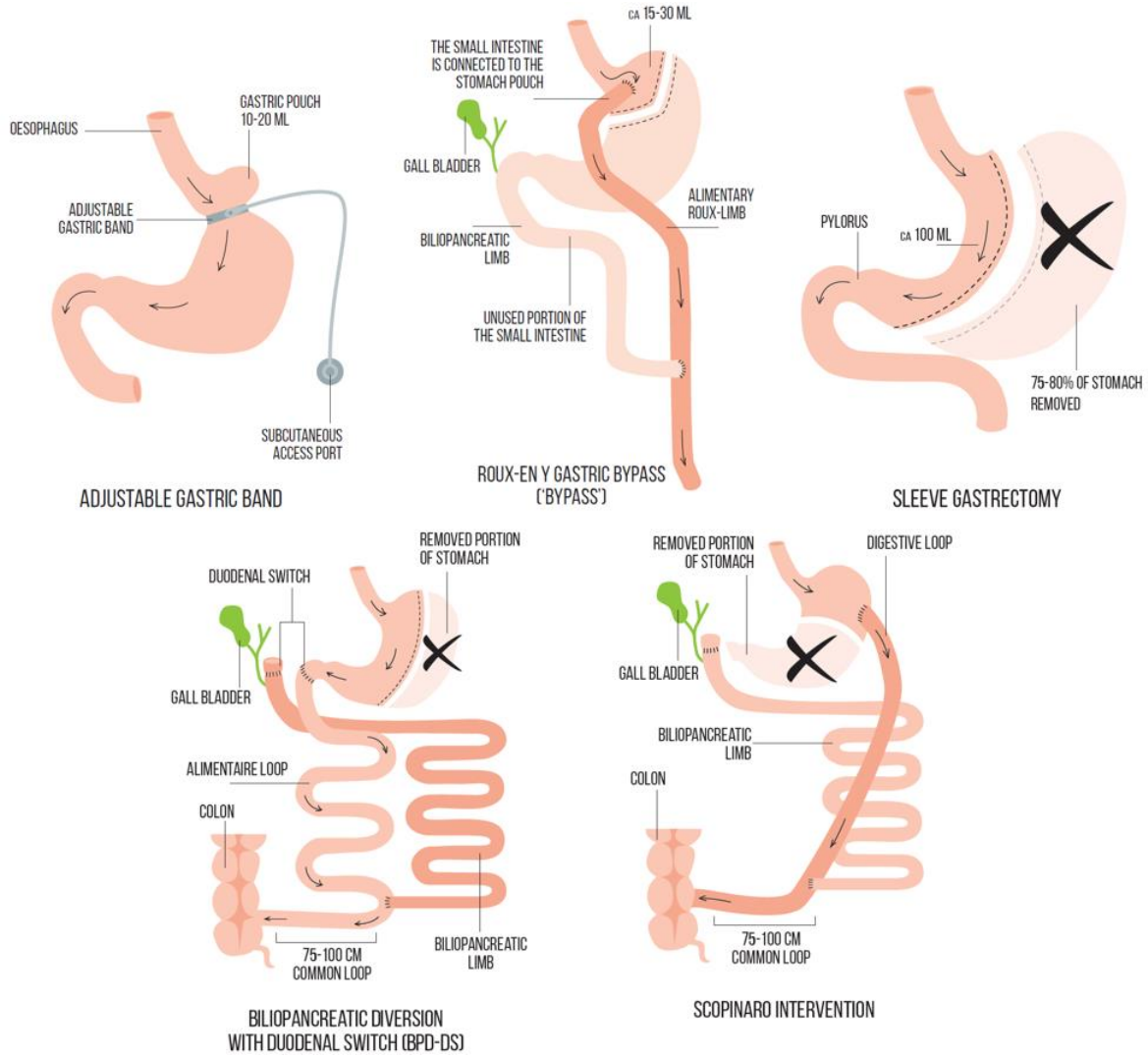
- **Biliopancreatic diversion with duodenal switch or BPD-DS** (a modification of the biliopancreatic diversion procedure or "Scopinaro intervention", which is no longer used) involves a combination of a sleeve gastrectomy and a bypass of part of the intestine. It is only rarely used.
  BPD-DS (often also briefly referred to as 'duodenal switch') is an example of a purely malabsorptive intervention, which is now only rarely performed for the surgical treatment of the super-obese patients, or sometimes as a revisional 'redo' bariatric intervention. Another intervention is the Single Anastomosis duodeno-ileal bypass (or SADI) which is a simplified version of the duodenal switch procedure.

Other purely malabsorptive interventions like the historical Scopinaro intervention have nowadays essentially been abandoned, because of 'too drastic' leading to important nutritional deficiencies.

Apart from their restrictive/malabsorptive nature, MBS interventions clearly may act through complex physiological alterations in weight regulation systems, including changes in hunger, satiation, taste and energy expenditure.

[c] Note that metabolic and bariatric surgery is evolving over time, which is a reflexion of the constant search to improve the benefit-risk balance of MBS. Metabolic procedures will always be in evolution as specialists seek the safest and most effective operative modality, explaining why there is no enduring gold standard operation.[25]

Figure 1 – Schematic drawings of the LAGB, RYGB, SG, BPD-DS and Scopinaro intervention



In clinical practice, some variations exist in the abovementioned procedures, e.g. characterised by a different size of the remaining stomach pouch, or the length of the small intestine that is bypassed (e.g. regular vs. long-limb RYGB). This report did not specifically look at variants of these interventions.

A relatively 'new' surgical technique of gastric bypass is the omega loop bypass, also known as single anastomosis bypass or 'mini-gastric bypass'. This one-anastomosis gastric bypass (OAGB), is a variation of the RYGB that is gaining increasing popularity (also in Belgium).[28]. Although seeming and sounding technically less invasive, the clinical 'effects' of OAGB might resemble the 'effects' of the RYGB, with the important remark that at current stage there are insufficient long-term data on durability of effect, nutritional consequences and possible remaining long-term safety questions (linked to bile reflux, and potential risk of stomal cancers). OAGB is a major malabsorptive procedure limiting absorption not only for micronutricients (as in RYGB) but also for proteins (as previously seen in Scopinaro procedures and in contrast with classic RYGB) which can lead to malnutrition. A recent position statement on this technique has been published by IFSO mentioning that there is a paucity of RCT evidence, with the majority of evidence coming from retrospective cohort studies.[28] Although the OAGB is a recognized bariatric/metabolic procedure, IFSO states that here is a need for well-designed large prospective cohort studies as well as RCT in to the future to better define where "mini" gastric bypass or OAGB should be placed in the current suite of bariatric procedures.[28] Whilst the initial use of the word "mini" reflected the minimally invasive approach used for the procedure, there is a risk that the term will be misinterpreted as meaning the surgery itself is a lesser procedure—both in terms of surgical risk and metabolic benefit. The systematic review made by IFSO reinforces that the procedure is effective in terms of weight loss and metabolic benefit, but also carries surgical risk that is very similar to RYGB. Therefore the IFSO recommends that this procedure is no longer referred to as mini gastric bypass (MGB), but as OAGB (one anastomosis gastric bypass). The IFSO taskforce also recommends that surgeons performing this, as well as any other bariatric/metabolic procedure, are encouraged to participate in a national or international registry so that long-term data may be more effectively identified.[28] The French HAS (Haute Autorité de Santé) is actually performing an assessment of this technique. An evaluation of this technique is out of scope of this report.

In addition, some other new 'less' invasive techniques are coming up. A variety of endoscopic treatments for obesity are in the stage of development. For some of them, short-term outcomes may appear promising but long-term results are lacking.[29] As these techniques are new and given the limited experience with no or very few mid-to-long-term data on durability and safety being available, they are out of scope in this HTA. An example is the endoscopic gastroplication realized via transoral gastroscopic access. Currently only a few centres in Belgium are offering this intervention, which is entirely at the cost of the patient. This type of intervention still needs to prove its place in the management of obesity. Prudent preliminary insight from literature and clinical expert feedback is that the endoscopic gastroplication constitutes a different/new approach, aiming at treating a different type of patients with obesity than SG or RYGB, such as younger patients or suffering from less pronounced obesity, however the main questions remain regarding both mid-to-long term outcomes on weight loss and safety.

Bariatric surgery is more and more being referred to as 'metabolic' surgery when applied as a treatment for type 2 diabetes mellitus. This notion is supported by the observation that several bariatric procedures cause rapid and pronounced improvements in glycaemic control above and beyond what can be expected merely on the basis of the weight loss itself.[30, 31] This might be explained by improved gut hormone signalling between the gastrointestinal system and the pancreas.[27]

Although the term metabolic surgery initially stems from and refers to bariatric surgery (BS) performed in obese type 2 diabetic patients, in the current contemporary paradigm both terms are very often used interchangeably. Therefore this type of surgery is also being named and grouped as metabolic and bariatric surgery (MBS). This is logic as metabolic and bariatric surgery aims and helps to improve more than 40 obesity-related diseases and conditions, including type 2 diabetes, heart disease, certain cancers, sleep apnoea, gastro-oesophageal reflux disease (GORD), high blood pressure, high cholesterol, sleep apnoea and joint problems.[32]

Another used but less preferable and more general term is weight loss surgery (WLS). This term however does not point in itself to the intended health gain aimed at and merely might give the impression of essentially focussing on reductions in weight and BMI. Therefore in this document the terms of bariatric surgery (BS), metabolic surgery and the more comprehensive term of metabolic and bariatric surgery (MBS) will be used interchangeably.

Key points

- **Lifestyle interventions are a first line treatment option for obesity for several reasons: 1) they are and do remain the basis and mainstay of each therapy, 2) they are relatively low-cost, and 3) they have a limited inherent direct risks of complications. However, weight regain is common after a patient completes a lifestyle intervention program.**
- **Pharmacotherapy for the treatment of obesity might be indicated as an adjunct to lifestyle interventions.**
- **An evaluation of the safety, efficacy/effectiveness and cost-effectiveness of lifestyle interventions or pharmacotherapy are out of scope of this HTA report.**
- **Bariatric surgery is an option to treat obesity and is the topic of this HTA. The evaluations made in this report essentially relate and apply to the most commonly performed Roux-en-Y gastric bypass (RYGB) and the sleeve gastrectomy (SG) interventions, and to some extent to the LAGB that was performed frequently in the past. The conclusion do not apply to the newer techniques such as e.g. the 'one-anastomosis gastric bypass' (OAGB) or the endoscopic gastroplication.**

2.3 Current reimbursed criteria for bariatric surgery in Belgium

At present, reimbursement of bariatric surgery is restricted with inclusion criteria dating from 2010. In summary, primary (first-time) bariatric surgery can be reimbursed for patients having failed dietary intervention (dietary attempt during at least 1 year without durable effect), who are ≥18 years of age and have a BMI ≥40, or have a BMI ≥35 associated with one or more of the following comorbidities being (type 2) diabetes mellitus which needs pharmacological treatment, therapy resistant hypertension necessitating at least three anti-hypertensive drugs, or obstructive sleep apnoe syndrome (OSAS), and only after having being evaluated by a multidisciplinary team composed of a bariatric (abdominal) surgeon, a physician-specialist in internal medicine, and a physician-psychiatrist or a clinical psychologist. A report of this multi-disciplinary consultation along with evidence of previous at least 1-year long dietary therapy to be kept in the medical chart of the patient-candidate for bariatric surgery. Reimbursement is also possible for revisional bariatric surgery ("re-do" surgery) after a complication or insufficient result following previous bariatric surgery. Although not explicitly mandated by law, in practice the dietician in general is also part of the multidisciplinary team that evaluates the patient. In general, the criteria (for primary bariatric surgery) of a BMI ≥40 or a BMI ≥35 associated with co-morbidities like type 2 diabetes, hypertension or OSAS, are largely in line with classic international guidelines and literature (see chapter 3). [3, 21, 22, 33]

As regards to the composition of the multidisciplinary team doing the pre-operative evaluation, and more specifically as to the specialist assuming the role of 'physician-specialist in internal medicine', we note that in practice this is most commonly assured either by a physician-specialist in internal medicine with specific competence in endocrinology-diabetology (=most of the cases) or, but probably to a lesser extent, by a physician-specialist in internal medicine with specific competence in gastroenterology or gastroenterologist.

An important note on this is appropriate, as during the last consultative external expert meeting on this HTA project, some experts informed us on the fact that changes are pending regarding the possible future reformation

and changes that will be made to the formation, curriculum and recognition of specialists in internal medicine. Based on this feedback it might be likely or possible that in the future we will only have 'endocrino-diabetologist' and 'gastroenterologists', but no longer have physician-specialists in internal medicine as a broader discipline. This change might have clinical and practical implications (e.g. issues related to workload and capacity). In general most experts seem to support or endorse the idea that, regarding the participation and representation of the 'internal medicine' speciality that is part of the formal pre-operative multidisciplinary team evaluation, the 'endocrino-diabetologist' probably is the most appropriate 'internal medicine discipline' specialist to perform this role.

Key points

- **In Belgium, primary (first-time) bariatric surgery can be reimbursed for patients having failed dietary intervention (dietary attempt during at least 1 year without durable effect),**
  - **who are ≥18 years of age and have a BMI ≥40, or**
  - **have a BMI ≥35 associated with one or more of the following comorbidities being (type 2) diabetes mellitus which needs pharmacological treatment, therapy resistant hypertension necessitating at least three anti-hypertensive drugs, or obstructive sleep apnoe syndrome (OSAS), and**
  - **only after having being evaluated by a multidisciplinary team composed of a bariatric (abdominal) surgeon, a physician-specialist in internal medicine, and a physician-psychiatrist or a clinical psychologist.**
- **Reimbursement is also possible for revisional bariatric surgery ("re-do" surgery) after a complication or insufficient result following previous bariatric surgery.**

3 INTERNATIONAL PRACTICE GUIDELINES ON BARIATRIC SURGERY

A search for formal ("evidence-based") guidelines (GL) on the Guidelines International Network website in September 2018 (https://www.g-i-n.net/) revealed two recently published documents, originating from Germany (February 2018[34]) and Denmark (January 2017[35]). Besides formal practice guidelines some other position statements from professional association, consensus reports and positions from official national health bodies or agencies have been considered. We also searched for practice guidelines on Ebpracticenet (https://www.ebpnet.be), a Belgian website aimed at general practitioners, and identified the Finnish Duodecim guideline on bariatric surgery (updated August 2017). A genuine Belgian Obesity GL was published in 2006 and updated in 2011. Furthermore, we identified GLs within and among the vast number of publications that we screened for the completion of this report. A non-exhaustive list and summary of recommendations with respect to the indications for bariatric surgery is provided in Appendix 2.

In general there is agreement among guidelines and recommendations that bariatric surgery is a treatment option for people with obesity if they have a BMI ≥40 kg/m², or ≥35-40 kg/m² in combination with other significant disease that could be improved with weight loss. Additional requirements are that appropriate non-surgical measures have been tried, and that the person commits to a long-term follow-up. The 2017 Danish GL sticks to a BMI threshold of 40 kg/m², even in the presence of co-morbidities.[35]

There is no consensus across GLs for considering bariatric surgery in young patients (Table 2). There is also no agreement on the age limits to consider surgery in young people. Whereas the Danish GL sets an age limit for bariatric surgery of 18 to 25 years, there is no lower limit for the American Society for Metabolic and Bariatric Surgery Paediatric Committee. It refers to the World Health Organization's definition of adolescents (10-19 years), but adds that "*younger children who meet the other criteria (BMI >40 kg/m², or 35-40 kg/m² in combination with co-morbidity) could be considered for bariatric surgery when benefit outweighs risk*".[36] In some GLs, the indication

for surgery in young people is linked to bone age, as shown in Table 2. The French GL considers young people for surgery if they have a BMI >40 kg/m² in combination with a moderate co-morbidity (e.g. hypertension, lipid disturbance) or a BMI >35 kg/m² in combination with a severe co-morbidity (e.g. T2DM). The German GL recommends considering surgery in the young (age below 18 years) in case of a BMI ≥35 kg/m² in combination with other disease, or in case of a BMI ≥50 if there is no co-morbid disease. According to NICE, bariatric surgery may be considered for young people only in exceptional circumstances, and if they have achieved or nearly achieved physiological maturity. The Dutch GL, dating from 2010, says that in children and adolescents, bariatric surgery can only be done in the setting of a clinical trial.

Table 2 – Indications for bariatric surgery in young (<18 years) patients across international guidelines, recommendations, consensus reports, position statements, or according to other HTA bodies and other national health bodies

GUIDELINE	Definition of "young"	BMI threshold for surgery if no co-morbidities	BMI threshold with co-morbidities	Strength of recommendation (wording)
GERMANY 2018	< 18 years	>50 kg/m²	≥35 kg/m²	Expert consensus
US (ASMBS) 2018	(<)10-19 years	>40 kg/m²	>35 kg/m²	Should be considered for surgery
ADA 2018	-		>35 kg/m²	May be considered (in adolescents with T2DM and uncontrolled glycemia and/or serious co-morbidities despite lifestyl and pharmcological internvetion)
JOINT STATEMENT by International Diabetes associations 2016		a recommendation for surgery in this population is inappropriate at present		
US ENDOCRINE SOCIETY 2016	Tanner 4 or 5 pubertal development and final or near-final adult height	>40 kg/m²	>35 kg/m²	"we suggest" = weak recommendation
FRANCE (HAS) 2016	Tanner ≥4 (bone age ≥13 in girls, ≥15 in boys)		>40 kg/m² if moderate co-morbidity, >35 kg/m² if severe (e.g. T2DM)	
UK (NICE) 2017		exceptional		Surgery may be considered only in exceptional circumstances
EASO 2014	skeletal and developmental maturity		> 40 kg/m² and at least 1 co-morbidity	could be considered in centres with extensive experience
NL (the Dutch NHG) 2010		in trial conditions only		can be only possible in a research setting

ADA: American Diabetes Association (www.diabetes.org/diabetescare); ASMBS: American Society for Metabolic and Bariatric Surgery;[36] HAS: Haute Authorité de Santé (https://www.has-sante.fr/portail/); NICE: National Institute for Health and Care Excellence (https://www.nice.org.uk/guidance/qs127); NHG: Nederlands Huisartsen Genootschap (https://www.nhg.org/standaarden); NL: the Netherlands; T2DM: type 2 diabetes mellitus. EASO: European Association for the Study of Obesity;[33] Joint International: Joint Statement by 45 international diabetes organizations.[30] US Endocrine Society[37]; GERMANY 2018: https://www.awmf.org/leitlinien/detail/ll/088-001.html. The Tanner score (ranging from 1 to 5) refers to the physical development of children and adolescents.

Some GLs discuss the option for surgery as a treatment option in patients with type 2 diabetes with a BMI below 35 kg/m² (Table 3).

In a consensus report, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consider surgery as a recommended treatment option for adults with T2DM and a BMI between 30 to 34.9 kg/m² who do not achieve durable weight loss and improvement of comorbidities with reasonable non-surgical methods.[38] DynaMed Plus makes a weak recommendation for surgery in patients with a BMI ≥30 kg/m² and with at least one severe obesity-related comorbidity or T2DM (http://www.dynamed.com). NICE proposes to consider an assessment for bariatric surgery for people with a BMI of 30-34.9 kg/m² who have recent-onset T2DM. The French HAS on the contrary stipulates that surgery cannot be recommended in obese patients with T2DM who have a BMI below 35 kg/m² whereas the Dutch recommend surgery in these patients in trial conditions only.

ADA published as part of annual updates of their 'Standards of Medical Care in Diabetes', version January 2019, a specific article on obesity management for people with type 2 diabetes.[39] With regard to MBS the ADA states that:[d]

- MBS should be recommended as an option to treat type 2 diabetes in appropriate surgical candidates with a BMI ≥40 kg/m^2
  (although not explicitly mentioned, implicitly this means that type 2 diabetic adolescents could be envisaged as well)
- MBS should be recommended as an option to treat type 2 diabetes in adults with a BMI ≥35 kg/ m^2
  who do not achieve durable weight loss and improvement in co-morbidities (including hyperglycaemia) with reasonable nonsurgical methods
- MBS may be considered as an option to treat type 2 for adults with a BMI 30-34.9 kg/ m^2
  who do not achieve durable weight loss and improvement in co-morbidities with reasonable nonsurgical methods

Most guideline developers acknowledge the presence of important gaps in our knowledge of the clinical effectiveness of bariatric surgery, especially the effect of bariatric surgery on hard clinical endpoints (cardiovascular complications and mortality) for which long-term RCT data are lacking.[13, 30]

[d] Note that for Asian Americans, the mentioned BMI threshold need to be subtracted by -2.5.

Table 3 – Indications for bariatric surgery in patients with a BMI<35 kg/m² across international guidelines, recommendations, consensus reports, position statements, or according to other HTA bodies and other national health bodies

GUIDELINE		Strength of recommendation (wording)
US and EU (ADA/EASD) 2018	if T2DM patients who do not achieve durable weight loss and improvment of comorbidities with reasonable non-surgical methods	recommend consideration as a recommended treatment option
US, ADA - Standards of Medical Care in Diabetes, annual update 2019	if T2D patients who do not achieve durable weight loss and improvment of comorbidities with reasonable non-surgical methods	BMI ≥ 35 : should be recommended as an option BMI 30-34,9 : may be considered as an option
JOINT STATEMENT by International Diabetes associations 2016	if T2DM, and if hyperglycemia is inadequately controlled despite optimal treatment with oral or injectable medications	should be considered
DynaMed Plus 2018	BMI >30 kg/m² with at least 1 severe obesity-related comorbidity or T2DM	weak recommendation
UK (NICE) 2014	if recent-onset T2DM	consider an assessment for bariatric surgery
EASO 2014	if T2DM (BMI 30 - 35 kg/m²)	may be considered on an individual basis
FRANCE (HAS) 2009	not if BMI<35 kg/m²	professional agreement
DENMARK	not if BMI<40 kg/m²	strong recommendation

ADA (American Diabetes Association)/EASD (European Association for the Study of Diabetes) 2018;[38] NICE: National Institute for Health and Care Excellence (https://www.nice.org.uk/guidance/cg189); T2DM: type 2 diabetes mellitus. EASO: European Association for the Study of Obesity;[33] HAS: Haute Authorité de Santé (https://www.has-sante.fr/portail/); DENMARK 2017: https://www.sst.dk/.

Key points

- **In general there is agreement among guidelines and recommendations that bariatric surgery is a treatment option for people with obesity if they have a BMI ≥40 kg/m², or ≥35-40 kg/m² in combination with other significant disease that could be improved with weight loss.**
- **There is no consensus across guidelines for considering bariatric surgery in young patients. The recommendation varies from 'a recommendation for surgery in this population is inappropriate at present', surgery may/could/should be considered, only in exceptional cases, only possible in a research setting, considered in centres with extensive experience. The definition of 'young patients' also varies between guidelines.**
- **Also for adults with T2DM and a BMI of 30-34.9 kg/m2 there is no agreement. For example, NICE proposes to consider this, while HAS does not recommend this and the Dutch guideline recommends this in trial conditions only. Recommendations based on a common consensus report from the American Diabetes Association (ADA, 2018) and the European Association for the Study of Diabetes (EASD) mention that MBS may be considered as an option to treat type 2 for adults with a BMI 30-34.9 kg/m² who do not achieve durable weight loss and improvement of comorbidities with reasonable non-surgical methods. This is also reflected in the 2019 ADA 'Standards of Medical Care in Diabetes', and is in lign with a previously published treatment algorithm (=joint statement by a.o. ADA/EASD and the International Diabetes Federation, Second Diabetes Sugery Summit - 2016).**

4 CLINICAL EFFECTIVENESS OF BARIATRIC SURGERY

4.1 Methodology

4.1.1 Search strategy

For the assessment of the clinical effectiveness of bariatric surgery, we restricted ourselves to data from randomised controlled trials (RCT) since they provide the most solid evidence of the efficacy of a therapeutic intervention. We excluded observational studies since these are prone to bias, but they may provide interesting data on long-term events and adverse effects, which will be addressed in a separate chapter.

We followed the KCE Process Book for conducting the search (http://processbook.kce.fgov.be/). A search strategy was developed in cooperation with an information specialist and adapted to each database. The research question was transformed into a PICO structured search question (Table 4). We searched in the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials: (Cochrane Library - Wiley), MedLine (OVID) and Embase (Embase.com) as specified in Appendix 1. Two separate searches were executed, one for systematic reviews (SR) and one for randomised controlled trials (RCTs). We did not perform a search for planned, ongoing or unpublished studies.

Table 4 – The PICO applied for the clinical effectiveness of bariatric surgery

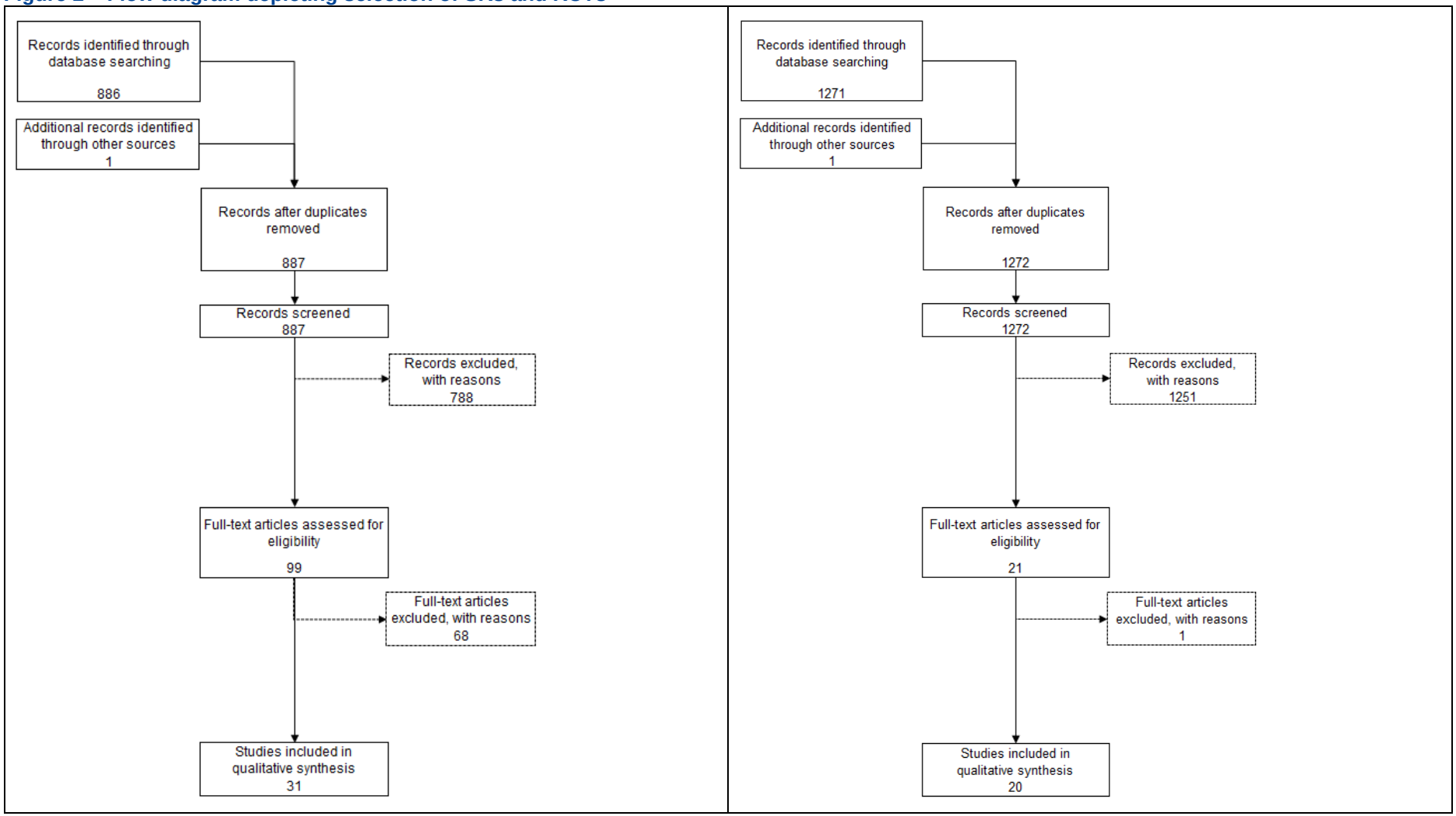
Project number	2017-05_HTA
Project name	Bariatric surgery
Research question	What is the clinical effectiveness of bariatric surgery?
Structured search question(s) (PICO, SPICE, ECLIPSE...)	
P (patient)	patients with overweight or obesity
I (Intervention)	Any of the following bariatric surgery techniques: LAGB, RYGB, Sleeve gastrectomy. (NOT: scopinaro, not endoscopic, no relatively new techniques)
C (comparison)	Diet. LAGB. RYGB. sleeve gastrectomy. (not scopinaro, not endoscopic, not comparisons of variations of the same basic technique)
O (outcome)	weight related parameters, T2DM remission parameters, hypertension, OSAS, Mortality, QoL, other hard endpoints such as infarction, stroke … Adverse events: separate search in separate chapter
S (study type)	RCTs or SRs (2 separate search strategies for each study type

LAGB: laparoscopic adjustable gastric banding; OSAS: Obstructive sleep apnea syndrome; QoL: quality of life; RCT: randomised controlled trial; RYGB: Roux-en-Y gastric bypass; SR: systematic review; T2DM: Type 2 diabetes mellitus

We used existing special queries such as Systematic Reviews for MedLine (OVID MedLine); Systematic Reviews for Embase (adapted from Wilczynski & Haynes[40]), Randomised Control Trials for Medline from the Cochrane Handbook (v.5.1.0), and Randomized Controlled Trials for Embase (adapted from Wong et al.[41]). The search in those sources was supplemented by collecting suggested references from different sources (external experts, exploratory searches in the bibliographical databases, and looking into the bibliography of key references). All identified references were imported in EndNote X.8, the duplicate search results were detected based on title match during the import process in EndNote, and supplemented by manual identification after sorting on title.

First, studies were screened on title and abstract using the PICO in- and exclusion criteria. Irrelevant studies were discarded. In a second step, the remaining papers were screened by reading the full text. If no full text was available, the study was excluded. The resulting flow diagrams for SRs and RCTs respectively are displayed in Figure 2.

Figure 2 – Flow diagram depicting selection of SRs and RCTs



Left column: Systematic Reviews (SRs); right column: Randomised Controlled Trials (RCTs)

4.1.2 Selection of systematic reviews

Our search starting-date for SRs was November 1, 2013, i.e. the search date of the most recent Cochrane review on bariatric surgery in adults.[42] From a total of 886 references, 788 were excluded based on title and abstract. We identified 1 additional SR during our search for recent RCTs.[43] After full text evaluation, we were left with 31 SRs (Appendix 1.4). Of these, 21 compared bariatric surgery with a non-surgical approach. In five of them, surgery was compared with non-surgery in “any overweight/obese subjects”, whereas in the remaining 16 the focus was on specific subpopulations: patients with type 1 diabetes (n=3), type 2 diabetes (n=5), obstructive sleep apnoea syndrome (n=1), adolescents (n=5), non-severely obese patients (n=2).

Of the 10 SRs that compared different surgical techniques, three SRs compare RYGB with sleeve gastrectomy and with LAGB.[44-46] Six compared RYGB with sleeve gastrectomy, reporting on a variety of outcomes and different follow-up requirements.[47-52] One SR compared laparoscopic one-anastomosis gastric bypass and sleeve gastrectomy.[53] An overview of these SRs and the 21 RCTs they consider is provided in the chapter on comparative effectiveness of different surgical techniques (4.5).

Most of these SRs included both RCTs and observational studies but as mentioned before, we considered only RCT data for the assessment of the clinical effectiveness of bariatric surgery. Sometimes, the SR included only 1 or 2 RCTs, and in these cases we discuss only the RCT involved instead of the SR (or meta-analysis). Outcomes for which there were no SRs available, were assessed directly from the available RCTs. The respective sources for all outcomes discussed in the chapter on clinical effectiveness are listed in Appendix 3.

4.1.3 Selection of randomised controlled trials

Based on findings in previous step, we conducted a sensitive search for RCTs, starting on July 1, 2015. Out of 1271 references, 1251 were rejected based on title and abstract. We found one additional RCT through hand searching in the SRs mentioned above.[54, 55] We excluded one RCT that focused on erectile dysfunction and hormonal imbalance after gastric bypass surgery.[56] Eventually, the 20 remaining references were related to 17 individual RCTs that compared bariatric surgery with medical treatment (Table 5).

Table 5 – Randomised trials comparing bariatric surgery with medical treatment

	First author_year	Study acronym	BMI target	Intervention - Population	Time window	Number of patients	mean BMI
1	AGUIAR_2014		35 -50	LAGB	2011 - 2013	16 LAGB + 36 Co	I(LAGB): 48.15±8.58 C: 46.20±6.13
2	COURCOULAS_2014	TRIABETES	30 - 40	LAGB RYGB T2DM	2009 - 2012	24 RYGB + 22 GB + 23 Co	I(RY): 35.5±2.6 I(GB): 35.5±3.4 Co: 35.7±3.3
3	CUMMINGS_2016	CROSSROADS	30 - 45	RYGB T2DM	2011 - 2012	23 RYGB + 20 Co	I(RY): 38.3 ±3.7 Co: 37.1 ± 3.5
4	DING_2015	SLIMM-T2D (2)	30 - 45	LAGB T2DM	2010 - 2013	23 LAGB + 22 Co	I(GB): 36.4±3.0 Co: 36.7±4.2
5	DIXON_2008		30 - 40	LAGB T2DM	2002 - 2006	30 LAGB + 30 Co	I(GB): 37.0±2.7 Co: 37.2±2.5
6	DIXON_2012		35 - 55	LAGB SLEEP APNOE	2006 - 2009	30 LAGB + 30 Co	I(LAGB): 46.3±6.0 Co: 43.8±4.9
7	FEIGEL-GUILLER_2015		>35	LAGB SLEEP APNOE	1999 - 2003	33 LAGB + 30 Co	I: 48.8±9.9 Co: 44.4±9.0
8	HALPERIN_2014	SLIMM-T2D (1)	30 - 42	RYGB T2DM	2010 - 2011	19 RYGB + 19 Co	I(RY): 36.0±3.5 Co: 36.5±3.4
9	IKRAMUDDIN_2013	DSS	30 - 40	RYGB T2DM	2008 - 2011	60 RYGB + 60 Co	I(RY): 34.4 ±3.2 Co: 34.9 ± 3.0
10	LIANG_2013		>28	RYGB T2DM + Hypertension	2008 - 2011	31 RYGB + 34 Co1 + 34 Co2	I(RY): 30.5±1.0 Co1: 30.3±2.0 Co2: 30.3±1.4
11	MINGRONE_2012	DIBASY	>35	RYGB or BPD T2DM	2009 - 2011	20 RYGB + 20 BPD + 20 Co	I(GB): 44.9±5.2 I(BPD): 45.1±7.87 Co: 45.62
12	OBRIEN_2006		30 - 35	LAGB	2000 - 2001	40 LAGB + 40 Co	I(LAGB): 33.7±1.8 Co: 33.5±1.4
13	OBRIEN_2010		>35	LAGB ADOLESCENTS	2005 - 2008	25 LAGB + 25 Co	I(LAGB): 42.3±6.1 Co: 40.4±3.1
14	PARIKH_2014		30 - 35	ANY SURGERY T2DM	NA	29 surgery + 28 Co	I: 32.8±1.7 Co:32.4±1.8
15	SCHAUER_2012	STAMPEDE	27 - 43	RYGB or SLEEVE T2DM	2007 - 2011	50 RYGB + 50 S + 50 Co	I(RY): 37.0±3.3 I(S): 36.2±3.9 Co:36.8±3.0
16	WENTWORTH_2014		25 -30	LAGB T2DM	2009 - 2013	25 LAGB + 26 Co	I(GB): 29±1 Co: 29±1
17	SCHIAVON_2018	GATEWAY	30 - 39.9	RYGB Hypertension	2013 - 2016	50 + 50	36.9±2.7

References: AGUIAR_2014,[55] COURCOULAS_2014,[57] CUMMINGS_2016,[58] DING_2015,[59] DIXON_2008,[60] DIXON_2012,[61] FEIGEL-GUILLER_2015,[62] HALPERIN_2014,[63] IKRAMUDDIN_2013,[64] LIANG_2013,[65] MINGRONE_2012,[66] OBRIEN_2006,[67] OBRIEN-2010,[68] PARIKH_2014,[69] SCHAUER_2012,[70] WENTWORTH_2014,[71] SCHIAVON_2018,[72]. NA: not available. LAGB: laparoscopic gastric banding; RYGB: Roux-en-Y gastric bypass; T2DM: type 2 diabetes mellitus; BPD: biliopancreatic diversion; SLEEVE: sleeve gastrectomy.

Longer-term follow-up data beyond the formal protocol of the original RCT have been published for a number of these trials.[13, 73-77] We include these follow-up reports in our assessment since they provide the most robust longer-term evidence on the effectiveness of bariatric surgery.

4.1.4 Note on observational studies

For the assessment of the clinical effectiveness of bariatric surgery, no systematic literature search was executed for observational studies, since these are prone to bias and hence do not provide solid evidence with regard to the clinical effectiveness of an intervention. Because in observational studies patients are not randomised to surgery or no-surgery, it cannot be excluded that they are clinically different from those that prefer medical treatment. Even a "matched control group" can be different with respect to unmeasured characteristics. Operated patients from clinical practices may be highly motivated and more likely to stick to a healthy lifestyle, and they may have been more intensely followed and treated for co-morbid diseases, which obviously can affect survival, independently of bariatric surgery. Therefore, results from observational studies must be interpreted cautiously. Several authors have stressed this methodological limitation.[46, 49, 78-82]

However, in the field of bariatric surgery, RCTs have limitations in their own right.[83] These studies are in general small, conducted in centres of excellence, and limited to only a few years of follow-up. They often also suffer from methodological limitations such as unclear randomisation procedures, absence of allocation concealment, and absence of blinding of outcome assessors. Furthermore, pooling data from these RCTs in a meta-analysis may not be valid because of the clinical heterogeneity of the studies. Therefore, results from meta-analyses of those RCTs have to be interpreted cautiously.

Since only 1 RCT has been conducted in adolescents we decided to use data from 3 observational studies that have received particular attention in recent scientific literature for our appraisal of the effectiveness of bariatric surgery in this specific subgroup of patients.[84, 85, 86] For assessing the outcome "long-term mortality", we will also use evidence form observational studies since data of patients enrolled in RCTs are at best available for a follow-up of 5 years.

Observational studies may provide interesting data on adverse effects, and particularly on rare and late events. A focused search for adverse effects with inclusion of observational studies has been executed and will be discussed in a separate chapter 5.

This literature search on adverse events (both short- and long-term) was broad, and one of the search terms being used was mortality. This resulted in the identification of articles, review articles, systematic reviews and meta-analyses discussing or reporting on the risk of mortality after bariatric surgery, compared to groups of obese patients that did not undergo bariatric surgery. Most of the meta-analyses are based on a mix of data coming to a large extent from observational research (prospective and retrospective studies, registry-based studies, clinical studies …) and to a very limited extent coming from randomized clinical trials. It was preferred to present the results related to the impact of bariatric surgery on mortality in this chapter. Data coming from RCTs and observational studies will be discussed separately in part 4.2.2.1 and part 4.2.2.2, respectively.

4.1.5 GRADE level of evidence

For critical outcomes (survival and quality of life), the quality of the supporting evidence was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. According to GRADE, we classified the quality of evidence into 4 categories: high, moderate, low, and very low (Table 6 and Table 7). The quality of evidence reflects the extent to which there is confidence in an estimate of the effect. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level (Table 6). The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.

Observational studies were by default considered low level of evidence (Table 6 and Table 7). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. risk ratio (RR) >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized in Table 8.

Table 6 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⨁⨁⨁⨁) Moderate (⨁⨁⨁⊖) Low (⨁⨁⊖⊖) Very low (⨁⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 7 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	

Quality level	Definition	Methodological Quality of Supporting Evidence
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 8 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of invalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

Key points – Methodology used for the analysis of the clinical effectiveness of metabolic and bariatric surgery

- **The assessment of the clinical efficacy of bariatric surgery in this report is based on data originating from randomised controlled trials (RCTs) and their respective follow-up reports.**
- **Meta-analyses are considered only if they are restricted to RCT data. Even then, pooled efficacy data have to be interpreted with caution, given the clinical heterogeneity of the studies involved.**
- **Because of the lack of evidence from RCTs with respect to "bariatric surgery in adolescents", and with respect to the outcome "long-term mortality", we decided to also consider systematic reviews & meta-analyses and large often-cited observational studies in assessing these issues.**
- **For critical outcomes (survival and quality of life), the quality of the supporting evidence was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.**

4.2 Clinical effectiveness in adults

In five of the SRs that we identified, bariatric surgery was compared with non-surgery in unselected populations of obese subjects. The 2014 Cochrane review that we used as a starting point for our search has now to be considered out-dated.[42] It included 7 of the 17 RCTs comparing surgery with medical treatment that were published until 2017. The most comprehensive SR of RCTs is by Cheng et al.[87] It included 11 of the 17 RCTs published up to 2017. Some of the meta-analyses in this publication are distorted because of double counting of data from the same study and we exclude the corresponding calculations from our discussions. The SR of Zhou et al. includes both RCTs and observational studies and studied only hard endpoints (all-cause mortality, cardiovascular events, cancer).[88] Cardoso et al. focus on mortality.[89] Juodeikis et al. performed a SR of outcomes after sleeve gastrectomy only.[78]

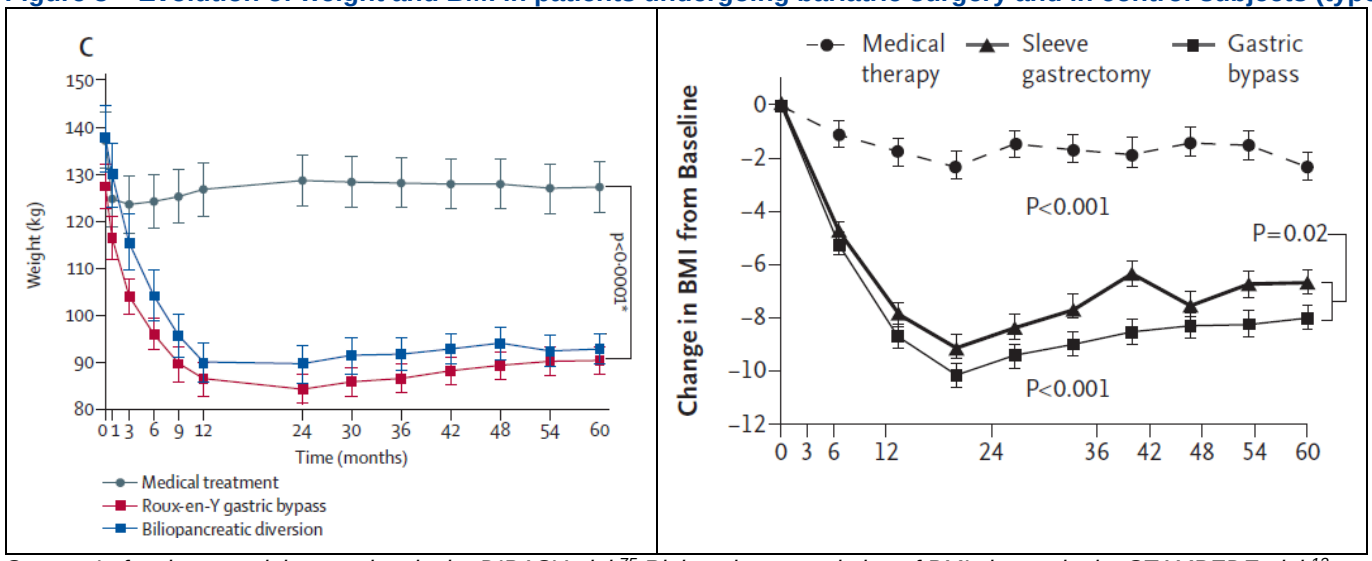
In the following discussions we summarise the RCT evidence extracted from these SRs, and complement them with data from recently updated RCT results and/or RCTs that were not included in the SRs.

4.2.1 Impact of bariatric surgery on weight

Pooled RCT data indicate a mean difference in weight loss between operated patients and medically treated patients of 17.71 and 27.96 kg after 1 and 2 years respectively. Absolute weight loss depends on baseline weight, and the pooled weight loss in those RCTs was 15.02 kg (16.71-13.32) in non-severely (BMI 30-35 kg/m²) obese individuals and 26.15 kg (30.98-21.32) in severely obese (BMI >35 kg/m²) individuals, however the publication does not specify the time-peirod after surgery where these data refer to.[87]

Longer-term follow-up data beyond the formal protocol of the original RCTs have been published: four of them reported 5-year data[13, 74, 75, 77] and 1 published outcomes after 10 years.[76] These data indicate a gradual slight increase in weight beyond 12 to 24 months (Figure 3).

Figure 3 – Evolution of weight and BMI in patients undergoing bariatric surgery and in control subjects (type 2 diabetic obese population)



Source: Left column: weight over time in the DIBASY trial.[75] Right column: evolution of BMI change in the STAMPEDE trial.[13]

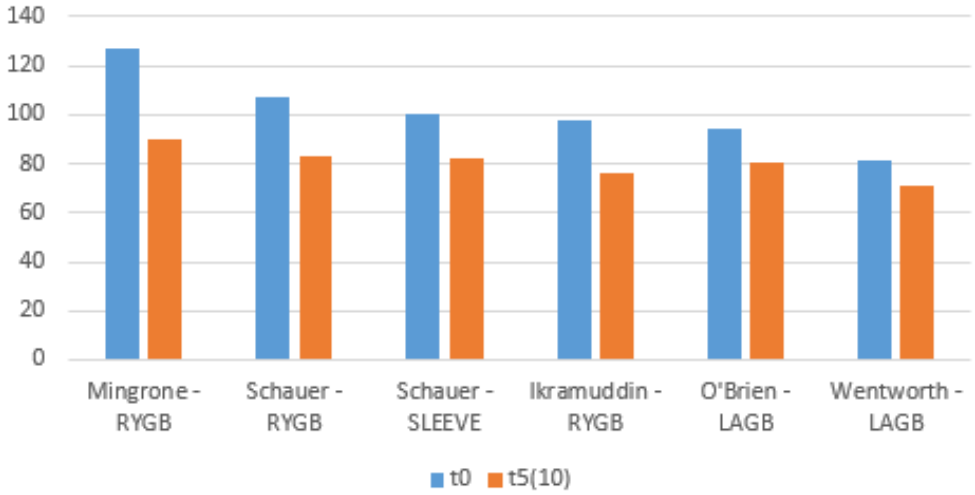
The relative weight loss after surgery varies across trials from 12.2 to 28.4% (Table 9). In patients that underwent RYGB, weight reduction at 5 years ranged between 21.8 and 28.4%. After gastric banding it was 12.2 and 15.0%. Absolute weight loss at 5 (or 10) years in the RCT participants, and its dependency on baseline weight, is depicted in Figure 4.

Table 9 – Impact of bariatric surgery on weight and on BMI after 5 to 10 years

Study (First author)	MINGRONE		IKRAMUDDIN		SCHAUER			WENTWORTH		O'BRIEN	
	RYGB	Control	RYGB	Control	RYGB	SLEEVE	Control	LAGB	Control	LAGB	Control
Follow-up data at:	5 years		5 years		5 years			5 years		10 years	
Weight at t_0	127,2 kg	137,1 kg	98,0 kg	99,0 kg	106,8 kg	100,4 kg	105,0 kg	81,0 kg	83,0 kg	94,7 kg	95,1 kg
BMI at t_0	44,0	45,4	34,4	34,9	37,0	36,0	36,4	29,0	29,0	42,3	40,4
Absolute BMI change at 5(10) yrs.	12.7	3.3	7,5	3,3	8,0	7,2	2,5	NA	NA	7,8	0,1
Weight at 5(10) yrs.	90,3 kg	127,1 kg	76,6 kg	89,5 kg	83,4 kg	81,9 kg	99,0 kg	71,1 kg	81,5 kg	80,5 kg	94,7 kg
Weight reduction at 5(10) yrs.	37,0 kg	10,0 kg	21,4 kg	9,5 kg	23,2 kg	18,6 kg	5,3 kg	9,9 kg	1,5 kg	14,2 kg	0,4 kg
% Weight reduction	28,4%	6,9%	21,8%	9,6%	27,8%	22,7%	5,4%	12,2%	1,8%	15,0%	0,4%

Follow-up data of randomised trials.[13, 74-77] Baseline (t_0) data are those of patients that completed 5-year follow-up.

Figure 4 – Weight before and 5 to 10 years after bariatric surgery



Source references: see text. y-axis: weight in kg. t0: baseline weight. t5(10): weight at 5 years (10 years for O'Brien).

Key points – impact on weight (data from RCT)

- **Absolute weight loss after bariatric surgery depends on baseline weight. The pooled weight loss in RCTs was 15.0 kg (16.7-13.3) in class I (BMI 30-35 kg/m²) obese individuals and 26.2 kg (31.0-21.3) in class II (BMI>35 kg/m² or severe) obese individuals (time point not specified).**
- **Weight loss after surgery corresponds with a decrease in BMI of 7.2 to 12.7 kg/m² (Table 9).**
- **Peak weight loss difference between operated patients and controls occurs at 12 to 24 months. There is a gradual slight increase in weight later on.**

4.2.2 *Impact of bariatric surgery on mortality*

4.2.2.1 *Evidence from randomised controlled trials: focus on short-term mortality*

Cardoso et al. analysed in their systematic review and meta-analysis short- and long-term mortality data after bariatric surgery.[89]. Short-term mortality was defined as death occurring ≤30 days of surgery. Short-term all-cause mortality based on 38 RCTs involving 4030 patients was 0.18% (95%CI 0.04% to 0.38%) and was higher for open surgeries (0.31%; 95%CI 0.03%-0.97).

Level of evidence according to GRADE was considered to be high (Appendix 4).

Regarding the long-term (>5 year), there are no solid long-term mortality data from RCTs comparing metabolic and bariatric surgery with non-surgical treatment of obesity.

4.2.2.2 *Evidence from observational studies: focus on long-term effects on mortality*

MBS encompasses a limited but definite risk of mortality in the perioperative period and short-term period after the intervention, which is inherent to the procedure as such. This essentially holds true for any abdominal surgery. With the remarkable progress made in metabolic and bariatric surgery and care over the last decade(s), average early post-operative mortality rates came grosso modo down into the order of 0.1-0.3%, which seem to be almost equivalent to relatively low-risk procedures such as cholecystectomy and hysterectomy.[90, 91]

The data discussed here on the effects of MBS on long-term mortality, are based on systemic review and meta-analyses (SR-MA) of underlying studies that for the majority are of observational nature. The data from the SR-MA are complemented with some other data from recently published registry based cohort-studies. The limitation of these observational data is their inherent risk of bias and results should thus be interpreted with caution.

The first clear indication that MBS might be associated with a long-term decrease in mortality came from the SOS (Swedish Obese Subjects) trial. The SOS trial may be considered as a landmark trial in the field of bariatric surgery. It was the first large, long-term, prospective, controlled trial aimed at investigating the effects of BS and weight loss on mortality and other objective endpoints in obese patients, who were compared to a well matched population of non-surgically treated obese individuals (n = 2010 for surgical group; n = 2037 for the non-surgical control group).[92]. The age of participants was 37-60 years and BMI was ≥34 kg/m^2 in men and ≥38 kg/m^2 in women.

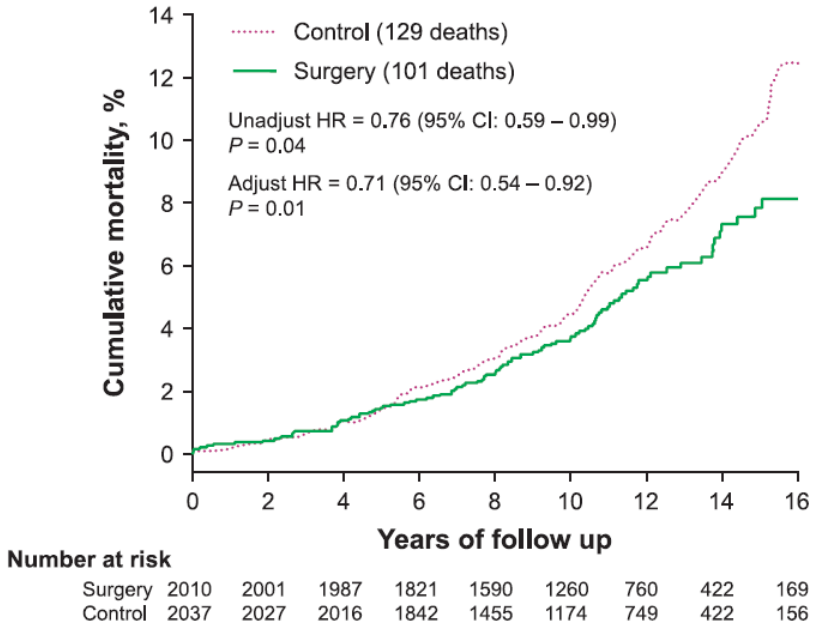
It was a non-randomized controlled study (as at time of study start in 1987 Ethic Committees did not accept this type of interventional trials to be randomized) for which the overall mortality risk after an average FU of 10.9 years was reported. The study group of the SOS trial applied matching of patients on the basis of 18 prognostic factors, used rigorous methods in maintaining patients' follow-up, and reported adjusted estimates after controlling for important factors. Nevertheless, the risk of bias cannot be

completely excluded since the 'allocation' of patients was based on patient desire to opt either for surgery or for conventional medical management.

The surgically treated subjects underwent nonadjustable or adjustable banding (n=376), vertical banded gastroplasty (VBG; n=1369) or gastric bypass (GBP; n=265) operations. The matched controls received the standard nonsurgical obesity treatment in their primary health care centres. No attempt was made to standardize the conventional treatment, which ranged from sophisticated lifestyle intervention and behaviour modification to, in many practices, no treatment at all.[92]

Compared to a matched non-surgical cohort, the adjusted HR for mortality was 0.71 (95%CI: 0.54-0.92; P = 0.01) in the bariatric surgery group. Overall cumulative data were available for up to 16 years, as depicted in Figure 5. Vital status was known in >99% by cross-checking the SOS database with the Swedish Mortality Registry.

Figure 5 – Cumulative mortality amongst patients in the control and the surgery groups during the 16 years of FU in the SOS study, according to Sjostrom et al., 2007 and 2013.



Source: Sjostrom L et al., J Intern Med 2013

Note that these SOS trial data stem from a time period where overall mortality and complications are in general higher than what is seen in contemporary bariatric medicine.

Three relatively recent systematic reviews and meta-analyses (SR-MA) provided relative risk reductions after MBS in all-cause mortality varying between -41% and -52%.[88, 89, 93] These three SR-MA had some overlap, explained by the slightly different eligibility criteria and their different time of periods. The results of these three SR-MA are essentially consistent, and

point to a large size effect with regard to a reduction (avoidance) of long-term mortality. These three SR-MA relate to an overall obese bariatric population, while a forth SR-MA by Sheng et al. relate to a severely obese type 2 diabetic population.[43]

- The **SR-MA by Cardoso et al.**[89] analysed both short- and long-term mortality data in obese patients (with or without T2DM). This SR-MA did not retrieve any RCTs reporting time-to-event data for the long-term mortality analysis, and most observational studies were retrospective in design. For the specific evaluation of long-term mortality (≥2 years), 8 observational studies (follow-up range: 2 to 14.7 years; average FU period 7.3-7.4 years) involving 23 647 operated patients and 89 628 non-operated controls, were eligible for meta-analysis. Two of the 8 studies were prospective studies and 6 were retrospective studies. The pooled effect estimate showed a reduction of 41% in all-cause mortality (hazard ratio, 0.59; 95%CI: 0.52 to 0.67). The relative risk reduction was -43% based on an adjusted HR of 0.57 (95%CI: 0.47-0.69). The pooled odds ratios to die from cardiovascular disease and cancer in operated versus control patients were 0.42 (OR; 95%CI: 0.25-0.72) and 0.47 (OR; 95%CI: 0.36-0.63), respectively. Looking separately at the 2 prospective and 6 retrospective studies the pooled HR were 0.67 (95%CI: 0.46-0.92) and 0.57 (95%CI: 0.492-0.66) respectively.
- The **SR-MA by Zhou et al.**[88] aimed to assess the effects of MBS on all-cause mortality, cardiovascular (CV) events, and cancer compared to non-surgical treatment. Eleven RCTs (n=890), 4 non-randomized controlled trials (n=4274) and 17 cohort studies (n=297 024) reporting one or more of the three outcomes at 1 year or longer were included. Data based on RCT suggested substantial uncertainty regarding the three outcomes. Pooling of the unadjusted data suggested statistically lower all-cause mortality in the surgical group (4.5%) vs. the non-surgical group (8.5%). Pooled adjusted estimates from the non-randomized studies indicated and suggested that the surgical group had lower risk of all-cause mortality (OR 0.55, 95%CI: 0.46-0.65; 10 studies). Besides risk for CV-events (myocardial infarction: OR 0.71, 95%CI: 0.54-0.94; stroke: OR 0.66, 95%CI: 0.49-0.89; and their composite: OR 0.67, 95%CI: 0.54-0.83; 1 study), and risk of cancer (OR 0.74, 95%CI: 0.65-0.85; 2 studies) was also reduced.
- The **SR-MA by Kwok et al.**[93] investigated the impact of MBS on all-cause mortality and cardiovascular disease. The MA included 14 studies encompassing 29 208 patients that underwent MBS and 166 200 non-surgical controls, with a follow-up that ranged from 2 years to 14.7 years. Two studies were considered at moderate-high risk of bias, whilst 10 studies were at moderate or lower risk of bias. Compared to nonsurgical controls there was more than 50% reduction in mortality amongst patients who had bariatric surgery (OR 0.48, 95%CI: 0.35-0.64, I2 =86%, 14 studies; crude rate 3.6% vs. 11.4%). The pooled estimate from adjusted data yielded a more conservative and less heterogeneous association (OR 0.60; 95%CI: 0.49-0.74, I2 = 64%, 10 studies; crude rate 4.0% vs. 8.3%). Exclusion of 4 studies with moderate-high risk of bias showed that there was a significant reduction in mortality (adjusted OR 0.67; 95%CI: 0.59-0.77, I^2 = 25%; crude rates of 3.8% vs. 8.3%). In pooled analysis of four studies with adjusted data, bariatric surgery was associated with a significantly reduced risk of composite cardiovascular adverse events (OR 0.54, 95%CI: 0.41-0.70). Bariatric surgery was also associated with significant reduction in specific endpoints of myocardial infarction (OR 0.46 95%CI 0.30-0.69, 4 studies) and stroke (OR 0.49 95%CI: 0.32-0.75, 4 studies).
- The **SR-MA by Sheng et al.**[43] evaluated the LT-effect (1 RCT and 9 cohorts with FU time ranging from 5 to 15 years) of MBS in patients with type 2 diabetes and found (based on one RCT with FU of 5 years, and 3 observational studies) a relative risk reduction (RRR) in mortality of -79% (RR=0.21; 95%CI = 0.209-0.213). The authors reported significant heterogeneity across the underlying studies and no clear indication for publication bias.

A summary of the findings of these 4 systematic review and meta-analyses can be found in Table 10.

Table 10 – Summary of results from the 4 SR-MA on outcome measures of interest (overall mortality – and where applicable cardiovascular and cancer related mortality or events)

Author, year	Type of research *(focus of interest underlined)*	Follow-up	Population/type of analysis Operated vs. non-operated obese patients	**Long-term all-cause mortality** **Measure of relative risk (reduction), (95%CI)**	**Absolute mortality rate** **(operated vs. non-operated)**	Absolute Risk Reduction (**ARR/ NNT**)	**CV-mortality** (95%CI)	**CV-(=macro-vascular) events** **(operated vs. non-operated) (95% CI)**	**Cancer mortality** **(operated vs. non-operated) (95% CI)**	**Cancer events**	Comments
Cardoso et al., 2017	SR-MA LT-mortality, CV-mortality and Cancer related mortality BMI ≥35 ≥2 y FU	mean FU 7.3-7.4 y	8 observational studies for LT-mortality 23 647 operated vs 89 628 non-operated obese 2 prospective studies, 6 retrospective	**RRR -43%, on adjusted HR 0.57 (0.47-0.69)**, based on 6 studies RRR -41%, on pooled-mixed synthesis HR 0.59 (0.52-0.67) prospective studies: RRR -35%, HR 0.65 (0.46-0.92) retrospective studies: RRR: -43%, HR 0.57 (0.49-0.66)	not reported		RRR – 58%; OR 0.42 (0.25-0.72)		RRR – 53%; OR 0.47 (0.36-0.63)		LT-data based on observational research, mostly retrospective; No significant difference was found between the 2 prospective and 6 retrospective studies
Zhou et al. 2016	SR-MA LT-mortality CV-events and Ca outcome BMI ≥30 ≥1 y FU *RCTs: non-contributive for mortality analysis*	FU in 4 non-RCT: SOS biggest trial with low risk of bias; 10 y FU); FU in 17 cohort trials: 9 studies FU of at least 5 y	20 studies reported all-cause mortality: including 4 non-RCT(4 274) and 16 cohort studies (21 9913)	RRR -62%,on unadjusted OR 0.38 (0.29-0.50) **RRR -45%, on adjusted HR 0.55 (0.46-0.65)**, based on 10 studies: 1 non-RCT and 9 cohort studies	4.5% vs. 8.5%	ARR: 4% NNT: 25		9.9% vs. 11.5% RRR -33%, based on adjusted OR 0.67 (0.54-0.83, 1 study)		- All Ca-types: no difference-- Obesity related Ca-types: 1.1% vs 1.5%; OR 0.49 (0.31-0.79)	For all the outcomes analysed by adjusted estimates, no significant difference was observed between: -non-RCT and cohort trials -BMI < vs. ≥40 -FU period <5 vs. ≥5 years)

Author, year	**Type of research** *(focus of interest underlined)*	**Follow-up**	**Population/type of analysis** **Operated vs. non-operated obese patients**	Long-term all-cause mortality Measure of relative risk (reduction), (95%CI)	Absolute mortality rate (operated vs. non-operated)	**Absolute Risk Reduction (**ARR/ NNT**)**	CV-mortality **(95%CI)**	CV-(=macro-vascular) events (operated vs. non-operated) (95% CI)	Cancer mortality (operated vs. non-operated) (95% CI)	Cancer events	**Comments**
Kwok et al., 2014	SR-MA on mortality and CV-disease	FU range: 2-14.7 years	14 cohort studies: 3 prospective and 6 retrospective, and 5 were it was unclear whether they were pro-or retrospective 29 208 operated vs 166 200 non-operated obese	Overall mortality: - **Pooled estimate based on adjusted data of all studies**: **RRR -40%, based on adj.OR 0.60 (0.49-0.74)** - **Pooled estimate after exclusion of 4 studies with moderate-high risk of bias: RRR – 33%, based on adj.OR 0.67 (0.59-0.77)**	4.0% vs 8.3% 3.8% vs 8.3%	ARR: 4.3% NNT: 23 ARR:4.5% NNT:22	NA	based on 4 studies: 2.4% vs. 4.0% RRR -46%, based on OR 0.54 (0.41-0.70)	NA	NA	LT-data based on observational research data on mortality similar after exclusion of studies with moderate-to-high risk of bias
Sheng et al. 2017	SR-MA in patients with type 2 diabetes; FU time ≥5y mortality, macro-vascular outcome	FU range : 5-15 y	10 studies: 1 RCT and 9 cohorts - Mortality analysis based on 28 605 type 2 diabetics from 4 studies - Macrovascular complications based on 29 026 T2DM from 5 studies	Overall mortality: RRR -79%, based on random model RR 0.21 (0.209-0.213)	NA	NA		RRR -48%, based on RR 0.52 (0.44-0.61)	NA	NA	LT-data based on observational research sensitivity analyses suggested that the pooled point estimates were not significantly affected by any single study

The most recent SR-MA by Cardoso et al. (2017)[89] and the SR-MA by Zhou et al. (2016)[88] did an appropriate quality appraisal with risk of bias assessment, and therefore the focus will be on these studies. The third SR-MA by Kwok et al. (2014)[93] also included an own modified variant of risk of bias assessment method which took into account the recommendations of the Cochrane Adverse Events Method Group, but which included some other elements. The fourth SR-MA by Sheng et al. (2017)[43] did not mention the way a quality and risk of bias assessment was done for the underlying primary studies. Therefore we opted to do a concise GRADE appraisal of the SR-MAs performed by the groups of Cardoso, Zhou and Kwok, and to supplement the mortality data from these 3 SR-MA's by a description of the results of the SR-MA in a type 2 diabetic population performed by the group of Sheng et al. However we decided not to do a formal GRADE appraisal on this SR-MA as the authors did not report on how they performed the quality and risk of bias assessment of the underlying studies. A quality assessment based on GRADE principles providing an appraisal of the quality of evidence and summary of findings on long-term mortality risk can be found in Appendix 4. **Overall the level of evidence according to GRADE was considered to be low-to-moderate for the outcome long-term mortality (risk reduction).** The level of evidence is based on the GRADE methodology and reflects the confidence in the estimated effect size.

A recent retrospective study (not yet included in the previous SR-MAs) included all patients (n=9895) that underwent RYGB in Denmark from 2006 to 2010. They were compared with an age- and gender matched cohort (n=247 366) with a median follow-up time of 4.2 years.[94] Noteworthy, the RYGB group had a much higher baseline BMI (46 kg/m²) than the comparison cohort (25 kg/m²). It is not clear why the comparator group was not matched on BMI. The mortality rate after RYGB was 2.05 per 1000 person-years. Despite the higher BMI in the BS surgery group vs. the comparison cohort, after 4.2 years, all-cause mortality was similar in the 2 cohorts: 0.89% (n=91) in the RYGB cohort, and 0.92% (n=2 204) in the comparison cohort. RYGB-related mortality (deaths due to intestinal obstruction/intra-abdominal leakage) was 0.15% (16/9895). Mortality due to suicide (2.78; 95%CI: 1.44-5.33), accidents (2.29; 95%CI: 1.16-4.54), gastrointestinal diseases (2.01; 95%CI: 1.06-3.84), and infectious diseases (1.75; 95%CI: 0.98-3.17) was higher in the RYGB cohort versus comparison groups, but mortality from cancer was lower (0.43; 95%CI: 0.27-0.70). Besides that, short-term perioperative (30-days) mortality after RYGB was 0.04% (4/9895).

Another very recently published retrospective cohort study from Reges et al., based on a large Israeli integrated health fund database, included 8385 patients who underwent bariatric surgery (LAGB n=3635, RYGB n=1388, SG n=3362) and 25 155 non-surgical patients matched and adjusted for BMI, age, sex, socio-economic status, diabetes, hyperlipidemia, hypertension, CV-disease and smoking.[95] There were 105 deaths (1.3%) among surgical patients during a median follow-up of 4.3 years (IQ: 2.8-6.6) (including 61 [1.7%] who underwent LAGB, 18 [1.3%] RYGB, and 26 [0.8%] SG), and there were 583 deaths (2.3%) among nonsurgical patients during a median follow-up of 4.0 (IQR: 2.6-6.2) years. The absolute difference was 2.51 (95%CI: 1.86-3.15) fewer deaths/1000 person-years in the surgical vs nonsurgical group. Compared with the surgical patients, the non-surgical group had almost a doubling of mortality risk as demonstrated by the adjusted hazard ratios (HRs) for mortality of 2.02 (95%CI: 1.63-2.52) for the entire study population. By surgical type, HRs for mortality *(non-surgical vs. surgical group)* were 2.01 (95%CI: 1.50-2.69) for LAGB, 2.65 (95%CI: 1.55-4.52) for RYGB, and 1.60 (95%CI: 1.02-2.51) for the SG.

Note however that despite the observation that all-cause mortality risk decreases over the long-term, there are some indications that death due to suicide and accidents might be higher in the surgical group vs. the non-surgical group (or the general population).[96] We refer to part 5.4.8 for further information.

Key points – mortality risk

- **Based on RCT data, short-term peri-operative mortality (≤30 days) after bariatric surgery is low (0.04% to 0.38%) (High level of evidence)**
- **Based on systematic reviews and meta-analysis, that are essentially based on underlying studies of observational nature, bariatric surgery is associated with a long-term relative risk reduction ranging between 30% to 45%. (Low-to-moderate level of evidence)**

  This is a net-effect on overall long-term mortality risk. The observations made in 2 out of the 4 SR-MA point to a decrease in cardiovascular disease or CV-mortality and cancer events or cancer related mortality.
- **It is important to remark that the long-term effects on mortality are based on observational data which are more prone to a risk of bias than RCT data. Caution is needed when interpreting these data.**

4.2.3 *Impact of bariatric surgery on quality of life*

We identified 1 systematic review of reviews on the relationship between obesity, weight loss and health related quality of life (QoL), also including studies on weight loss obtained through bariatric surgery.[82] Since it searched for studies published until July 2016, it missed important recent publications. Therefore, we decided to focus in this chapter on the individual RCTs and their respective follow-up reports. We restrict our analysis to RCTs that compared bariatric surgery with medical treatment and excluded studies that compared different surgical techniques since they do not allow to assess how QoL would have evolved in case patients would not have been operated.

Of 16 RCTs that have been conducted in adults (Table 5), 8 reported QoL data, most often measured with the EQ-5D and/or the SF-36 (or RAND-36) instrument. Some researchers reported QoL data at the end of the trial only (i.e. after 1 or 2 years), others reported follow-up data up to 3 to 5 years, and 1 one case after 10 years. Below we summarise the most relevant of those data. QoL data after bariatric surgery in adolescents have been studied in one RCT and will be discussed in the corresponding chapter.

4.2.3.1 *QoL scores 1 year after surgery*

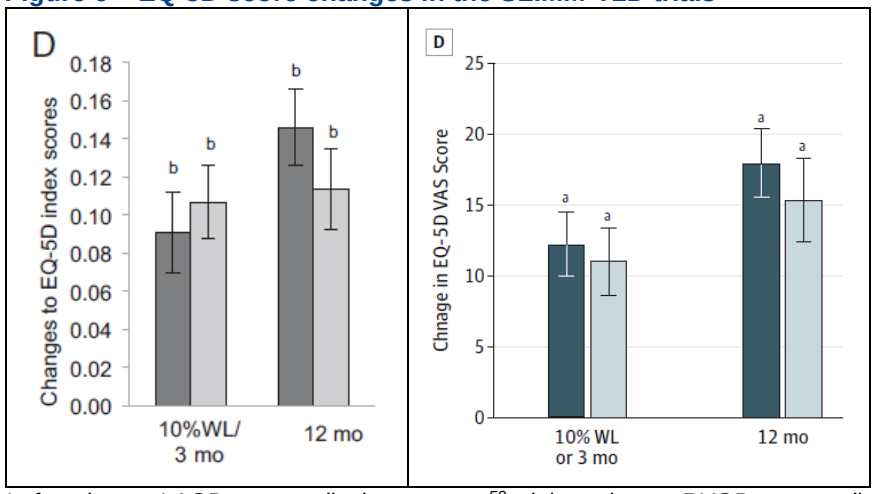
Generic QoL instruments

- EQ-5D scores

EQ-5D scores at 1 year were reported in 3 RCTs.[59, 63, 97] In the CROSSROADS trial (RYGB vs. medical) overall health ratings from the EQ-5D questionnaire improved significantly within each group: from 77.5±14.3 to 87.2±8.2 for RYGB, and from 62.1±20.7 to 76.5±11.9 for medical intervention. The magnitude of this improvement was not different between groups (p=0.34).[97]

The Surgery or Lifestyle with Intensive Medical Management in Treatment of Type 2 Diabetes (SLIMM-T2D) trials were designed as two parallel RCTs comparing medical treatment with different surgical approaches. They originate from the same research institution, and reported EQ-5D data after RYGB (the SLIMM-T2D-1 trial)[63] and after LAGB (the SLIMM-T2D-2 trial)[59] versus medical treatment, respectively. The visual analogue scale score of the EQ-5D, and the EQ-5D index score improved significantly, although without significant difference between groups (Figure 6).

Figure 6 – EQ-5D score changes in the SLIMM-T2D trials



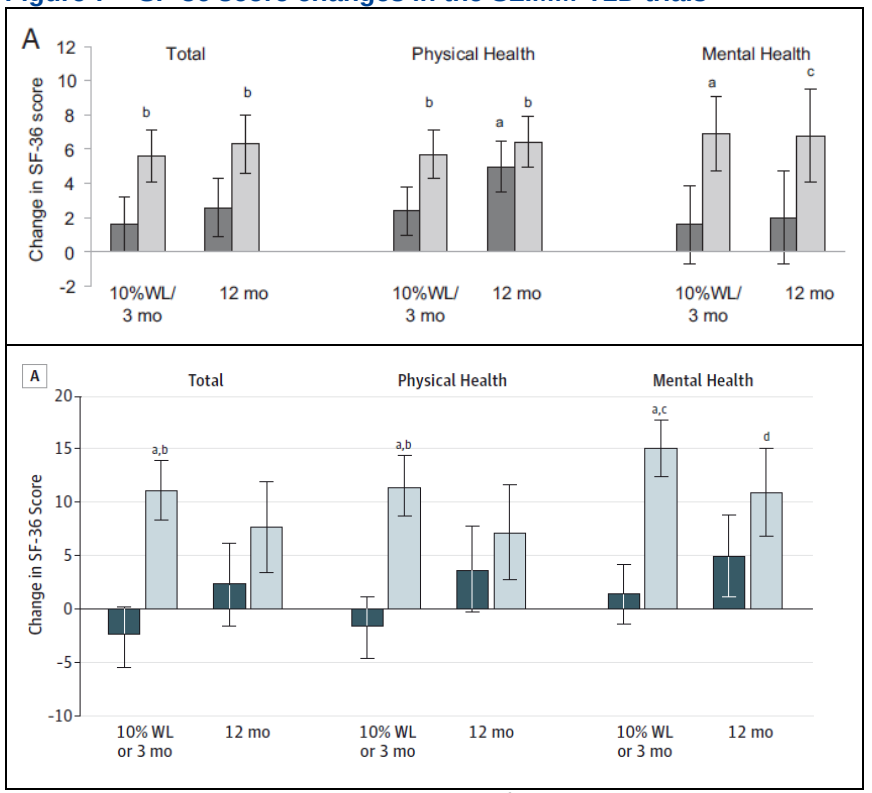
Left column: LAGB vs. medical treatment,[59] right column: RYGB vs. medical treatment.[63] Dark bars refer to data from the surgical group. 10%WL/3 mo: if 10% weight loss did not occur, assessment was performed at 3 months.

- SF-36 scores

The SLIMM-T2D trials also reported improvements at 1 year in SF-36 Total, Physical Health and Mental Health scores.[59, 63] In both studies the change was more pronounced in the medical group, but the observed difference did not reach statistical difference between groups (Figure 7).

The level of evidence according to GRADE for QoL after 1 year was considered to be low due to significant loss of FU and the small number of patients (Appendix 4).

Figure 7 – SF-36 score changes in the SLIMM-T2D trials



Upper panel: LAGB vs. medical treatment,[59] lower panel: RYGB vs. medical treatment.[63] Dark bars refer to data from the surgical group.

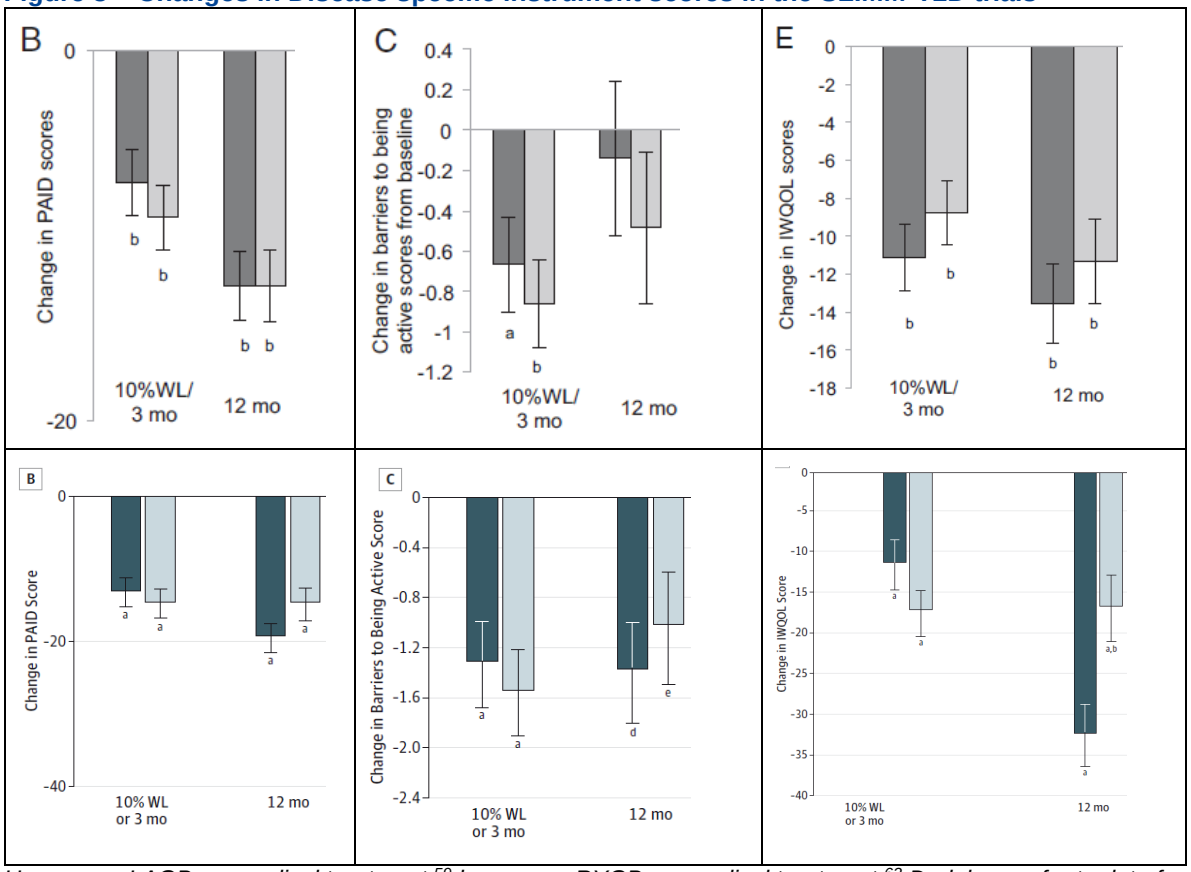
Disease-specific QoL instruments

The SLIMM-T2D trials also reported QoL results measured with the following disease specific instruments: “Impact of Weight on Quality of Life (IWQOL)”, “Problem Areas In Diabetes (PAID)” and “Barriers to Being Physically Active”.

In the SLIMM-T2D-2 trial, IWQOL and PAID improved from baseline to early assessment (i.e. at 10% of initial body weight loss or at 3 months if 10% weight loss did not occur), with similar improvements in both groups. Changes from baseline further improved at 12 months in both groups, but again effects were similar in surgical and medical treatment arms. Barriers to Being Active scores improved from baseline to a similar magnitude in both groups at early assessment. This change from baseline was not sustained at 12 months in either group, with no differences between groups (Figure 8).[59]

In the SLIMM-T2D-1 trial, PAID and Barriers to Being Active score improvements were similar in magnitude between the groups. The IWQOL score also improved significantly in both groups, but the magnitude of improvement was significantly greater in the RYGB group at 1 year (Figure 8).[63]

Figure 8 – Changes in Disease specific instrument scores in the SLIMM-T2D trials



Upper row: LAGB vs. medical treatment,[59] lower row: RYGB vs. medical treatment.[63] Dark bars refer to data from the surgical group.

4.2.3.2 *QoL scores 2 years after surgery*

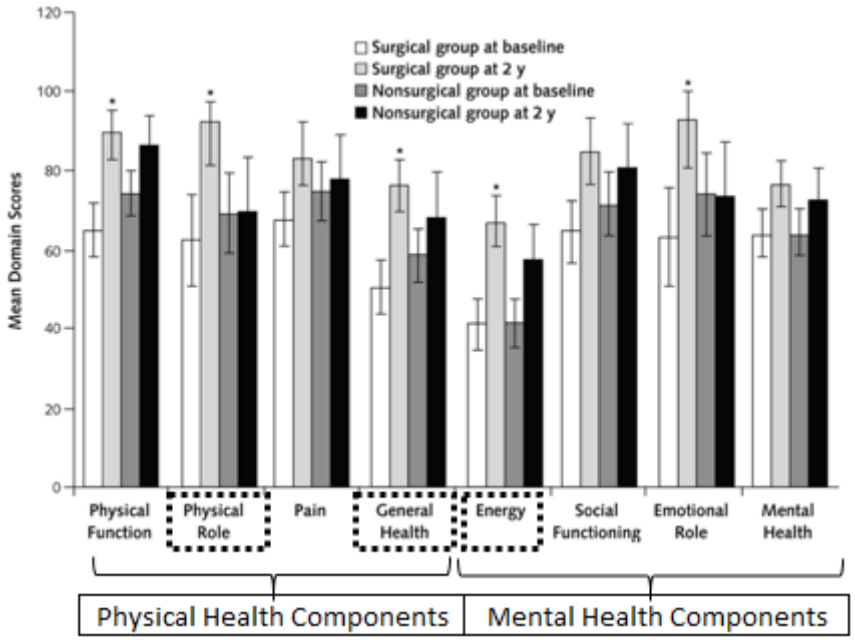
Generic QoL instruments

Two RCTs reported 2 year changes in the SF-36 domain scores after LAGB and compared them with changes after a medical weight loss strategy.[61, 67] In one there was a statistically significant greater improvement in 5 of the 8 domains in the surgical group. Pain, social functioning and mental health improvements were not significantly different at 2 years (Figure 9).[67]

In the second RCT that studied bariatric surgery in patients with OSAS the surgical group had a significantly greater improvement in scores between baseline and 2 years compared to the medical group for Physical Role, General Health, and Vitality and the Physical Component Summary. The improvement was not statistically significant for the items Mental Health, Physical Function, Body Pain, Social Function, Role Emotional and the Mental Component Summary.

The level of evidence according to GRADE was considered to be low due to significant loss of FU and the small number of patients (Appendix 4).

Figure 9 – SF-36 QoL domain scores for surgical and non-surgical groups at baseline and after 2 years



Adapted from O'Brien et al.[67] Asterisk (*) indicates statistically significantly greater improvement in the surgical group at 2 years compared with the nonsurgical group. Domain scores highlighted in dotted squares are those for which the surgical group had a significantly greater improvement in Dixon et al.[61] as well.

Disease-specific QoL instruments

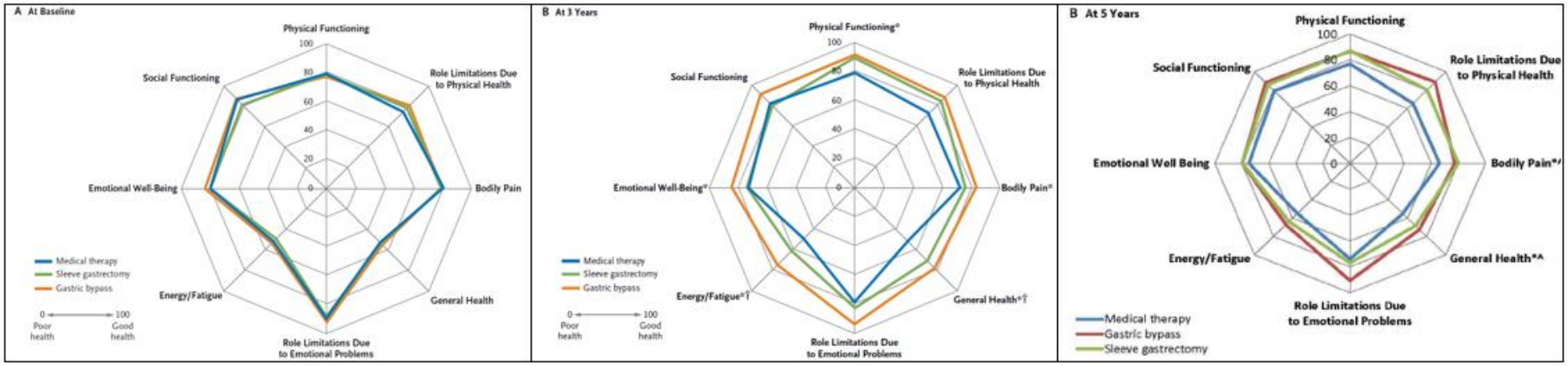
The RCT on bariatric surgery in patients with OSAS also reported disease-specific QoL data ("functional measures"): the Epworth Sleepiness Scale score (ESS), the Beck Depression Inventory, and the 6-minute walk test.[61] Both groups experienced a reduction in daytime sleepiness as measured with the Epworth Sleepiness Scale, reductions in symptoms of depression, and improvement in the 6-minute walk test, but there were no significant between-group differences.

4.2.3.3 QoL scores 5 years after surgery

Three RCTs published 5-year QoL data.[13, 75, 77] They report QoL measured with generic instruments only.

From the STAMPEDE trial (in a type 2 diabetic population), baseline characteristics, as well as 3- and 5-year follow-up data have been reported. Although a substantial number of patients were lost to follow-up, this RCT provides the currently best available QoL assessment after bariatric surgery (Figure 10).[13, 98] At 3 years there were significant improvements in five of eight mental and physical domains among patients in the RYGB group, and in two of eight domains among patients in the sleeve gastrectomy group, as compared with the medical therapy group (Figure 10). At 5 years, among patients in the RYGB and sleeve gastrectomy groups as compared with the medical therapy group, significant changes from baseline remained in two of eight domains: General Health and Bodily Pain.

Figure 10 – Evolution of Quality of Life scores over 5 years from the STAMPEDE trial



Adapted from Schauer et al.[13, 98] At baseline 50 patients were enrolled in each study group. After 3 years QoL data were available from 40 medical patients, 48 RYGB patients and 49 sleeve gastrectomy patients. After 5 years, these numbers dropped to 24, 39 and 37 respectively. The corresponding absolute response changes from baseline are shown inTable 11.

Table 11 presents QoL domain score changes from baseline at 3 and 5 years next to each other. It shows that the impact of surgery on QoL diminishes over time.

Table 11 – RAND-36 questionnaire response changes from baseline at 3 and 5 years in the STAMPEDE trial

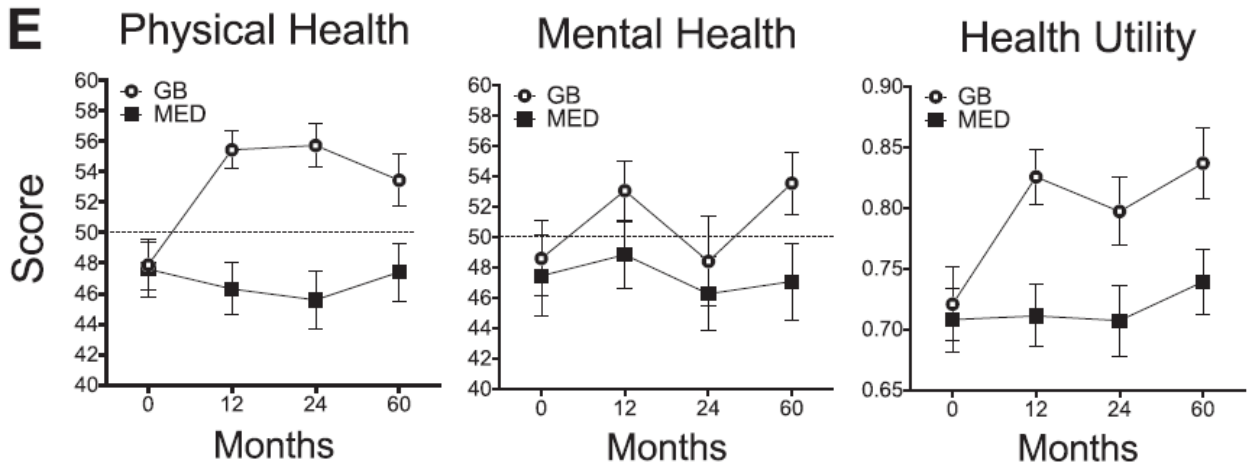
Physical Health Components					
At 3 years			At 5 years		
Medical	RYGB	Sleeve	Medical	RYGB	Sleeve
Physical Functioning					
1.0 ± 21.63	14.8 ± 16.28	9.9 ± 23.35	1.6 ± 17.65	8.1 ± 18.28	7.2 ± 29.19
Role Limitations due to Physical Health					
-2.6 ± 45.49	6.5 ± 36.82	5.2 ± 43.19	-10.4 ± 55.62	4.1 ± 36.87	0.7 ± 44.59
Bodily Pain					
-8.7 ± 16.62	4.9 ± 24.09	-2.7 ± 33.11	-16.6 ± 25.35	-2.4 ± 25.20	0.5 ± 20.55
General Health					
-0.4 ± 19.54	23.7 ± 19.69	17.6 ± 22.96	0.3 ± 16.04	17.4 ± 20.02	16.0 ± 22.20

Mental Health Components					
At 3 years			At 5 years		
Medical	RYGB	Sleeve	Medical	RYGB	Sleeve
Role Limitations due to Emotional Problems					
-11.5 ± 41.09	1.6 ± 19.65	-5.8 ± 43.29	-14.5 ± 38.70	-3.4 ± 23.93	-12.0 ± 40.75
Energy/Fatigue					
-2.2 ± 21.70	21.6 ± 18.35	12.8 ± 30.23	5.3 ± 25.63	11.4 ± 19.40	17.6 ± 27.15
Emotional Well Being					
-7.0 ± 16.17	0.6 ± 12.14	-6.3 ± 21.76	-8.8 ± 18.13	-5.9 ± 15.43	0.3 ± 21.40
Social Functioning					
-5.6 ± 20.48	3.4 ± 17.68	-2.5 ± 36.05	-9.4 ± 28.13	-0.3 ± 20.30	3.7 ± 28.70

Adapted from Schauer et al.[13, 98] Highlighted figures indicate statistically significant (p<0.05) differences in surgically versus medically treated patients. These data have to be interpreted with caution because of the small number of patients involved, the substantial loss to follow-up (especially after 5 years) and the potential bias introduced by multiple testing.

Five-year follow-up results have also been reported in Wentworth's trial which studied LAGB in overweight T2DM patients (BMI: 29 kg/m²).[77] Of 51 participants who enrolled in the study, 45 were followed until 5 years (22 randomised to LAGB and 23 to medical care). At enrolment, their BMI ranged between 25 and 30 kg/m², with a mean of 29 kg/m². QoL and health utility remained relatively constant in medically treated participants but improved in the LAGB group. At 5 years, composite scores of physical and mental health in the LAGB group had increased to above the general Australian population mean (50±10) to 53±8 and 54±10, respectively. This corresponded to a mean difference in health utility after 5 years of 0.10 (0.02–0.18) favouring LAGB participants (Figure 11). The results of this study may be less relevant with respect to the present report given the fact that participants were overweight, but by no means obese.

Figure 11 – QoL and Health Utility in overweight but not obese patients before and after surgery

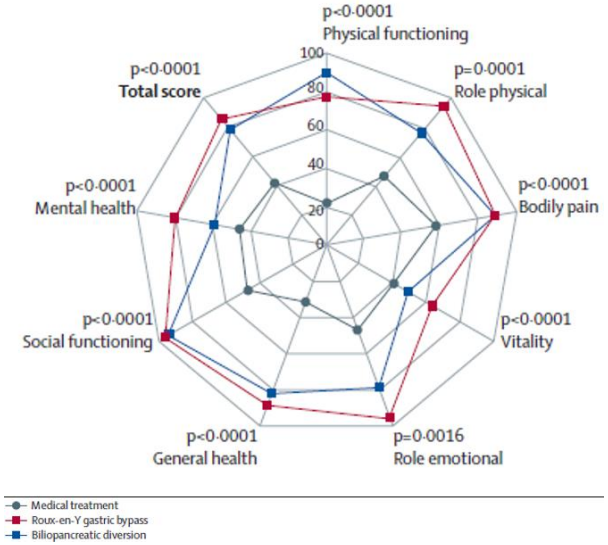


Source: Wentworth et al.[77] In this study baseline BMI was 29±1 kg/m². Dotted line: general Australian population mean (50±10).

In the DIBASY trial, QoL was not a predefined study endpoint, but QoL assessment with the RAND-36 instrument was added as an endpoint later on.[66, 75] Therefore, there are no baseline data of the study participants. At 5 years, surgical patients scored significantly better than medically treated patients for all subdomains of quality of life and for the total score domains. Of note, QoL scores of medically treated patients at 5 years were much lower than the corresponding figures from the STAMPEDE trial discussed above.[13]

The level of evidence according to GRADE was considered to be low due to significant loss of FU and the small number of patients (Appendix 4).

Figure 12 – Quality of Life at 5 years from the DIBASY trial



Source: Mingrone et al.[75] Baseline data were not available from this study.

Two of the abovementioned RCTs compared medical treatment with 2 different surgical techniques in separate study groups. In the STAMPEDE trial, none of the QoL scores were statistically different at any time between RYGB and sleeve gastrectomy.[13, 61, 98] In the DIBASY study, patients who underwent RYGB had significantly higher scores for the domains of vitality and mental health than did those who underwent biliopancreatic diversion.[75]

4.2.3.4 QoL scores 10 years after surgery

One RCT that studied LAGB in patients with mild to moderate obesity (BMI 30 to 35 kg/m²) published 2-year[67] follow-up results (cf. chapter 1.1.1.1) as well as 10-year[76] data. In the latter report a significant number of patients were lost to follow-up (12/40 of the operated and 7/40 of the medically treated patients) and crossed over to surgical treatment (23/33). The authors published QoL data for surgical, medical and cross-over patients separately, but not for the original (intention-to-treat) medical patients. Ten-year QoL scores for each of the three groups did not differ significantly from the Australian norms for either the Physical Health Composite or the Mental Health Composite.

The substantial number of patients lost to follow-up, and the selection bias introduced by the high number of patients crossing over to bariatric surgery, hampers a meaningful interpretation of these 10-year QoL data. (GRADE 0 – Very low level of evidence)

Key points – impact on QoL (data from RCT)

- **RCT data on QoL after bariatric surgery suffer from a number of methodological limitations such as a low number of patients involved, a substantial number of patients lost to follow-up, statistical bias introduced by multiple testing, and absence of baseline data in one study.**
- **In 3 RCTs reporting 1-year data, the improvement of the generic QoL at 1 year is similar in the surgical and medical study groups. (Low level of evidence) In 1 out of 6 disease-specific measurements, a significant improvement is observed in the surgical group.**
- **In 2 RCTs reporting 2-year data, generic QoL scores are significantly better in the surgical group in 3 domains (Physical Role, General Health, Energy) in both RCTs. (Low level of evidence)**
- **In the most relevant and best documented RCT (the STAMPEDE trial) QoL improvements are noticed in 5 out of 8 domains at 3 years after surgery. The improvement at 5 years is observed in physical health components only (general health and bodily pain). (Low level of evidence)**
- **Reliable long term QoL data (beyond 5 years) from RCTs are lacking. (Very low level of evidence)**

4.2.4 *Impact of bariatric surgery on type 2 diabetes remission*

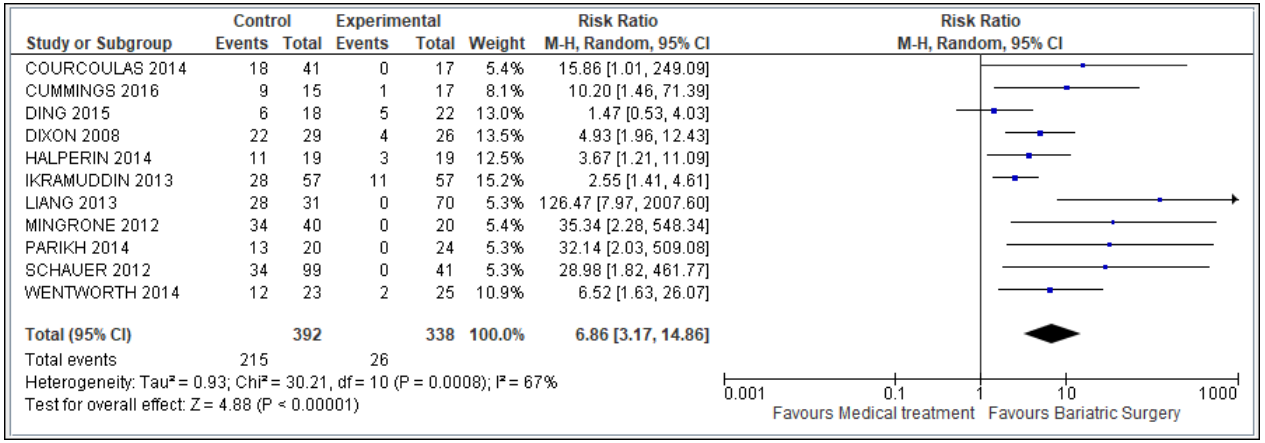
In 2009 the ADA (American Diabetes Association) defined complete remission of diabetes as a return to normal measures of glucose metabolism ($HbA1_C$ <6% and fasting glucose <100 mg/dL [5.6 mmol/L]) of at least 1 year's duration in the absence of medication. Partial remission indicates sub-diabetic hyperglycaemia ($HbA1_C$ value 6-6.5% and fasting glucose 100-125 mg/dL [5.6-6.9 mmol/L]) of at least 1 year's duration in the absence of medication.[99] In 2015 the ASMBS published standardized outcomes for reporting on the effects of MBS, including diabetes outcomes.[100] In some bariatric surgery studies remission is not clearly defined, in others diverging definitions are used, which reportedly may result in a twofold difference in observed remission rates.[101, 102]

An important note is that 'remission' does not equal definitive cure.

Patients that underwent bariatric surgery have higher rates of diabetes remission than medically treated patients. Pooled data from 3 RCTs with a follow-up of at least 3 years result in an odds ratio of 33.39 (95%CI 6.39-174.54).[87] Yan et al. performed a meta-analysis of 6 RCTs in which patients with T2DM underwent RYGB. Surgery was associated with a higher T2DM remission rate (OR: 76.37; 95%CI: 20.70-281.73).[102]

The diabetes remission rates reported in the RCTs are presented in Figure 13. This corresponds to follow-up periods ranging from 6 months[69] to 2 years[71, 75]. T2DM remission occurred in 215/392 (arithmetic mean: 55%) patients undergoing surgery and in 26/338 (arithmetic mean: 7.7%) in controls.

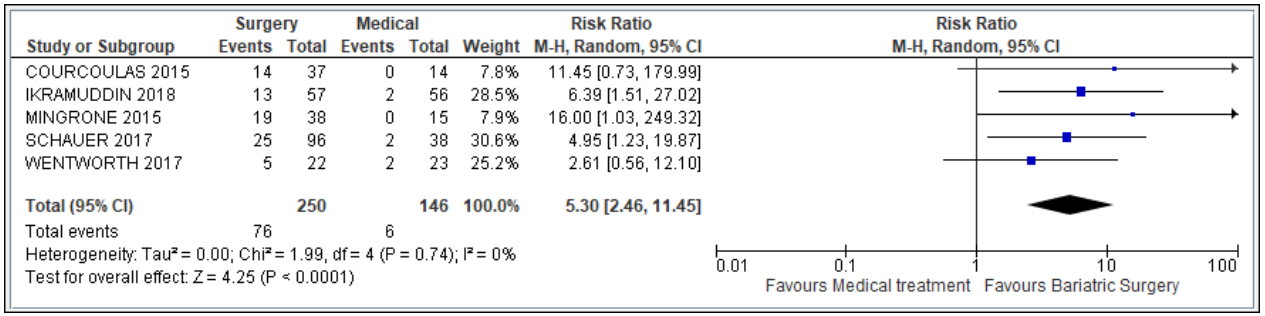
Figure 13 – Diabetes remission 0.5 to 2 years after surgery



Software source: RevMan 5.3. References: References: COURCOULAS_2014,[57] CUMMINGS_2016,[58] DING_2015,[59] DIXON_2008,[60] DIXON_2012,[61] HALPERIN_2014,[63] IKRAMUDDIN_2013,[64] LIANG_2013,[65] MINGRONE_2012,[66] PARIKH_2014,[69] SCHAUER_2012,[70] WENTWORTH_2014.[71]

After the completion of these RCTs, some of them reported longer time follow-up beyond the formal trial protocol. These data are displayed in Figure 14 and here T2DM remission rates were 76/250 (arithmetic mean: 30.4%) in operated patients versus 6/146 (arithmetic mean: 4.1%) in controls, indicating that after an initial remission (Figure 13) some of the patients relapsed.

Figure 14 – Diabetes remission 3 to 5 years after surgery



Software source: RevMan 5.3. References: COURCOULAS_2015,[73] IKRAMUDDIN_2018,[74] MINGRONE_2015,[75] SCHAUER_2017,[13] WENTWORTH_2017.[77]

Because of varying definitions of diabetes remission, data on the impact of surgery on HbA1c levels may be of interest. Cheng et al. meta-analysed HbA1c data and found a mean difference in surgically treated patients as compared with medically treated group of -1.43 (95%CI -1.56 to -1.31) at 1 year, -1.42 (95%CI -2.62 to -0.22) at 2 years and -1.27 (95%CI -1.77 to -0.77) at 3 years or more. In a meta-analysis of RCT data after RYGB, the pooled difference in serum HbA1c level was -1.25% (95%CI -1.88% to -0.63%).[102]

In RCTs that published 5-year results, 5 to 22.4% of operated patients had an HbA1c ≤6% without glucose-lowering drugs after RYGB,[13, 74, 75] 14.9% after sleeve gastrectomy,[13] and 37.0% after biliopancreatic diversion.[75]

Key points – impact on diabetes remission (data from RCT)

- **Within the first 1-2 years, T2DM remission is observed in 55% of patients undergoing surgery, versus in 8% of controls.**
- **Remission rates decrease over time, and half of the operated patients that experienced diabetes remission relapse within 5 years.**
- **An important note is that 'remission' does not equal definitive cure.**

4.2.5 *Impact of bariatric surgery on micro- and macrovascular complications of T2DM*

We did not find meta-analyses of RCT data related to micro- and macrovascular complications of T2DM. Five-year follow-up data from some RCTs have been published recently but the number of observed events is very low.

In Wentworth et al., of 51 participants enrolled in the study, 45 (22 randomised to receive RYGB and 23 to medical care) were followed up to 5 years. In the control group, one patient developed angina requiring a cardiac stent, another was hospitalised for stroke, and another underwent retinal photocoagulation. From the surgery group, one patient experienced proteinuria and a transitory renal failure.[77]

From the STAMPEDE trial, of the 150 patients initially enrolled in the study, 134 completed 5 years of follow-up.[13] A fatal myocardial infarction occurred in 1 of the medically treated patient versus none in those who underwent surgery. One stroke occurred in a patient from the sleeve gastrectomy group, versus none in the gastric bypass or medical group. Besides that, at 5 years, the average number of cardiovascular medications was reduced from baseline in all study groups, but more so in the surgically treated patients: it decreased from 2.74 to 2.16 in the medically treated group, from 2.78 to 1.37 in the gastric bypass group, and from 2.21 to 1.57 in the sleeve gastrectomy group.

In the DIBASY study, of the 20 patients enrolled in the trial, 5-year follow-up data were available from 15 patients of the control group and 19 of both the RYGB and the biliopancreatic diversion group.[75] A myocardial infarction occurred in one patient in the control group and in none of the other groups. Retinopathy was observed in one patient in the control group and in none of the others. Proteinuria was observed in 1 control patient and in 12 RYGB patients and in none of the biliopancreatic diversion group. Neuropathy was observed in 2 control patients and in none of the other groups. Besides that, over the course of the study, surgical patients used significantly fewer cardiovascular drugs (lipid-lowering or blood-pressure drugs) than medically treated patients.

There are no longer-term (beyond 5 years) RCT data on the effect of bariatric surgery on the occurrence of micro- or macrovascular diabetes complications. There are however some observational data on macrovascular outcome (showing improvement), as well as on microvascular outcome (showing improvement, however mainly relating to the diabetic population).

After the search strategy was performed, a meta-analysis (including RCT and observational data) that evaluated metabolic surgery versus medical treatment for microvascular complications in patients with type 2 diabetes mellitus was published. The overall effect for the RCT and observational data combined showed a significant reduction of microvascular complications, though the result was not significant for the pooled RCT data only.[103] Another systematic review and meta-analysis[43] evaluated among others the long-term effects of bariatric surgery on type 2 diabetes microvascular and macrovascular complications, which was based on one RCT and nine cohort trials. The RCT[75] included in this review is the DIBASY study already included above.

Key points – impact on microvascular and macrovascular complications (data from RCT)

- **In published RCTs, with a follow-up of no longer than 5 years, the number of observed micro- or macrovascular events is very low. These data do not allow to make firm conclusions on the impact of surgery on these outcomes.**
- **There are no longer-term (>5 years) RCT data on the effect of bariatric surgery on the occurrence of micro- or macrovascular diabetes complications.**

4.2.6 Impact of bariatric surgery on hypertension

Pooled mean difference in systolic blood pressure in surgically versus medically treated patients in RCTs was -3.72 mmHg (95%CI -5.81 to -2.19), -1.65 mmHg (95%CI -4.78 to 1.47), and -3.86 mmHg (95%CI -7.17 to -0.55) after 1, 2 and 3 years or more. Diastolic pressure differences were not statistically significant: -1.53 mmHg (95%CI -4.21 to 1.14), -1.10 mmHg (95%CI -4.70 to 2.50) and 1.75 mmHg (0.14 to 3.36) after 1, 2 and 3 years or more, respectively.[87]

In the DSS trial, the primary endpoint was a composite triple endpoint of HbA1c <7.0%, LDL cholesterol <100mg/dL, and a systolic blood pressure <130 mmHg. At 5 years follow-up 13 participants (23%) in the RYGB and 2 (4%) in the medical management group had achieved the composite triple end point (difference 19%; 95%CI 4%-34%). There were no significant differences in systolic blood pressure.[74]

In the STAMPEDE trial, no significant differences in blood pressure were observed among the three study groups. Besides that the number of cardiovascular medications used at 5 years, when compared with the medically treated patients (2.16 ± 1.33), was significantly lower in the RYGB group (1.37 ± 1.35) but not so in the SG group (1.57 ± 1.32).[13]

In Wentworth et al.'s trial, blood pressure did not differ significantly between the groups at 5 years.[77]

Very recently, the first results of the GATEWAY trial were published, an RCT that studied the impact of bariatric surgery in patients with obesity and arterial hypertension.[72] The primary end point was a reduction of ≥30% of the total number of antihypertensive medications while maintaining systolic and diastolic blood pressure <140 mm Hg and 90 mm Hg, respectively, at 12 months. This occurred in 41 of 49 patients from the gastric bypass group (83.7%) compared with 6 of 47 patients (12.8%) from the control group. Remission of hypertension, which was a post hoc defined secondary endpoint, was present in 25 of 49 (51%) and 22 of 48 (45.8%) patients randomised to gastric bypass considering office and 24-hour ambulatory blood pressure monitoring, respectively, whereas no patient submitted to medical therapy was free of antihypertensive drugs at 12 months. Definition of remission of hypertension was defined as having obtained a systolic and diastolic blood pressure <140 mm Hg and 90 mm Hg respectively (on office measurement or on 24h-ambulatory blood pressure monitoring), without anti-hypertensive medications at 12 months. Of note, at baseline the arterial hypertension appeared to be extremely well controlled, both in the medical (mean office blood pressure: 122.8/78.0 mmHg) and the surgical therapy group (123.0/77.6 mmHg).

Key points – impact on hypertension (data from RCT)

- **RCT evidence on the impact of bariatric surgery on hypertension is inconsistent. In one RCT, remission of hypertension is observed in half of the patients after surgery. In other trials, no clear impact on remission was demonstrated, although there was a decrease in the number of antihypertensive drugs needed.**

4.2.7 Impact of bariatric surgery on serum lipids

Cheng et al. report pooled mean difference of serum triglycerides, total cholesterol and HDL cholesterol.[87] Although initially triglycerides and total cholesterol decreased more after surgery than in the control groups, the difference was no longer statistically significant at 3 years follow-up. Pooled HDL levels remained higher in the surgical group at 3 years.

In the STAMPEDE trial, the primary end point was the proportion of patients with an HbA1c of 6.0% or less 12 months after treatment.[70] Secondary endpoints included lipid levels. The decrease from baseline in triglyceride levels and the increase from baseline in HDL cholesterol levels were significantly greater at 5 years after the surgical procedure than after intensive medical therapy. Besides that, the patients in the surgical groups had a significant reduction in the use of lipid-lowering agents.[13]

In the DIBASY trial, the primary end point was the rate of diabetes remission at 2 years and an HbA1c <6.5% in the absence of pharmacologic therapy.[66] Secondary endpoints included plasma levels of cholesterol, HDL cholesterol, and triglycerides. At 5 years, surgical procedures were

associated with significantly lower plasma lipids and lipid lowering drug use.[75]

In the DSS trial, secondary outcome measures included HDL cholesterol and triglycerides levels.[64] At 5 years, 13 participants (23%) in the gastric bypass group and 2 (4%) in the lifestyle-intensive medical management group had achieved the composite triple end point (difference, 19%; 95%CI, 4%-34%). At 5 years, there were statistically significant differences in LDL cholesterol, HDL cholesterol, and total cholesterol levels and triglycerides, favouring the gastric bypass group. Besides that, at baseline, gastric bypass and medical management participants required a mean number of medications of 4.1 and 4.3, respectively, to control glucose, lipid levels, and blood pressure. At 5 years, medications for the composite triple end point had been reduced to 2.0 in the gastric bypass group compared with an increase to 4.4 in the control group.[74]

Key point – impact on serum lipids (data from RCT)

- **Total cholesterol decreased more after surgery than in the control groups, the difference was no longer statistically significant at 3 years follow-up. Pooled HDL levels remained higher in the surgical group at 3 years.**
- **At 5 years, bariatric surgery is associated with significantly lower plasma lipids and lipid lowering drug use.**

4.2.8 *Impact of bariatric surgery on Obstructive Sleep Apnoea Syndrome*

Two RCTs compared the effect of bariatric surgery and medical treatment on Obstructive Sleep Apnoea Syndrome (OSAS).

Dixon et al. randomised 60 obese patients with recently diagnosed OSAS and with an apnoea-hypopnea index (AHI) of 20 events/hour or more to surgery (LAGB) or a conventional weight loss program.[61] At 2 years, bariatric surgery compared with conventional weight loss therapy did not result in a statistically greater reduction in AHI despite major differences in weight loss. Patients lost a mean of 5.1 kg (95%CI 0.8 to 9.3 kg) in the conventional weight loss program compared with 27.8 kg (95%CI 20.9 to 34.7 kg) in the bariatric surgery group. The AHI decreased by 14.0 events/hour (95%CI 3.3 to 24.6 events/hour) in the conventional weight loss group and by 25.5 events/hour (95%CI 14.2 to 36.7 events/hour) in the bariatric surgery group. The between-group difference was -11.5 events/hour (95%CI -28.3 to +5.3 events/hour). CPAP adherence did not differ between the groups.

Feigel-Guiller et al. randomised 63 obese patients with obstructive sleep apnoea (OSA) that were treated by non-invasive ventilation (NIV) to intensive nutritional care and LAGB. The primary endpoint was the rate of weaning from NIV at years 1 and 3. Data were also collected from patients 10 years after randomisation. The rate of weaning from NIV did not differ significantly between the LAGB and nutritional groups at year 1 (35 vs. 13%) or year 3 (14 vs. 21%). After 10 years, the weaning rate was low and similar between groups: 3 out of 22 (14%) patients in the nutritional group could be weaned versus 4 out of 21 (19%) in the LAGB group.

Key point – impact on OSAS (data from RCT)

- **Limited RCT data show a non-significant effect with regard to improvement or resolution of OSAS. The abovementioned RCTs are relatively small and evaluated the effect of LAGB, a technique which results in less weight loss than the RYGB and SG, and which nowadays has largely been abandoned. There are no good RCT data available that compare the non-surgical management of obesity vs. SG or vs. RYGB as to what concerns their effect on the improvement of OSAS.**

4.2.9 Discussion

Randomised trial evidence indicates that metabolic and bariatric surgery (MBS) leads to a substantial loss of weight in obese patients. In absolute terms, surgery induces a weight loss at 5 years between 18.6 and 37.0 kg, depending on pre-surgery weight. This corresponds to a relative weight loss between 22.7 and 28.4% and a loss of BMI ranging from 7.5 to 12.7 kg/m².Table 9 Observational studies suggest that this weight loss is maintained at 10 years.

Short-term (perioperative) mortality of metabolic and bariatric surgery is low: 0.04% to 0.38%.

Regarding the long-term (>5 year), there are no solid mortality data from RCTs comparing metabolic and bariatric surgery with non-surgical treatment of obesity. Individual observational studies suggest a long-term survival benefit after bariatric surgery. However, such studies are prone to bias (e.g. possible selection of healthier or more motivated patients) and do not allow to make firm conclusions. The evaluation of the effect of MBS on long-term mortality, is based on systemic review and meta-analyses of studies that are essentially of observational nature. They are complemented with some other data from recently published registry based cohort-studies. The data from these sources show in general a consistent effect with regard to long-term mortality risk. In general one observes relative reductions in overall mortality (reductions in premature death) that may vary between 30% and 45%. The observed effect is a net-effect on overall mortality risk. The underlying observations point at a decrease in cardiovascular disease related mortality and cancer-related deaths.

The best available QoL data shows an improvement 3 years after surgery in 5 out of 8 domains from the generic SF-36 QoL instrument. At 5 years, a statistically significant improvement is observed in 2 physical domain components only (Bodily Pain and General Health).

In patients with type 2 diabetes, at short-term, remission of diabetes is observed in 55% of cases. Many of these patients relapse to T2DM at some point after their initial remission and at 5 years, the remission proportion has halved. Although not in scope of this review, there are data that indicate that remission proportion can be influenced by several patient characteristics, like e.g. the diabetes duration at moment of surgery.[39] Whether bariatric surgery is associated with a long-term reduction in complications from diabetes when compared with modern-day diabetes therapy is unknown. [39]

The impact of surgery on serum lipids most often is a secondary study outcome. A pooled analysis of RCT data at 3 years showed a significant improvement (increase) in HDL cholesterol after surgery, but no statistically significant difference in serum triglycerides nor in total cholesterol. Follow-up data of RCTs that published 5-year results showed a significant improvement in all measured lipid parameters and a reduction in the use of lipid lowering drugs. The effect on arterial hypertension is inconsistent across trials but a reduction in the need of anti-hypertensive drugs has been demonstrated.

Limited RCT data show no statistically significant effect with regard to resolution of OSAS. Probably the trials are too small to show a statistically significant difference. Furthermore, the small number of RCTs evaluated the effect of LAGB, a technique which results in less weight loss than the RYGB and SG, and which nowadays has been largely abandoned. Data from these RCT are not conclusive regarding the improvement of OSAS. Improvements of OSAS have been described in observational data and is being observed in clinical practice (chapter 7), though in some patients OSAS does not improve or resolve. In this context, one needs to realize that here are no good RCT data available that compare the non-surgical management of obesity vs. SG or vs. RYGB regarding their effect on the improvement of OSAS. In conclusion, the impact of MBS on OSAS improvement seems to be less supported by strong evidence compared to for example the remission percentages observed for diabetes in obese type 2 diabetic patients who undergo MBS.

4.3 Clinical effectiveness of bariatric surgery in adolescents

4.3.1 Context

Given the limited success of behavioural and lifestyle modifications, there is increasing interest in performing MBS in adolescents with severe or morbid obesity, especially in those at very high risk or those with associated co-morbidities like hypertension, diabetes and non-alcoholic steatohepatitis (NASH), as well as in those with extreme BMI values, who cannot be managed successfully otherwise. A particular medical challenge constitute children and adolescents with monogenic traits causing morbid or super-obesity. Psychopathology and social problems are very prevalent in severely obese patients who are candidates for MBS, and prevalence is even higher in the population of severely or morbidly obese children and young adolescents. (Cf. personal communication and report based on preliminary data analysis from the medical centre taking care of obese children in Walony: Centre Médical Pédiatrique Clairs Vallons ASBL; link to report: http://www.clairsvallons.com/kce-obesity-final/).

Very often, severe and morbid obesity in young people may be interwoven both with individual and/or familial psychopathology. Severe obesity is a complex disease, with somatic and psychological aspects.

According to the strict definition of the WHO adolescent age goes from 10-19 years, while the WHO definition of young people starts at 10 and ends at 24 years of age. Others consider 'youth' which corresponds to the group of 15-24 years of age.[104, 105]

In a larger sense than only calendar age, adolescence comprises the transitional phase of growth and development between childhood and adulthood. It is a particular period with specific developmental features, characterized in particular by significant physical, psychological and relational changes. Therefore adolescence encompasses physical as well as psychosocial components of maturation.

The population of interest in the context of this HTA report essentially relates to adolescents that are in the age group between 14/15 years and 18 years of age. This is based on the following arguments:

- The general current expert considerations are that MBS should not be performed if adolescents are not post-pubertal and have not attained (or nearly attained) mature bone age. This consideration is reflected in many literature reports, recommendations or position statements, national health delivery services and HTA bodies. This contextual element essentially brings the lower age-range of interest to 14/15 years of age.
- The current Belgian reimbursement criteria for bariatric surgery apply as from the age of ≥18 years, so that strictly spoken the age group between 18-24 years is not the topic of interest here when discussing about a possible extension of reimbursement criteria.

The increasing amount of literature on the topic, and the observed (prudent) recommendations made by some professional associations or groups to consider MBS as a possible treatment option in the management of severe obesity in adolescents, can be explained by following factors:

1. Most literature on the subject and most observational data stem from the US, where severe adolescent obesity is more prevalent than in most European countries. Adolescents with a BMI >40 or even >50 kg/m^2 are not that rare in the US.
2. Observations show that severe childhood and adolescent obesity often further progress during adult life.
3. If diabetes mellitus type 2 occurs in obese adolescents, the condition might be more aggressive and more difficult or challenging to treat compared to the adult type 2 diabetic population.[106]
4. If Non-alcoholic Steato-Hepatitis (NASH) is present, which is the more aggressive and progressive form of Non-alcoholic Fatty Liver Disease (NAFLD), the disease course may be even more serious than in adults.[107]

4.3.2 Evidence review

4.3.2.1 Evidence from randomised controlled trials

The only RCT on bariatric surgery in adolescents was conducted in Australia and enrolled 50 adolescents between 14 and 18 years with a BMI higher than 35 kg/m².[68] They were assigned either to a supervised lifestyle intervention or to undergo laparoscopic adjustable gastric banding (LAGB), and followed up for 2 years. The primary endpoint of the study was weight loss. At entry, the mean age of the participants was 16.5 (±1.4) years in the LAGB group and 16.6 (±1.2) in the lifestyle group. Their respective weights were 120.7 (±25.3) and 115.4 (±14.0) kg, with a BMI of 42.3 (±6.1) and 40.4 (±3.1) kg/m² respectively. Two thirds of the participants were girls. Twenty-four of 25 patients in the LAGB group, and 18 of 25 in lifestyle group completed the study. At 2 years, the mean weight loss in the LAGB group was 34.6 kg (95% CI, 30.2-39.0) with a mean change of 12.7 BMI kg/m² (95% CI, 11.3-14.2). In the lifestyle group mean weight loss was 3.0 kg (95% CI, 2.1-8.1), with a mean change of 1.3 BMI kg/m² (95% CI, 0.4-2.9). Eight re-operations (33%) were required in 7 patients either for proximal pouch dilation or tubing injury.

Quality of life was a secondary endpoint in this trial. It was measured with the Child Health Questionnaire (CHQ CF-50) which has 11 validated sub-scores: General Behaviour, Family Activities, Family Cohesion, General Health, Mental Health, Physical Functioning, Self-Esteem, Change in Health, Behavioural Limitations, Emotional Limitations and Physical Limitations. The sub-scores for Behavioural, Emotional, and Physical Limitations did not differ from community values at entry into the study and were not different within or between groups over the 2-year follow-up period. At follow-up, the LAGB group showed improvements in Physical Functioning, General Health, Self-Esteem, Family Activities, and Change in Health. Both groups experienced significant improvement in General Health. The difference in score at 2 years between the LAGB and lifestyle groups was statistically significant only for Physical Functioning and Change in Health.

The GRADE level of evidence for the impact on QoL was very low (Appendix 4). For long-term mortality the level of evidence was considered very low as no direct evidence for adolescents was available.

4.3.2.2 Evidence from observational studies

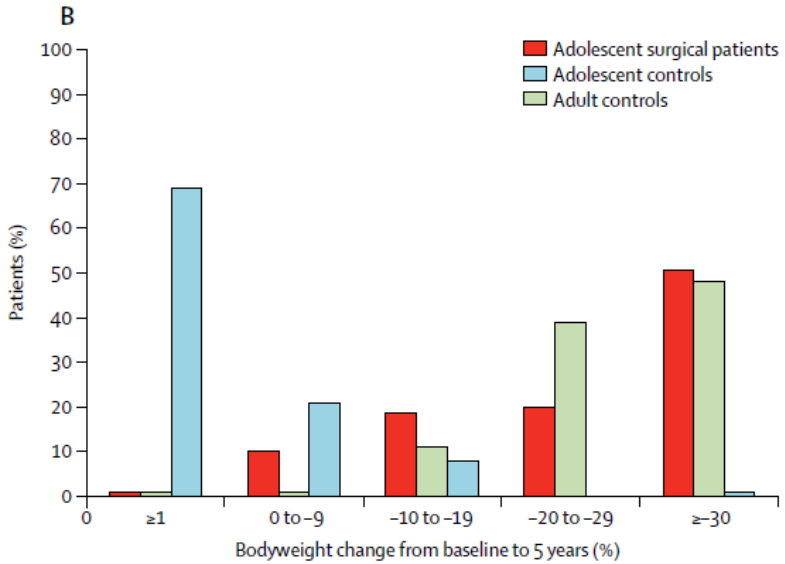
Three observational studies on bariatric surgery in adolescents have received particular attention in recent scientific literature: Teen-LABS,[84] AMOS[85] and FABS-5+[86]. Below, we summarise data originating from those studies since they represent the best presently available scientific evidence of modern bariatric surgery techniques in adolescents.

The Teen-LABS Consortium published a prospective observational study reporting on 228 severely obese adolescents (≤19 y) undergoing bariatric surgery (161 RYGB and 67 sleeve gastrectomy) at 5 US centres from 2007 to 2012.[84] The mean baseline age of the participants was 17±1.6 years (29% were 13-15y, 41% were 16-17y, 30% were 18-19y), and the mean BMI was 53 kg/m² (range: 34-88; BMI >40 in 98% of participants); 75% of the participants were female. At 3 years the mean weight had decreased by 27% (95%CI: 25 to 29) in the total cohort. Remission of type 2 diabetes occurred in 95% (95%CI: 85 to 100) of participants who had had the condition at baseline (n=32), remission of elevated blood pressure in 74% (95%CI: 64 to 84), and remission of dyslipidaemia in 66% (95%CI: 57 to 74). At 3 years, low ferritin was found in 57% (95%CI: 50 to 65) of the participants (66% after RYGB and 32% after SG). Thirteen percent (95%CI: 9 to 18) of participants had undergone one or more additional intra-abdominal procedures. One participant with known type 1 diabetes died 3.3 years after RYGB from complications of a hypoglycaemic event.

In the Adolescent Morbid Obesity Surgery (AMOS) study, 81 adolescents (aged 13 to 18 years; mean age 16.5 years) with severe obesity underwent RYGB (2006-2009) at three specialised paediatric obesity treatment centres in Sweden.[85] Their mean body weight was 132.8 kg (±22.1), and mean BMI 45.5 (±6.1) kg/m². Their change in body weight over 5 years was -36.8 kg (95%CI -40.9 to -32.8), resulting in a reduction in BMI of 13.1 (95%CI 14.5 to 11.8) kg/m². A weight loss less than 10% occurred in nine (11%). The BMI change was similar to that in adult matched (BMI, gender) control patients

(mean change -12.3 kg/m², 95% CI -13.7 to -10.9). A rapid weight reduction during the first year was followed by modest weight regain between 2 and 5 years. Adolescents were more likely than adults to have suboptimum weight loss, defined as a less than 30% decrease in bodyweight (Figure 15). Comorbidities and cardiovascular risk factors showed improvement over 5 years. Twenty (25%) patients underwent additional abdominal surgery for complications of surgery and 58 (72%) showed some type of nutritional deficiency, despite the prescription of nutritional supplements.

Figure 15 – Body weight change (kg) at 5 years in the AMOS cohort



Source: Olbers et al.[85]

The Follow-up of Adolescent Bariatric Surgery (FABS-5+) study reports the 5-12 years outcomes of a cohort of 74 young people aged 13-21 (mean 17.1) years who underwent RYGB at one centre in the US between 2001 and 2007.[86] Of these, 58 (78%) were included in the long-term analysis. At baseline, the mean BMI was 58.5 (±10.5) kg/m². In the first 12 months after gastric bypass, BMI decreased by mean 22.8 (±5.5) kg/m². At mean follow-up of 8.0 years (range 5.4-12.5), the mean BMI was 41.7 (±12.0) kg/m². At the long-term follow-up visit 21 (37%) participants had a BMI <35 kg/m². From baseline to long-term follow-up, significant declines were recorded in the prevalence of elevated blood pressure (27/57 [47%] vs 9/55 [16%]), dyslipidaemia (48/56 [86%] vs 21/55 [38%]), and type 2 diabetes (9/56 [16%] vs 1/55 [2%]). At follow-up, 25 (46%) of 58 patients had mild anaemia (i.e. not requiring intervention), 22 (45%) had hyperparathyroidism, and eight (16%) had low amounts of vitamin B12.

A Belgian study reports the outcomes of 28 adolescents that underwent a RYGB between 2003 and 2008.[108] All patients previously underwent medical, dietary and multimodal treatment in the De Haan Sea Preventorium, a health care facility that offers multidisciplinary care for children with a variety of clinical conditions (http://www.zeepreventorium.be/nl/home). Follow-up data were available for 19 (68%) patients, with a follow-up between 2.4 and 10.2 years (mean 7.2 years). The average BMI dropped from 38.9 kg/m² preoperatively to 27.5 kg/m² after 7 years. This was comparable to the BMI decrease observed in a matched adult patient group in which average BMI decreased from 39.4 to 27.1 kg/m² over the same time period.

4.3.3 *Discussion*

Based on data from one RCT, bariatric surgery in adolescents has a significant impact on weight loss and some QoL domains. This is in line with the findings from RCTs with adult patients. On the other hand, observational data from the AMOS cohort show a greater variability in long-term weight outcome in adolescents than in matched adults. According to the authors, this could indicate greater phenotypical heterogeneity and/or a greater need for postoperative support to optimise outcomes in adolescents.[85] Furthermore, complications such as vitamin deficiency and re-operation may be slightly higher than that seen in the adult cohort.[109, 110] Although rare, fatal complications have also been reported in adolescents.

These results have to be interpreted cautiously. Published data are derived from specialist adolescent centres and the results may not be reproducible if not performed by such teams.[110] Furthermore, almost all data on bariatric surgery in adolescents are derived from observational studies in patients with extreme obesity (mean BMI across studies varying from 45.5 to 58.5 kg/m²). Moreover, only short- to medium-term data are available in those patients who have a remaining life expectancy of 60 years and more. There is almost no literature on the outcomes of adults who underwent bariatric surgery as teens.[111]

Most studies are conducted in adolescents whose growth was near complete. It has not been excluded that vitamin and micronutrient deficiency may induce a growth retardation in younger patients.[109]

The fact that many children who are extremely obese often suffer from significant psychological problems including anxiety, depression, attention-deficit hyperactivity as well as emotional and eating disorders,[112] may interfere with their ability to deliberately make a therapeutic decision that has an important impact on their later life. In this contex, the benefit-risk balance needs to be made taking into account the level of the medical need, the risk of not intervening surgically and the risk associated with MBS.

Key points – Efficacy of bariatric surgery in adolescents

- **Only 1 RCT on bariatric surgery (LAGB) in adolescents has been conducted (mean BMI of about 42 kg/m² in the LAGB arm). Weight loss achieved by surgery was comparable to that documented in studies in adults. At 2 years, the mean weight loss in the LAGB group was 34.6 kg (95% CI: 30.2-39.0), with a mean BMI change of 12.7 (95% CI: 11.3-14.2) kg/m². The study showed an improvement in quality of life with a statistically significant difference at 2 years between the LAGB and lifestyle groups in scores related to Physical Functioning and Change in Health. (Very low level of evidence)**
- **No RCT data on other outcomes such as diabetes remission were identified.**
- **Next to the impact on mortality and QoL (see first bullet), observational data (from adolescent populations with a mean BMI between 39 and 59 kg/m²) show promising results related to type 2 diabetes and cardiovascular risk factors (e.g. blood pressure). On the other hand, additional abdominal surgery for complications and nutritional deficiencies, despite the prescription of nutritional supplements, are also noted.**
- **Robust long-term data on the effectiveness and safety of bariatric surgery in adolescents are lacking. (Very low level of evidence)**

4.4 Clinical effectiveness in patients with diabetes and a BMI<35

As mentioned earlier (chapter 4.2.1), the absolute weight loss reached after bariatric surgery depends on baseline weight, and the pooled weight loss in RCTs was 15.0 kg (16.7-13.3) in non-severely (BMI 30-35 kg/m²) obese individuals, and 26.2 kg (31.0-21.3) in severely obese (BMI>35 kg/m²) individuals.[87]

The primary focus in the present paragraph is on the impact of bariatric surgery on the outcome “diabetes remission” in patients who are not severely obese. The cut-off BMI value of 35 kg/m² corresponds with the upper limit of “class I obesity” (BMI 30 to <35 kg/m²) and it is also the BMI threshold currently required for T2DM patients to qualify for bariatric surgery reimbursement in Belgium.

4.4.1 Evidence base

We identified two SRs that compared diabetic outcomes of surgery versus medical therapy in non-severely obese patients with T2DM. In the most up-to-date SR the authors reviewed RCTs that enrolled patients with “mild obesity” and in which the intervention group underwent RYGB.[113] Studies were included in the meta-analysis if they enrolled patients with BMI a 30 to 40 kg/m². A second SR reviewed RCTs in non-severely obese patients, with

no restriction in the type of bariatric surgery.[114] It included in its meta-analysis studies in which each treatment group allowed enrolment of patients with BMI<35 kg/m² and in which the mean BMI of each treatment group was <40 kg/m². **Since in both SRs less than half of the patients had a BMI<35 kg/m², they cannot be used to assess the effect of bariatric surgery in patients with a BMI<35 kg/m²**.

In the absence of a valid SR, we investigated the impact of bariatric surgery on diabetes remission starting from primary studies. In Table 12, we list all RCTs (with their respective follow-up studies) comparing surgery with conventional treatment in T2DM, ranked according to the lowest BMI that was allowed for enrolment in the trial.

Table 12 – RCTs and follow-up reports in T2DM, ranked according to study target-BMI

#	First author_year	Target population, follow-up	BMI inclusion	Baseline BMI of study participants		
				Intervention-1	Intervention-2	Control
Studies that set a BMI upper limit for enrolment of ≤35 kg/m²						
1	PARIKH_2014	ANY SURGERY T2DM 6-mo data	30 - 35	32.8±1.7		32.4±1.8
2	WENTWORTH_2014	LAGB T2DM 2-year data	25 -30	LAGB 29±1		29±1
	WENTWORTH_2017	LAGB T2DM 5-year data				
Studies allowing enrolment of BMI<35, and in which mean BMI of participants at enrolment was <35 kg/m²						
3	IKRAMUDDIN_2013	RYGB in T2DM 1-year data	30 - 40	RYGB 34.4 ±3.2		34.9 ± 3.0
	IKRAMUDDIN_2015	RYGB in T2DM 2-year data				
	IKRAMUDDIN_2016	RYGB in T2DM 3-year data				
	IKRAMUDDIN_2018	RYGB in T2DM 5-year data				
4	LIANG_2013	RYGB T2DM + HT 1-year data	>28	RYGB 30.5±1.0		30.3 ± 2.0
Studies allowing enrolment of BMI<35, but in which mean BMI of participants at enrolment was >35 kg/m²						
5	COURCOULAS_2014	LAGB RYGB T2DM 1-year data	30 - 40	RYGB 35.5±2.6	LAGB 35.5±3.4	35.7±3.3
	COURCOULAS_2015	LAGB RYGB T2DM 3-year data				
6	CUMMINGS_2016	RYGB in T2DM 1-year data	30 - 45	RYGB 38.3 ±3.7		37.1 ± 3.5
7	DING_2015	LAGB T2DM 1-year data	30 - 45	LAGB 36.4±3.0		36.7±4.2
8	DIXON_2008	LAGB T2DM 2-year data	30 - 40	LAGB 37.0±2.7		37.2±2.5
9	HALPERIN_2014	RYGB in T2DM 1-year data	30 - 42	RYGB 36.0±3.5		36.5±3.4
10	SCHAUER_2012	RYGB or SG T2DM 1-year data	27 - 43	RYGB 37.0±3.3	SLEEVE 36.2±3.9	36.8±3.0
	SCHAUER_2014	RYGB or SG T2DM 3-year data				
	SCHAUER_2017	RYGB or SG T2DM 5-year data				
Study that set a BMI lower limit of enrolment >35 kg/m²						
11	MINGRONE_2012	RYGB or BPD T2DM	>35	RYGB 44.9±5.2	BPD 45.1±7.9	45.6

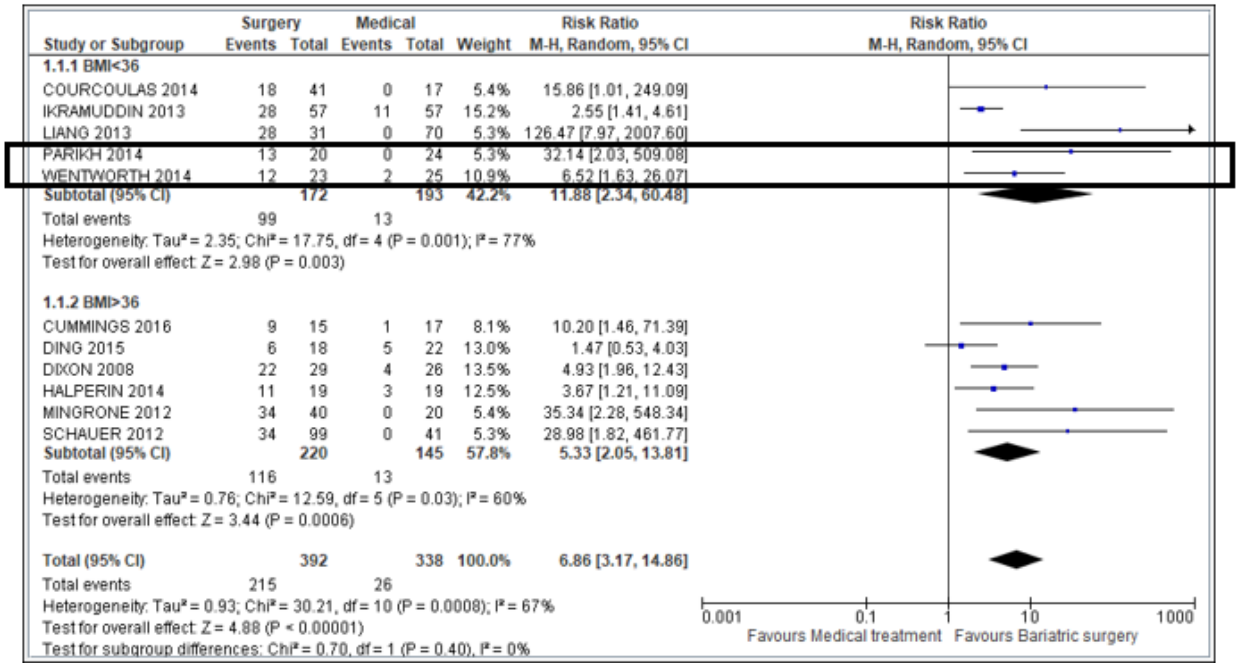
RYGB: Roux-en-Y-Gastric Bypass; LAGB: laparoscopic gastric banding; SLEEVE: sleeve gastrectomy. References: COURCOULAS_2014,[57] CUMMINGS_2016,[58] DING_2015,[59] DIXON_2008,[60] HALPERIN_2014,[63] IKRAMUDDIN_2013,[64] LIANG_2013,[65] MINGRONE_2012,[66] PARIKH_2014,[69] SCHAUER_2012,[70] WENTWORTH_2014.[71] COURCOULAS_2015,[73] WENTWORTH_2017),[77] IKRAMUDDIN_2018),[74] MINGRONE_2015),[75] SCHAUER_2017.[13]

Only two RCTs (#1 and #2 in Table 12)[69, 71] set a BMI upper limit of 35 kg/m² for patient enrolment. Parikh et al. randomised 57 patients with T2DM and a BMI of 30 to 35 kg/m² to medical weight management or surgery (RYGB, SG, or LAGB, based on patient preference). The primary outcomes assessed at 6 months were a change in a calculated parameter of insulin resistance, and diabetes remission. Mean BMI was 32.4 kg/m² in the medical group and 32.8 kg/m² in the surgical group. The surgery group had improved insulin resistance and higher diabetes remission rates (65% vs. 0%; P<0.0001)).[69] Wentworth et al. randomised patients aged 18-65 years with T2DM and a BMI of 25 to 30 kg/m² to LAGB or multidisciplinary diabetes care alone. The primary outcome was diabetes remission 2 years after randomisation. Mean BMI was 29 kg/m². Of patients that underwent LAGB, 12 (52%) achieved diabetes remission versus two (8%) in the medical care group (P=0.0012). At 5 years, diabetes remission was observed in five (23%) LAGB patients and in two (9%) medically treated participants (P=0.2427, NS).[71, 77]

In two other RCTs (#3 and #4 in Table 12),[64, 65] the upper limit for inclusion was above 35 kg/m², but the mean BMI of study participants was below 35 kg/m², whereas in a third trial (#5 in Table 12)[57] it was slightly above (35.5 kg/m²) this threshold. In order to broaden our perspective, we decided to pool the data from studies in which the mean BMI of study participants was <36 kg/m² to compare them with pooled data from studies where the mean BMI was above 36 kg/m². The resulting forest plot of diabetes remission by BMI is shown in Figure 16 and Figure 17.

Short-term follow-up data (Figure 16) show a remission in 99/172 patients (arithmetic mean 57.6%) after bariatric surgery in trials were pre-operative mean BMI was below 36 kg/m², versus 116/220 (arithmetic mean 52.7%) when mean BMI was above 36 kg/m².

Figure 16 – Diabetes remission by mean BMI after 0.5 to 2 years follow-up

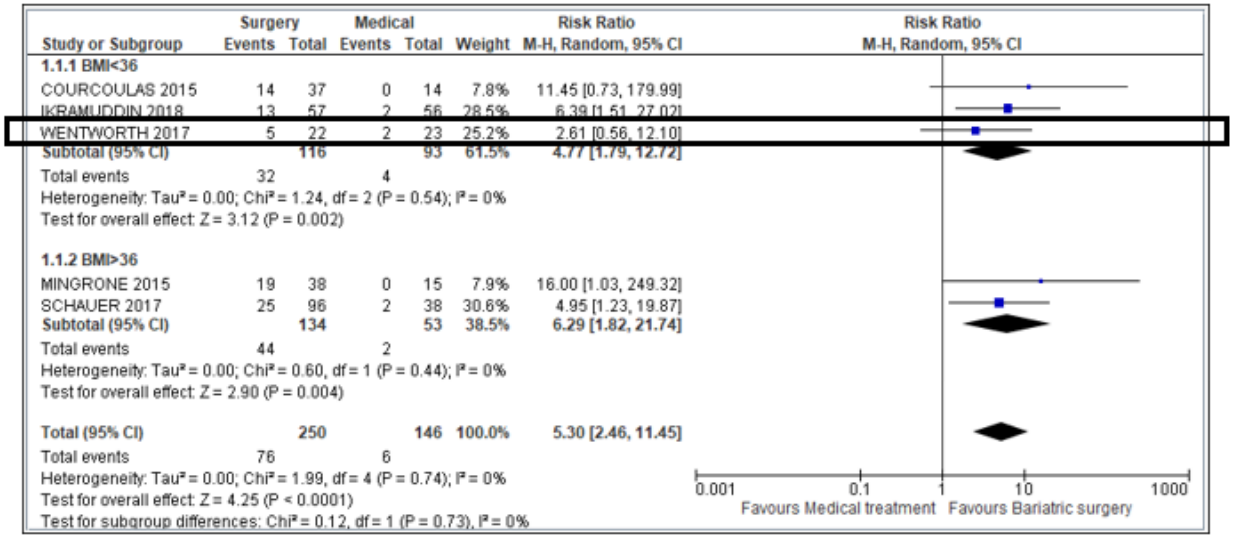


Software source: RevMan 5.3. BMI<36: studies in which the mean BMI of study participants was <36 kg/m²; BMI>36: studies where the mean BMI was >36 kg/m². References: COURCOULAS_2014,[57] CUMMINGS_2016,[58] DING_2015,[59] DIXON_2008,[60] HALPERIN_2014,[63] IKRAMUDDIN_2013,[64] LIANG_2013,[65] MINGRONE_2012,[66] PARIKH_2014,[69] SCHAUER_2012,[70] WENTWORTH_2014.[71] PARIKH_2014[69] and WENTWORTH_2014[71] (framed) are the only studies that strictly limited enrolment to patients with a BMI <35 kg/m².

Overall; the level of evidence according to GRADE for diabetes remission after 0.5-2 years in this patient group was considered to be moderate (Appendix 4). The level of evidence was downgraded with one level due to indirectness.

Looking at the longest term data available (Figure 17), it appears that many of the patients with an initial remission, relapse at some point, resulting in a remission proportion of 27.6% (32/116) in studies where the mean BMI was below 36 kg/m², versus 32.8% (44/134) when the mean BMI was above 36 kg/m² after 3 to 5 years.

Figure 17 – Diabetes remission by mean BMI after 3 to 5 years follow-up



Software source: RevMan 5.3. BMI<36: studies in which the mean BMI of study participants was <36 kg/m²; BMI>36: studies where the mean BMI was >36 kg/m². WENTWORTH_2017[77] (framed) was the only study that strictly limited enrolment to patients with a BMI <35 kg/m². References: COURCOULAS_2015,[73] WENTWORTH_2017),[77] IKRAMUDDIN_2018),[74] MINGRONE_2015),[75] SCHAUER_2017.[13]

One study in patients with diabetes and BMI between 25 and 30kg/m2 reported QoL results after 5 years.[77] Of 51 participants who enrolled in the study, 45 were followed to 5 years (22 randomised to LAGB and 23 to medical care). At enrolment, their BMI ranged between 25 and 30 kg/m², with a mean of 29 kg/m². QoL and health utility remained relatively constant in medically treated participants but improved in the LAGB group. At 5 years, composite scores of physical and mental health in the LAGB group had increased to above the general Australian population mean (50±10) to 53±8 and 54±10 respectively. This corresponded to a mean difference in health utility after 5 years of 0.10 (0.02–0.18) favouring LAGB participants.

The GRADE level of evidence for the impact on QoL was low (Appendix 4).

Data on long term survival after bariatric surgery in this patient group were not available in the RCTs.

4.4.2 Discussion

RCT evidence on diabetes remission in patients with a BMI below 35 kg/m² is relatively scarce. Data from trials that predominantly enrolled non-severely obese patients suggest that with up to 2 years of follow-up 50 to 60% of patients show diabetes remission. This proportion diminishes to around 30% three to five years after surgery, with no obvious relationship with baseline BMI.

Additional trials studying the impact of surgery on T2DM in patients with a BMI<35 kg/m² are ongoing. A multicentre trial (DiaSurg2 trial, Identification: DRKS00004550 study on www.drks.de) has been initiated to compare RYGB with medical treatment in 400 non-severely obese patients with insulin-dependent T2DM followed over 8 years.[115] Patient enrolment started in March 2013. No interim results have been published yet (e-mail communication with authors on 13/4/2018). Another RCT (ESINODOP, ClinicalTrials.gov Identifier: NCT02488733) has been initiated in 2015 and compares sleeve gastrectomy with conventional medical therapy in patients with newly diagnosed T2DM and a BMI between 30 and 42 kg/m². Randomisation will be stratified according to patient BMI above or below 35 kg/m².[116] The estimated study completion date is September 2024.

Key point – Efficacy of bariatric surgery in patients with diabetes mellitus and a BMI <35 kg/m²

- **In the identified SRs that included non-severly obese patients with T2DM, less than half of the patients had a BMI <35 kg/m². The results of these SRs cannot be used to assess the effect of bariatric surgery in patients with a BMI <35 kg/m².**
- **RCT evidence on diabetes remission in T2DM patients with a BMI <35 kg/m² suggests that T2DM remission rates are similar to that observed in T2DM patients with a BMI >35 kg/m². (Moderate level of evidence)**
- **Bariatric surgery may improve quality of life in diabetic patients with BMI between 30 and 35kg/m². (Low level of evidence)**
- **Direct evidence on long term survival specifically for diabetic patients with BMI between 30 and 35kg/m² are not available.**
- **There are two ongoing RCTs studying the impact of bariatric surgery on T2DM patients with a BMI <35 kg/m².**

4.5 Comparative effectiveness of different surgical techniques

As discussed earlier, we retrieved 10 SRs that compared different surgical techniques (RYGB, LAGB and sleeve gastrectomy) (Table 13). After full text evaluation one of the SRs was excluded because it only considers studies that enrol patients with a BMI of at least 35, thus excluding a significant number of relevant RCTs.[46] We excluded six other SRs since the RCTs they considered were also included in more recent SRs, or reported only short-term outcome data (details provided in Table 13).[45, 48-52] Eventually we were left with 3 recent SRs.[44, 47, 53] From these SRs, we focus in the following paragraphs on the analyses extracted from RCTs.

Table 13 – Systematic reviews of RCTs that compare bariatric surgery techniques

SRs				RCTs																							
First author_year of publication		Comparison	Outcomes	RYGB vs SLEEVE															LAGB				OAGB		
	SR footnotes			KEHAGIAS_2011_ 3 yrs.	ZHANG_2014_5 yrs.	YANG_2015_3 yrs.	TANG_2016_2 yrs.	IGNAT_2017 _5 yrs.	PETERLI_2017_3 yrs.	SCHAUER_2017 _5 yrs.	HELMIO_2014_6 mo	DE BARROS_2015_ 3 mo.	KEIDAR_2013_1 yr.	KARAMANAKOS_2008_1 yr.	PALUSKIEWICZ_2012_1 yr.	VIX_2014_1 yr.	WOELNERHANSSEN_2011_1 yr.	NGUYEN_2009 RYGB vs LAGB_4 yrs.	ANGRISANI_2007 RYGB vs LAGB_5 yrs.	RAMON_2012 RYGB vs LAGB_1 yr.	HIMPENS_2006_LAGB vs SLEEVE_3 yrs.	LEE_2014_SLEEVE vs OAGB_5 yrs.	LEE_2005_RYGB vs OAGB_2 yrs.	SEETHARAMAIAH_2016 SLEEVE vs OAGB_1 yr.
RCT footnotes						6	6		7		8				9			10	11				12	13
ETTLESON_2017	1	RYGB vs SLEEVE	≥2 yrs. data; weight, T2DM, co-morbidities, QoL;	✔	✔	✔	✔	✔	✔	✔														
OSLAND_COMORBID_2017		RYGB vs SLEEVE	co-morbidities;	✔	✔	✔			✔		✔	✔												
OSLAND_DIABETES_2017		RYGB vs SLEEVE	T2DM;	✔	✔	✔			✔		✔	✔	✔											
OSLAND_WEIGHT_2017		RYGB vs SLEEVE	weight;	✔	✔	✔			✔		✔	✔	✔	✔		✔								
GOLZARAND_2017	2	RYGB vs SLEEVE vs LAGB	≥5 yrs data; weight;																✔					
KANG_2017	3	RYGB vs SLEEVE vs LAGB	weight;	✔	✔				✔				✔	✔	✔	✔		✔	✔	✔	✔			
SHOAR_2017		RYGB vs SLEEVE	weight; co-morbidities;	✔	✔	✔								✔	✔	✔				✔				
LI_2016	4	RYGB vs SLEEVE	weight; co-morbidities;	✔	✔				✔		✔		✔			✔	✔							
WANG_2017		OAGB vs SLEEVE	weight; co-morbidities;																			✔		✔
COCHRANE REVIEW 2014	5								✔	✔			✔	✔	✔	✔		✔	✔		✔	✔		

References: see text. Footnotes: 1. includes only studies with at least 2 years follow-up, misses SALMINEN_2018; 2. only long-term (>5 years) studies; includes only 1 RCT which is also included in KANG_2017; 3. network meta-analysis; includes more studies than SHOAR_2017, except for YANG_2015 that also recruited patients with BMI<30; 4. outdated: literature search until May 2015; 5. added for comparison (data in Cochrane review are limited to those extracted from the primary RCT publication, with no longer-term follow-up data being available); 6. includes BMI 28-35 and therefore excluded from some SRs; 7. a 5-years update of this SM-BOSS trial was published in 2018; 8. 6-months results of SLEEVEPASS trial; 5-yr results published in 2018 by Salminen et al. which is not represented in any of the other SRs; 9. laparoscopic sleeve vs. open RYGB; 10. 10-yr follow-up data published in 2017; 11. RYGB vs LAGB 5 years follow-up; in 2013 a 10-year follow-up was published which is not represented in any of the other SRs; 12. not represented in any of the SRs; identified through DELUCA_2018; 13. focus on adipokines and metabolic effects.

4.5.1 RYGB versus sleeve gastrectomy

Ettleson et al. provide data on the effect of RYGB compared with sleeve gastrectomy.[47] It included 7 RCTs that reported ≥2-year outcome data.[13, 117-122] This SR misses the most recent data from the SLEEVEPASS trial[123] as well as a recent update of the SM-BOSS trial,[124] both published in 2018 A summary of findings of these RCTs is depicted in Table 14. No additional relevant RCTs were identified by Kang et al.[44]

Table 14 – Outcome differences after RYGB vs. sleeve gastrectomy

	Total number of patients	Difference in weight parameter	Parameter	Statistical significance	Number of diabetics	Difference in % DM remission**	Statistical significance
Studies with weight loss as primary outcome							
KEHAGIAS_2011	60	-6.4	%EWL	NS (p=0.13)	10	0	-
ZHANG_2014*	64	+13.0	%EWL	S (p=0.02)	17	-1.4	-
IGNAT_2017 *	100	+9.7	%EWL	S (p=0.02)	-	-	-
PETERLI_2018*	217	+7.2	%EBMIL	NS (p=0.22)	54	+6.4	NS (p=0.77)
SALMINEN_2018*	240	+8.2	%EWL	-	101	+8	NS (p>0.99)
Studies with diabetes remission as primary endpoint							
YANG_2015	64	+10.4	%EWL	S (p=0.003)	64	+6.6	NS
TANG_2016	80	-0.3	ΔTWBL	NS	80	-13.2	NS
SCHAUER_2017 *	150	+4.6	ΔTWBL	S (p=0.01)	150	+5.2	NS (p=0.53)

*Source: Adapted and updated from Ettleson et al.[47] Postive numbers indicate greater effect with RYGB. %EWL: percent excess weight loss. %EBMIL: percent excess BMI loss. ΔTWBL: change in total weight from baseline. * RCTs that report 5-years follow-up results. **Definitions vary across studies. References: KEHAGIAS_2011,[118] ZHANG_2014,[122] IGNAT_2017,[117] PETERLI_2018,[124] SALMINEN_2018,[123] YANG_2015,[121] TANG_2016,[120] SCHAUER_2017.[13]*

Four out of eight RCTs found a significantly greater weight loss with RYGB compared to sleeve gastrectomy. Across the 3 largest RCTs, at 5 years follow-up, one found no significant difference in excess BMI loss,[124] in another study the confidence interval for the difference extended both above and below the pre-specified equivalence margin,[123] and in one study a statistically significant greater loss in body weight was found after RYGB compared to SG.[13] None of the RCTs found a significant difference in diabetes remission or QoL scores between the two surgery types.

Osland et al. specifically analysed changes in non-diabetic comorbid disease following RYGB and sleeve gastrectomy and found comparable results in improving or resolving them.[50] The impact of both procedures on gastro-oesophageal reflux disease (GORD) was studied in two RCTs.[118, 119] Kehagias et al. reported 100 % resolution of GORD in all patients having undergone either procedure at 3 years postoperatively.[118] Peterli et al. observed more frequently remission after RYGB (60.4%) than after SG (25.0%). Gastric reflux worsened more often after sleeve gastrectomy (31.8%) than after RYGB (6.3%).[124]

Differences in late adverse effects between the two surgery types are reported in detail in two recent RCTs (Table 15). There was no statistically significant difference in overall reoperation/reintervention rates across the two procedures in both trials, but the reason for reoperation was different. Sleeve gastrectomy was associated with a 5-year risk of reoperation for gastroesophageal reflux of 5.8%[123] and 8.9%[124] versus nil for RYGB. RYGB was associated with a reoperation risk for internal hernia of 14.3%[123] and 8.7%[124] respectively. There was no treatment related mortality during the 5-year follow-up in the SLEEVEPASS trial and one 1 early treatment related mortality in SM-BOSS.

Table 15 – Major early and late (5 yrs.) adverse events after sleeve gastrectomy and RYGB

Table 5. Complications Reported for Laparoscopic Sleeve Gastrectomy and Laparoscopic Roux-en-Y Gastric Bypass

Complication Category and Type	Sleeve Gastrectomy (n = 121)	Gastric Bypass (n = 119)
Major Early (<30 d) Complications, No. (%)		
Bleeding	3 (2.5)	7 (6.0)
Intra-abdominal infection/infection of unknown origin	1 (0.8)	3 (2.6)
Pneumonia	1 (0.8)	
Bowel perforation	1 (0.8)	
Torsion of the enteroanastomosis		1 (0.9)
Outlet obstruction	1 (0.8)	
Total	7 (5.8)	11 (9.4)
Major Late (>30 d) Complications, No. (%)		
Gastroesophageal reflux	7(5.8)	
Internal herniation		17 (14.3)
Incisional hernia	3 (2.5)	1 (0.8)
Total	10 (8.3)	18 (15.1)

Table 5. Mortality and Adverse Events Requiring Reoperation or Endoscopic Int

Events	No. With Event/Total No. (%) Sleeve Gastrectomy	Roux-en-Y Gastric Bypass
Early morbidity (0-30 d)	1/107 (0.9)	5/110 (4.5)
Leak	0	1
Infection	0	3
Obstruction	1	1
Death	0	1[b]
Late morbidity (1 mo-5 y)	15/101 (14.9)	18/104 (17.3)
Operative		
Conversion to Roux-en-Y gastric bypass due to gastroesophageal reflux	9	NA
Small bowel obstruction	0	2
Internal hernia	0	9
Incisional hernia	1	1
Gastroscopy necessary: laparoscopy	NA	1
Severe dumping	0	3[c]
Insufficient weight loss	5[d]	2
Death	0	1[e]
Total reoperations or interventions	16/101 (15.8)	23/104 (22.1)
Total mortality	0	2/104 (1.9)

Left column data extracted from the SLEEVEPASS trial.[123] The late major complications in both study groups in the SLEEVEPASS trial were all reoperations. The observed differences in major early and major late complications were not statistically significant (difference in major early complications: p=0.29; major late: p=0.10). There was no treatment related mortality during the 5-year follow-up in this study. Right column data extracted from the SM-BOSS trial.[124] Reported events where those requiring reoperation or endoscopic intervention. The observed differences in early and late morbidity and in total reoperations or interventions were not statistically significant. Footnotes: b: surgical complication (leakage). c: 2 pouch revisions and 1 bypass reversal. d: 3 laparoscopic biliopancreatic diversions (duodenal switch) and 2 conversions to RYGB; e: lymphoma.

Wang et al. published a SR in which they compared sleeve gastrectomy with one-anastomosis gastric bypass (OAGB).[53] Their study includes the results of two RCTs[125, 126] and 12 cohort studies. The authors conclude that the available data indicate that one-anastomosis gastric bypass is a simpler, safer, and more effective bariatric procedure than sleeve gastrectomy, but that their findings may be unreliable because of bias in the data, small sample size and short follow-up time.

A more comprehensive SR[28] on OAGB that was published after we completed our literature search, analysed the results from 4 RCTs[125-128] and 48 cohort studies. It concluded that OAGB provides effective weight loss that is durable to 5 years. Early and late complication rates were considered as acceptable. Reconversion of OAGB to RYGB because of intractable bile reflux has been reported.[125] Some authors have raised concerns about reflux of bile acids into the stomach, which might lead to gastritis and cancer.[128] An evaluation of OAGB was considered out of scope of this HTA report. Further research on the efficacy and safety of new techniques is needed before they are widely used.

4.5.2 Laparoscopic gastric banding versus other techniques

Kang et al.[44] identified 2 RCTs that compared RYGB with LAGB[129, 130] and one that compared LAGB with sleeve gastrectomy.[131] Ten-year follow-up data of the RYGB vs. LAGB trials have been published, but these updates were not considered in the SR by Kang et al.

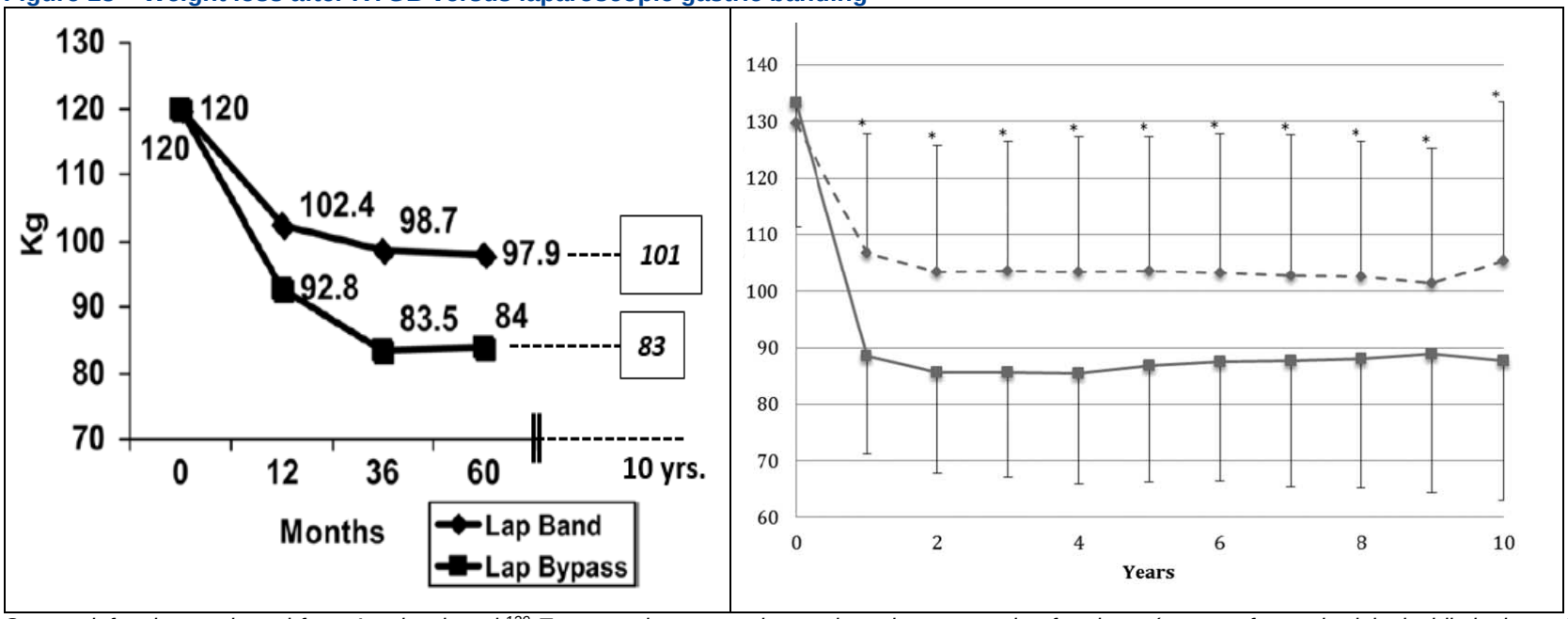
4.5.2.1 *Laparoscopic gastric banding versus RYGB*

Angrisani et al. randomised 51 patients to laparoscopic RYGB or laparoscopic adjustable gastric banding.[129, 132] This RCT has a number of methodological weaknesses: the low number of patients in each study group (27 and 24 resp.), the randomisation procedure was unclear, it is not stated whether concealment of allocation was guaranteed, there was no blinding of the outcome assessors, and there was no intention-to-treat analysis. All patients were recruited in the year 2000. The authors had only limited experience with laparoscopic RYGB surgery. At 5 years, 1 LAGB was lost to follow-up.

At 5 years, the RYGB patients had a lower weight and BMI than the LAGB patients (Figure 18) with a roughly estimated weight loss of 20 kg in the LAGB and 35 kg in the RYGB groups respectively. The available (inadequate) data suggest that body weight remains similar from 5 to 10 years follow-up.

Early postoperative complications occurred in 2 (8.3%) patients (pouch leak, jejunal perforation) after RYGB and in none of the gastric banding patients. 10-years data are uncertain since 5/27 LAGB and 3/24 RYGB patients were lost to follow-up, and information on weight loss was only available through telephone contact in almost half of the patients. Late complications were reported at 10 years in 2 RYGB patients (internal hernia at 15 months; incisional hernia at 115 months) and in 10 LAGB patients (5 band removals with no further bariatric surgery; 4 band removals and conversion to other surgery; 1 port replacement.

Figure 18 – Weight loss after RYGB versus laparoscopic gastric banding



Source: left column adapted from Angrisani et al.[129] Ten-year data are estimates based on a sample of patients (see text for methodological limitations of these data). Right column extracted from Nguyen et al. (intention-to-treat analysis); upper curve represents LAGB and lower curve RYGB patients.[133]

Nguyen et al. randomised 197 patients from 2002 and 2007.[130, 133] This RCT is of better quality than the previous since it enrolled more patients and followed a stricter randomisation methodology with data analysis on an intention to treat basis. Of the patients with 4 years data, follow-up was available for 83.1% of the RYGB and 93.3% of the LAGB patients. Again, 10-year data are less solid because of loss to follow-up of half of the patients. The definition of "late complication" has also changed from the 2009 publication (>30 days) compared to the 2017 version (>90 days).

At 10-year follow-up, the mean total body weight loss for the gastric bypass group was 42.4±19.6 kg for gastric bypass versus 27.4±14.5 kg for the gastric banding group. Major early complications occurred in 7 (6.3%) patients in the gastric bypass group. Two patients developed postoperative gastrointestinal haemorrhage. Five patients developed early postoperative bowel obstruction. Two major complications (2.3%) occurred in the gastric banding group. One patient developed postoperative obstruction requiring replacement of the band, and 1 patient had temporary renal failure.

The occurrence of individual late complications is not consistently reported across the two follow-up publications of this study. At 10-year follow-up, late reoperation (>90 days) was more prevalent in the LAGB group (31.4%) than in the RYGB group (8.1%). Long term band erosion/slippage/obstruction was reported in 17 cases (out of the original 86 patients, with an unknown number of patients with adequate long-term data available).

4.5.2.2 *Laparoscopic gastric banding versus sleeve gastrectomy*

In one RCT 80 patients (all recruited in 2002) were randomised to LAGB or SG.[131] Median weight loss after 3 years was 17.0 kg for LAGB and 29.5 kg for sleeve gastrectomy. Median decrease in BMI for LAGB was 18.0 and for SG was 27.5. Early postoperative complications occurred in 2 patients after SG (peritonitis, sleeve ischaemia) and in none after LAGB. Late complications requiring surgery occurred in 7 patients after LAGB (pouch dilation, gastric erosion, port disconnection) and in none after SG.

4.5.3 *Conclusion*

A substantial and durable weight loss has been documented for RYGB, LAGB and SG. In a systematic review and network meta-analysis of RCTs that compared 2 bariatric procedures, the differences in mean BMI reduction were -0.76 kg/m² (95%CI: -3.1 to 1.6) for RYGB versus SG, -5.8 kg/m² (95% CI: -9.2 to -2.4) for RYGB versus LAGB, and -5.0 kg/m² (95%CI: -9.0 to -1.0) for SG versus LAGB. The mean differences in percentage excess weight-loss between RYGB and SG, RYGB and LAGB, and SG and LAGB were 3.8% (95%CI: -8.5% to 13.8%), -22.2% (95%CI: -34.7% to -6.5%), and -26.0% (95%CI: -40.6% to -6.4%), respectively.[44]

There is no significant difference in overall reoperation (or endoscopic intervention) rates after RYGB versus SG, but the reason for reoperation was different. SG was associated with a 5-year risk of reoperation for gastro-oesophageal reflux of 6 to 9%, while RYGB was associated with a reoperation risk for internal hernia of 9 to 14%.

While LAGB was worldwide the most frequently performed procedure in 2008, it is almost abandoned nowadays because of the need for band removal for pouch dilation, gastric erosion, or port disconnection.[134] In a recent economic study, the authors reviewed data from 25 042 Medicare beneficiaries who underwent gastric band placement between 2006 and 2013, looking for gastric band-related reoperations, including device removal, device replacement, or revision to a different bariatric procedure.[135] After an average of 4.5-year follow-up, 4636 patients (18.5%) underwent 17 539 reoperations (an average of 3.8 procedures/patient). From 2006 to 2013, the proportion of payments from Medicare for reoperations increased from 16.4% to 77.3% of their annual spending on the gastric band device. Similar data were published from Belgium and France. In a Belgian single-centre series, of 151 patients operated between 1994 and 1997, nearly 50% required removal of their bands.[80, 136] Of all adults that underwent LAGB in France between 2007 and 2013, removal rate was 6% per year.[23]

Key points

- **Substantial weight loss has been documented for RYGB and SG. Four out of eight RCTs found a significantly greater weight loss with RYGB compared to SG. On the other hand, in the three largest RCTs, no significant difference in excess BMI loss was found at 5 years follow-up. In general one could conclude that efficacy in terms of weight loss is more or less similar between RYGB and SG, with possibly a slight advantage in favour of the RYGB.**
- **There is no significant difference between the two surgeries in terms of impact on QoL and T2DM remission.**
- **Based on the results of two RCTs, there was no statistically significant difference in overall reoperation/reintervention rates between RYGB or SG. However, the reason for reoperation was different. Sleeve gastrectomy is associated with a 5-year risk of reoperation for gastro-oesophageal reflux of 6 to 9%, while RYGB is associated with a reoperation risk for internal hernia of 9 to 14%.**
- **Gastric banding is almost abandoned as a bariatric procedure because of the need for band removal (e.g. for pouch dilation, gastric erosion, or port disconnection).**

5 CLINICAL SAFETY OF BARIATRIC SURGERY

5.1 Introduction

Based on the evaluation in chapter 4, and as can be appreciated in scientific literature on the topic, metabolic and bariatric surgery (MBS) is the most effective treatment for severe obesity associated with complications and for morbid obesity, and can lead to better health status and outcomes. However, no intervention is exempt from possible complications or adverse effects, and this is no different for bariatric surgery. In addition, both the outcome of long-term success (= a sustained healthier weight) and the occurrence of some possible tolerance issues, may to a considerable extent also depend on patient compliance factors, especially with regard to the life-long lifestyle modifications and dietary restrictions, the need for vitamin/micronutrient supplementation and the need for lifelong medical follow-up.

Complications and adverse effects linked to bariatric surgery can be described as short-term complications (linked to the surgical act of the MBS as such) and as long-term complications, adverse effects or other possible unfavorable long-term health consequences that need to be taken into account.

- **Early complications** are most often and 'classically' considered to happen within 30 days of the intervention. They can be **surgical ('anatomical') or medical in nature.** These **early post-operative complications** will be briefly described and discussed, though they are not the major focus of this safety review as they are relatively well known and established. This short-term perioperative risk may however vary from patient to patient in function of their age, presence and severity, possible co-morbidities, and other factors. Surgical complications can occur both early post-operatively (<30 days; often as a direct consequence of the surgical act), as well as late (>30 days) post-operatively. Therefore, even when looking only at short-term

surgical complications, some experts will set a cut-off at ≤90 days (instead of classic and limitative cut-off of ≤30 days post-op).[92].

- **It is also key to consider 'late' complications when occurring beyond 1 to 2 years after surgery, more than 5 years, or even more than 10 or 15 years after surgery.** In fact, some authors recently considered data to be long-term when available data are equal to or go beyond 5 years,[100] or even, and better, when available data are equal to or go beyond 10 years.

Regarding the long-term complications or AE's, we can essentially distinguish surgical complications, medical complications (including neurological) and psychiatric complications. Medical, neurological and psychiatric complications mostly occur beyond the initial 30 days, and they may actually present (many) years after surgery. In some of them the patient also may have an important role or contribution, e.g. when there is lack of compliance with regard to the intake of vitamin/mineral/trace element supplements, non-respect regarding dietary restrictions, and/or non- or insufficient compliance with regard to required lifelong medical (multidisciplinary) follow-up.

Although and notwithstanding the fact that the number of reports in bariatric/metabolic surgery and medicine 'literally' explodes, good solid long-term safety data (>5-10 years) based on RCTs, evaluating possible long-term unfavorable effects of bariatric or metabolic surgery, are less well described and especially less well quantified. In fact, these type of big size, long-term RCT-based data are essentially non-existing. Therefore **long-term safety data are essentially based on observational data and research. These data come from SR-MA (with essentially observational underlying data), from prospective or retrospective cohort trials and registries, single institutions research, or even only case reports. Inherently these data are at higher risk of bias and confounding, compared to data coming from well designed and performed RCTs. Besides, this type of safety outcomes are much more difficult to quantify and therefore the evaluation and discussion made in the context of this HTA can only be considered qualitative (or at maximum semi-quantitative in nature), pointing to possible specific clinical points for attention and vigilance.**

The following short- and long-term complications will be discussed in this chapter:

- Short term or 'early' post-operative complications
  - Surgical and medical complications (part 5.3.1 & 5.3.2)
  - General incidence rates for complications, readmissions and mortality (part 5.3.3)
  - Surgical complications that are more likely to occur in function of the type of surgical intervention (part 5.3.4)
  - Safety in adolescent patients (concise note) (part 5.3.5)
- Late adverse effects and complications
  - General reporting rates for late complications / overall effect on long-term mortality (part 5.4.1)
  - Complications that are (to some extent) more procedure specific (part 5.4.2)
  - Gastrointestinal late adverse effects (AE) (part 5.4.3)
  - Metabolic and nutritional late AE (part 5.4.4)
  - Haematological late AE (part 5.4.5)
  - Neurological late AE (part 5.4.6)
  - Alcohol and substance use disorder (part 5.4.7)
  - Psychiatric adverse effects and psychological well-being (part 5.4.8)
  - (Re-) emergence of maladaptive or problematic eating behaviours and eating disorders after MBS (part 5.4.9)
  - Potential for changes in drug pharmaco-kinetics (part 5.4.10)
  - Pregnancy outcome related effects (part 5.4.11)

- Dermatological AE (part 5.4.12)
- Miscellaneous effects and new safety topics of potential interest (part 5.4.13)
- Weigh regain and need for revisional surgery *(albeit a topic which encompasses both a clinical effectiveness and safety aspect or point of view)*[e] (part 5.4.14)

5.2 Search strategy – clinical safety of metabolic and bariatric surgery

The research question was transformed into a PICOS structured search question, we did not limit the search by adding specific outcomes. Keywords and search concepts were collected through expert's knowledge and analysis of keywords and subject headings from articles retrieved after preliminary literature searches. We applied the following PICO for the evaluation of the clinical safety of bariatric surgery:

[e] Not in the initial primary scope of this 'safety' chapter, is the problem of insufficient weight loss or weight regain after initial surgery. However, after a few years all bariatric procedures will be characterized by at least some extent of weight regain, though for most patients this will be limited and weight loss will be considered durable.[24, 137] However some other patients might have more substantial weight regain.[137-139] Although this may be due to anatomical changes or 'organic' causes or complications (e.g. formation of fistula, or a wide open gastro-jejunal stoma), a substantial part of cases of weight regain seen is linked to problems of poor compliance to dietary restrictions and/or the fact that the patient disappears from life-long (multidisciplinary) medical follow-up.[138, 139] Apart from patient compliance factors, the risk and incidence of weight regain may vary with the surgical technique employed. The risk of weight regain and durability of weight loss will however be briefly touched upon.

Table 16 – The PICO applied for the clinical safety of bariatric surgery

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Population	Patients with obesity or morbid obesity eligible for bariatric surgery	Type 1 diabetes mellitus
Intervention	Bariatric surgery (or metabolic surgery), abbreviated as BS; main focus on Sleeve Gastrectomy (SG), RYGB (Roux-en-Y Gastric bypass).	Duodenal switch (operation), biliopancreatic diversersion, endoscopic (procedures). Reports were only LA-GB is evaluated will not be evaluated in depth (as this procedure is now largely abandonned for safety reasons); VBG (vertical banded gastroplasty); mini-baypass, ..., (special) technical variants of procedure, ... robot modality surgial techniques. Revisional/redo surgery will not be specifically addressed. Open (laparotomy) access interventions.
Comparison	NOT MANDATORY : not specified, though could include: conservative medical management (diet and excercise, life style only), pharmacological treatment (not specifically in focus, though not excluded), where specific relevant data are avaible, comparison between different bariatric surgical techniques or approaches	
Outcome	Short- or long-term adverse effects or adverse outcomes related to BS.	Initial (primary) failures or secondary weight regain : discussed in clinical effectiveness part; if the safety aspect is not sufficiently elaborated and/or when it adds nothing to the existing knownledge base when it comes to potential new safety signals

For the purpose of this safety evaluation, the focus will be on the laparoscopic RYGB and the laparoscopic SG, with only a brief discussion on the disappearing LAGB and the BPD-DS (a procedure which still may have a small limited place in the surgical treatment of super-obese patients, or as a revisional 're-do' surgery). Neither the different technical variants of primary MBS (e.g. use of different stapling or suturing techniques of the established SG or RYGB, closure or non-closure of mesenteric defects and variations of length of the alimentary or biliary limbs of the RYGB, etc.), nor the safety of revisional surgery (undo, or redo bariatric interventions) are in scope of the present review. Likewise, the safety evaluation of upcoming (not yet or much less established) procedures like e.g. the transoral endoscopic gastroplication, gastric balloon, endoscopic endo-barrier, and new mal-absorption operations (e.g. one anastomosis gastric bypass or 'mini'-gastric bypass) are not included in this evaluation, nor is the possible role of robotic variants of established bariatric interventions.

Many of these techniques need more in depth, larger and longer evaluations in clinical trials, before firm conclusions can be made regarding their mid- and long-term clinical outcomes.

Older procedures such as e.g. the jejuno-ileal bypass, the Scopinaro intervention (biliopancreatic diversion without duodenal switch) and the vertical banded Mason's gastroplasty are not included in the review as they have become obsolete because of their inherent high rate of complications such as excessive malabsorption, and problems of intolerance. This is also the case for the LAGB, it was at one point a widespread BS procedure, but has now largely been abandoned for reasons of long-term complications and tolerance problems. As a matter of fact there are nowadays more LAGB (gastric bands) being removed than put in place.

The current most-frequently used and established procedures are the laparoscopic Sleeve Gastrectomy (SG) and the Roux-en-Y gastric bypass (RYGB), and this is the reason why these two interventions are the main focus of this HTA evaluation. The laparoscopic access procedure is nowadays used in >95% of the patients, while the open access (via laparotomy) has now become essentially unnecessary and thus largely abandoned. The historic open techniques are in general characterised by higher rates of short-term complications, though essentially they are not different from the laparoscopic techniques when it comes to their long-term metabolic and nutritional effects, cardiovascular effects and effect on long-term mortality risk (reduction). Therefore, and **when not otherwise explicitly specified, the use of 'RYGB' and 'SG' essentially refers to their respective contemporary laparoscopic techniques.**

The safety search strategy was deliberately very broad, as are the safety topics discussed, with the aim to provide sufficient qualitative 'alimentation' with important clinical considerations and points for attention to the subsequent and ongoing Health Service Research (HSR) project on bariatric surgery that will aim to optimize and improve the organisation of pre- and post-operative care for metabolic and bariatric surgery in Belgium.

The initial basic literature search executed for the clinical safety of bariatric surgery applied to the period 2008 till 2018-09-06. However being confronted with an overwhelming amount of literature leading to 'saturation' we decided to: 1st) withdraw all case reports 2nd) to censor observational studies/cohort studies that were published before 2013, and 3rd) take a less systematic approach in the sense that we deliberately decided not to investigate and analyse all existing reports that were published on a specific sub-topic when we felt, after review of title and abstract, they would not further contribute to or add further value to what is already been described abundantly (problem of saturation of literature), and 4th) to add, to the results obtained via our initial search strategy, data or considerations from articles which we found useful and which were identified through hand-searching.

5.3 Short-term or 'early' post-operative complications

5.3.1 Surgical complications

Early 'surgical' intra- and post-operative complications linked to the surgical technical act itself may among others encompass bleeding, perforation/leaks, surgical site infection and obstruction. These specific type of complications will not be discussed in much detail, as these are typically possible complications that may also occur after other types of laparoscopic surgeries. Besides, some perioperative complications might also be linked to anaesthetic procedures or interventions.

In general, the majority of patients are nowadays discharged within 3 days post-operatively.[140] When patients need to be readmitted, for almost 50% of them this seems to occur within one week after discharge.[141]

Short-term surgical complications that are more specific for SG and/or RYGB are discussed in 5.3.4.

5.3.2 Medical complications

Early medical complications (in)directly linked to surgery typically encompass venous thromboembolic disease (deep vein thrombosis/pulmonary embolism), infection (e.g. respiratory, operation site infection, septic shock), myocardial infarction, respiratory insufficiency, rhabdomyolysis, etc.. The risk of occurrence is clearly influenced by patient factors, like age, presence and severity of possible co-morbidities, their medical history and other factors like e.g. difficulty and length of the operation, etc. Most of these are typical possible complications that may occur after most types of abdominal surgeries, and they will not be discussed in detail. General reporting rates after bariatric surgery are quoted/mentioned in sections 5.3.3 and 5.3.4.

5.3.3 General incidence rates for complications, readmissions and mortality

The SOS (Swedish Obese Subjects) trial is historically important because it was the first large, long-term, prospective, controlled trial aimed at investigating the effects of MBS and weight loss on mortality and other objective endpoints, and that did compare the surgical population to a matched population of non-surgically treated obese individuals (n = 2010 for surgical group; n = 2037 for the non-surgical control group).[92] Study setup of this SOS trial have been mentioned in chapter 4. The SOS trial has reported up to 20 years of follow-up data. Two important remarks need to be made about this trial: *1st* the investigators reportedly could not go for an RCT because at that time ethical committees considered the potential high postoperative mortality rate not acceptable for randomising patients (first patients were recruited in 1987), and *2nd* 89% of all operations in the SOS study were undertaken as open surgery, which likely will influence the risk and occurrence rate of early postoperative complications. By contrast, the effect of open vs. laparoscopic surgical access should on itself have little effect on long-term mortality. As mentioned before the SOS trial applied matching of patients on the basis of 18 prognostic factors, used rigorous methods in maintaining patients' follow-up, and reported adjusted estimates after controlling for important factors.[88]

The primary aim of SOS study was to evaluate health outcome on the long-term, however the study also provided short-term (≤90 day) data on surgical complications and postoperative mortality. Over the first 90 days after inclusion in the intervention study, five deaths (short-term mortality 0.25%) were observed in the surgery group and two (0.1%) in the control group. Four of the 5 deaths in the surgery group died during primary hospital stay, of whom three were due to anastomotic leaks with subsequent general organ failure and 1 due to myocardial infarction. The fifth surgical patient died 60 days postoperatively from an acute myocardial infarction.[92]
Amongst the patients in the surgery group, 292 (14.5%) had at least one nonfatal complication over the first 90 days. Pulmonary complications were most common (total 5.2%, including thromboembolism in 0.8%) followed by vomiting (3.0%), wound infection (2.1%), haemorrhage (1.3%) and

anastomotic leak (1.2%). In 2.9% of the patients, these complications were serious enough to require a second operation during the first 90 days.[92]

A recent SR-MA based on 38 RCT involving 4030 patients found a 30 day mortality rate of 0.18% (95%CI: 0.04-0.38%).[89] The rate was similar for both restrictive surgeries (0.17%; 95%-CI: 0.03-0.45%) and mixed surgeries (0.17%; 95%CI: 0.03-0.43%). Restrictive surgeries consisted of gastric banding, vertical banded gastroplasty, gastric plication and SG. The mixed restrictive and malabsorptive techniques were the gastric bypass, including the RYGB; the mini-gastric bypass, the biliopancreatic diversion (BPD), with or without duodenal switch, and the biliopancreatic diversion with RYGBP. As expected short-term mortality was higher for open surgeries (0.31%; 95%CI: 0.03-0.97%). Based on this work one could estimate the overall average 30 days mortality to be around. 0.2% or 2/1000.[89]. If one would only have analysed laparoscopic techniques, overall mortality would probably have been lower than the reported average.

A SR-MA of observational studies and randomized trials with incomplete reporting of trial quality evaluated mortality within 30 days (and after 30 days) after MBS:[142] 164 studies (37 RCTs and 127 cohort studies) evaluating bariatric surgery risks and efficacy in 161 756 obese patients were included. The overall ≤30 day mortality was estimated at 0.08% (95%CI: 0.01%-0.24%) in an analysis of 15 eligible RCTs and 0.22% (95%CI: 0.14%-0.31%) in an analysis of 48 eligible observational studies. The evaluation of the overall surgical complication rates is based on a follow-up duration of ≥2 years in 56% of studies and of <2 years in the remaining studies, and typically included bleeding, stomal stenosis, leak, vomiting, reflux, gastrointestinal symptoms, and nutritional and electrolyte abnormalities. Sixty-four studies (16 RCTs and 48 observational studies) contributed to meta-analyses of complications. The complication rate was 17% (95%CI, 11%-23%) for RCTs but lower for OBSs (10%; 95%CI,7%-13%). This pattern persisted across all surgical procedures. For RCTs, complications rates were relatively low for SG (13% [95%CI, 1%-44%]) and adjustable gastric band (13% [95%CI, 5%-26%]) compared with gastric bypass (21% [95%CI, 12%-33%]).

A SR-MA based on 4 RCTs and 67 observational studies all performed in the US specifically assessed the early (≤30 days) risk of anastomotic leaks, myocardial infarction and pulmonary embolism.[143] The SR-MA included bariatric interventions such as gastric banding, sleeve gastrectomy and gastric bypass. Overall the rate of ≤30 day complications rates were respectively for anastomotic leak, pulmonary embolism and myocardial infarction 1.15%, 1.17% and 0.37%, with some differences being reported according to the type of procedure performed (cf. 5.3.4).

With the remarkable progress made over the last (two) decade(s) in metabolic and bariatric surgery and care, early post-operative mortality rates appear to have come down to 0.1-0.3%, which seems to be similar or even lower than mortality rates for other common elective surgeries like for instance cholecystectomy, hysterectomy, and clearly lower than for knee or hip arthroplasty, or colorectal surgery.[91]

According to some recent publications, contemporary readmission rates (≤30 days) are estimated to be in the order of 5%.[141, 144] In general the reported readmission rates are slightly higher for RYGB than for SG (respectively ca. 6% and 4%).[141, 144]. Almost half of the 30-day readmissions seem to occur in the first week after discharge, and the most common reasons for readmission are procedure (surgery) related, and among them the main causes are gastrointestinal issues.[90, 141].

Various causes for 30-day readmissions can be found in Table 17 according to recent data published by Khorgami et al., based upon a large scale US nationwide validated data set (the ACS-NSQIP participant use data file). The data reported by Khorgami et al. are based on 35 655 patients that underwent either a SG or a RYGB in 2012 and 2013. Of these 1758 patients were readmitted within 30 days, corresponding to 4.9% of the patients.[141] The specific causes for readmission may slightly differ from procedure to procedure (cf. 5.3.4). Among the most frequent important early complications occurring after bariatric surgery are infection, haemorrhage, leaks/perforation, obstruction, venous thromboembolism (=DVT/PE), myocardial infarction.

Table 17 – Causes of 30-day readmissions after bariatric surgery (SG and RYGB combined), according to Khorgami et al., 2016

Suspected cause of readmission	*N*	%
Nausea, vomiting, or dehydration	377	22.6
Abdominal pain	200	12.0
Postoperative intraabdominal/GI bleeding	114	6.8
Anastomotic leak/abdominal abscess/fistula	106	6.4
Intestinal obstruction	97	5.8
Other gastrointestinal problems	167	10.0
Wound complications	83	5.0
Cardiopulmonary complications	91	5.5
DVT/PE	90	5.4
HBP related	45	2.7
Renal insufficiency	22	1.3
Urinary tract infection	18	1.1
Other (non-gastrointestinal)	255	15.3

Recorded causes of 1665 readmissions (87.4 %) out of 1904 readmissions corresponding to 1758 patients

DVT deep vein thrombosis; *PE* pulmonary emboli; *HBP* hepato-biliary-pancreatic

Source: Khorgami,Z. et al., Surg Endosc, 2016

Key points- short-term complications following MBS, referring to 5.3.1, 5.3.2, and 5.3.3.

- **Contemporary 30 day average mortality rates following MBS can be estimated to be in the order of magnitude of 0.1-0.3% or 1-3/1000.**
- **Some data indicate slightly lower mortality rates in short-term RCT vs. short-term observational studies/registries (SR-MA by Chang et al. 2014: 0.8/1000 in RCT vs. 2/1000 in observational studies). This could possibly be explained by the fact that relatively more experienced centres are relatively more represented in RCT research.**
- **Based on a large US dataset of patients receiving RYGB or SG, contemporary readmission rates (≤30d) are estimated to be in the order of 5%, with almost half of which seeming to occur within the first week after discharge. In general the reported readmission rates seem to be slightly higher for RYGB (6%) than for SG (4%). The specific reasons and underlying causes for readmission may slightly differ from procedure to procedure (see part 5.3.4).**
- **Taken together among the most frequent important early complications occurring after bariatric surgery (surgical and medical combined) are infection, haemorrhage, leaks/perforation, obstruction, venous-thromboembolism, myocardial infarction.**

5.3.4 *Surgical complications more likely to occur in function of the type of surgery*

Young et al. evaluated the use and outcomes of SG vs RYGB using the ACS-NSQIP database.[145] They analysed 24 117 patients who underwent SG or RYGB between 2010-2011. The main outcome measures are risk-adjusted 30-day morbidity and mortality. Gastric bypass comprised 79.5% of cases and sleeve gastrectomy comprised 20.5%. Noteworthy is that the proportion of SG cases increased from 14.6% in 2010 to 25.8% in 2011. Compared to RYGB, sleeve gastrectomy had a shorter mean operative time (101 vs. 133 minutes, p <0.01), a lower rate of blood loss requiring transfusion (0.6% vs. 1.5%, p <0.01), a lower rate of deep wound infections (0.06% vs. 0.20%, p = 0.05), lower serious morbidity rate (3.8% vs. 5.8%, p <0.01), and 30-day reoperation rate (1.6% vs. 2.5%, p <0.01), but a higher rate of deep venous thrombosis (0.47% vs. 0.21%, p <0.01). Serious morbidity comprised of UTI, wound infection, abscess, pneumonia, pulmonary embolism, deep vein thrombosis, acute renal failure, transfusion need, stroke/CVA, myocardial infarction, sepsis and cardiac arrest. Compared with sleeve gastrectomy, gastric bypass patients had higher risk-adjusted 30-day serious morbidity (odds ratio [OR] 1.32; 95%CI: 1.11-1.56, p <0.01). Patients who were older, had higher BMI, smoked, or had hypertension were at significantly greater risk of serious morbidity. The 30-day mortality was similar between groups (0.10% for sleeve vs 0.15% for bypass). The authors concluded that compared with the laparoscopic gastric bypass, laparoscopic sleeve gastrectomy is associated with lower 30-day risk-adjusted serious morbidity and equivalent 30-day mortality (Table 18).

Table 18 – Intraoperative and postoperative outcomes (≤30 days) of patients undergoing RYGB vs. SG in 2010 and 2011, according to Young et al., 2015

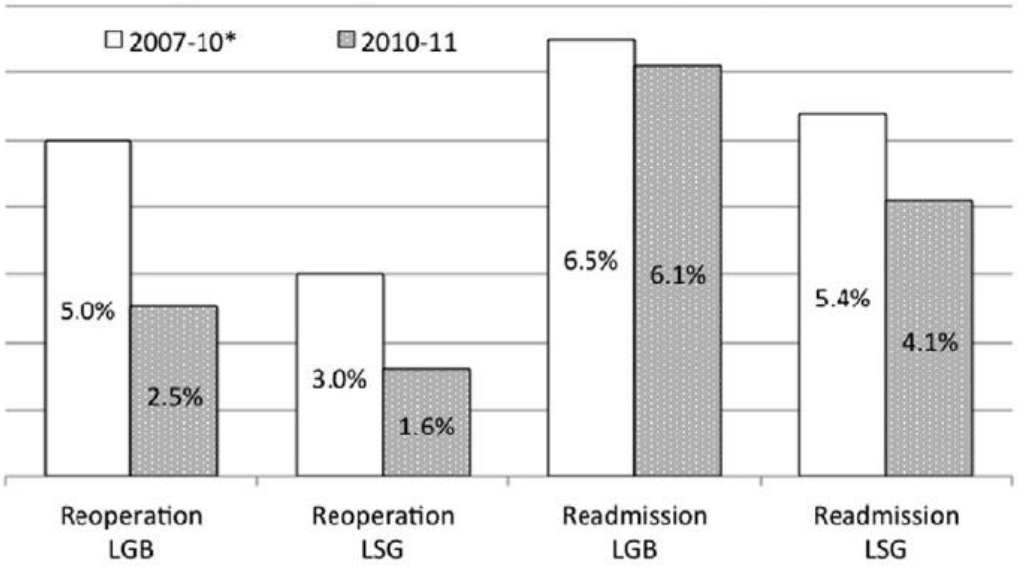
Variable	Laparoscopic gastric bypass (n = 19,172)	Laparoscopic sleeve gastrectomy (n = 4,945)	p Value
Operative time, min, mean (SD)	133 (56)	101 (50)*	<0.01
Anesthesia time, min, mean (SD)	187 (70)	147 (65)*	<0.01
Complications, %			
Urinary tract infection	0.91	0.71	0.21
Wound infection	0.2	0.06*	0.05
Abscess	0.63	0.69	0.73
Pneumonia	0.5	0.38	0.37
Pulmonary embolism	0.21	0.18	0.79
Deep venous thrombosis	0.21	0.47*	<0.01
Acute renal failure	0.11	0.14	0.72
Bleeding requiring transfusion	1.5	0.65*	<0.01
Stroke/CVA	0.03	0.02	0.82
Myocardial infarction	0.1	0.06	0.53
Sepsis	0.58	0.34*	0.05
Cardiac arrest	0.08	0.04	0.55
Serious morbidity, %	5.8	3.8*	<0.01
Length of stay, d, mean (SD)	2 (6)	2 (11)	0.99
30-day readmission, %†	6.08	4.05*	<0.01
30-day reoperation, %	2.46	1.6*	<0.01
30-day mortality, %	0.15	0.1	0.58

*p ≤ 0.05, compared to laparoscopic gastric bypass.
†Based on 2011 data only.
CVA, cerebrovascular accident.

Source: Young ,J. et al., J Am Coll Surg, 2015

The authors also demonstrate that over time, compared to a previous analysis of the same ACS-NSQIP database relative to the period 2007-2010, the rates for short-term (≤30 day) reoperations and readmissions had decreased, with especially a sharp fall in short-term reoperations rates (Figure 19).

Figure 19 – Evolution of short-term readmission and reoperation rates after RYGB and SG, comparing data from 2007-2010 and 2010-2011, according to Young et al., 2015



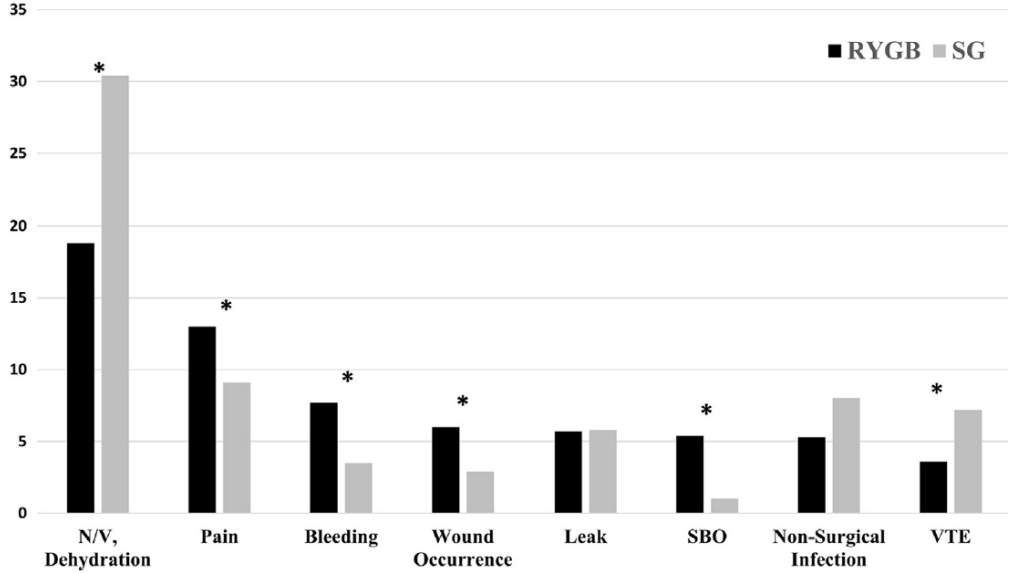
Source: Young ,J. et al., J Am Coll Surg, 2015

Data analysis from the same ACS-NSQIP participant use data file, based on SG and RYGB interventions performed in 2012 and 2013, further consolidate these results.[146] Comparative 30-day readmission rates based on 34 983 patients undergoing SG and RYGB (46% SG, 54% RYGB) in 2012 and 2013 were included. Readmission was more common after RYGB compared with SG (6.1% versus 3.8%, P<.001, adjusted OR 1.59, 95%CI: 1.44-1.76, P<.001). Nausea, vomiting, and dehydration were more commonly a reason for readmission after SG than LRYGB (30.4% versus

18.8%, P =<.001). Additionally, venous thromboembolism was a more frequent readmission cause for SG compared with LRYGB patients (7.2% versus 3.6%, P = .002). Postoperative pain, bleeding, intestinal obstructions, and wound occurrences were more commonly a readmission cause for LRYGB compared with SG. Nausea, vomiting, dehydration were more commonly a reason for readmission after SG. Also venous thromboembolism and post-operative leaks are relatively more reported after SG, compared to RYGB. When leaks occur, they may present on average over a longer time span after surgery in case of SG compared to RYGB (timing from surgery to leak ranged from 1 to 12 days for LRYGB versus 1 to 35 days for LSG). Post-operative pain, bleeding, intestinal obstructions, wound problems, infection, myocardial infarction was on average more commonly reported as reasons for readmission after RGYB.

Common causes for readmissions within 30 days among patients with an established readmission diagnosis after RYGB and SG can be found in Figure 20.

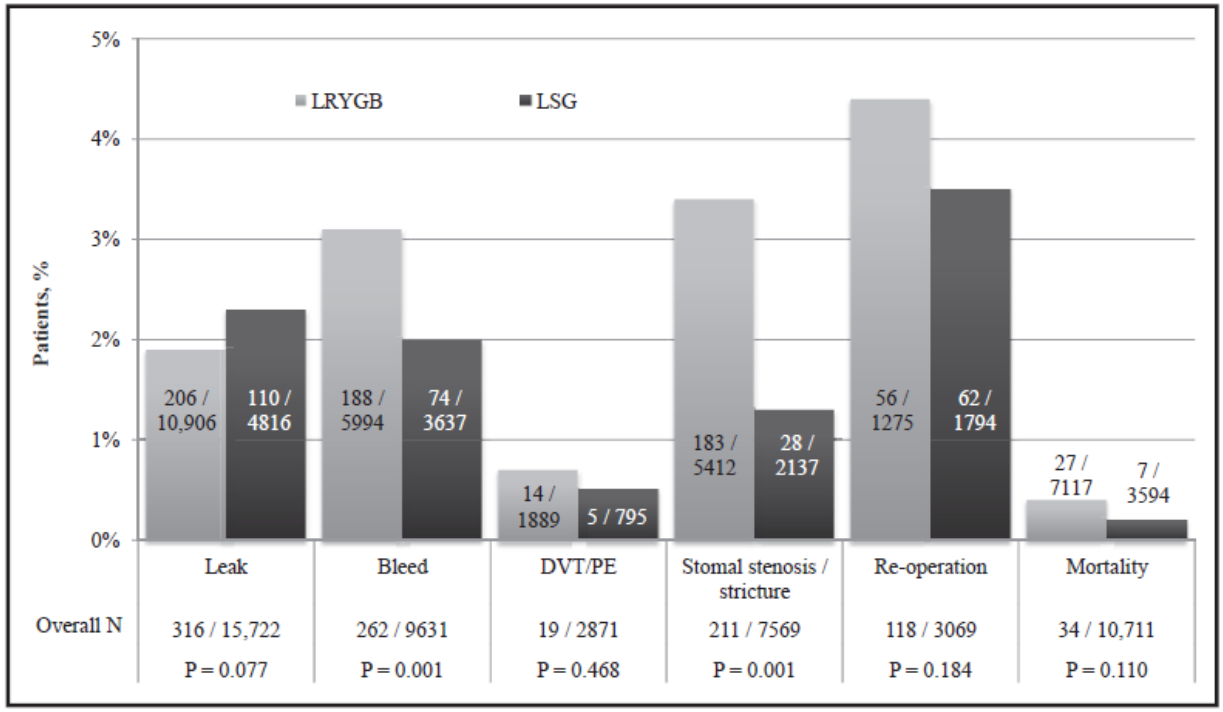
Figure 20 – Most common causes for 30-day readmission after RYGB and SG, according to Sippey et al., 2016



Most common causes for readmission after laparoscopic Roux-en-Y gastric bypass (LRYGB or 'RYGB') and sleeve gastrectomy (LSG or 'SG'), among patients with an established readmission diagnosis. Y-axis: %
*N/V = nausea/vomiting; SBO = small bowel obstruction; VTE = venous thromboembolism; * P <0.05;*
Ungrouped causes of readmission are not illustrated due to rarity and minimal value.
Source: Sippey,M et al., Surg Obes Relat Dis, 2016

A systematic review and meta-analysis of observational research that was primarily aimed at comparing the risk of postoperative leaks and mortality between lap-RYGB ('RYGB') and lap-SG ('SG') is based on 28 observational studies evaluating laparoscopic-RYGB (10 906 patients) and 33 studies evaluating laparoscopic-SG in (4816 patients). Mortality rates were 0.4% for RYGB and 0.2% for SG (P=0.110).[147] Leak rates after RYGB versus SG were 1.9% versus 2.3%, respectively (P=.077). See Figure 21 for 30-day complications rates, reoperation rate and mortality.

Figure 21 – 30-Day complication, reoperation and mortality rates following laparoscopic RYGB and laparoscopic SG, according to Zellmer et al., 2014



DVT = deep vein thrombosis; PE = pulmonary embolism
Source: Zellmer,J. et al., Am J of Surg, 2014

A SR-MA based on 4 RCTs and 67 observational studies all performed in the US specifically assessed the risk of early (≤30 days) risk of anastomotic leaks, myocardial infarction and pulmonary embolism.[143] In total 107 874 patients underwent gastric banding, sleeve gastrectomy and gastric bypass. Overall the rate of ≤30 day complications rates were respectively for anastomotic leak, pulmonary embolism and myocardial infarction 1.15%, 1.17% and 0.37%. Among procedures, sleeve gastrectomy had a slightly higher anastomotic leak rate (1.21%; 95%CI: 0.23-2.19%) than gastric bypass (1.14%; 95%CI: 0.84-1.43%). Gastric bypass had a higher rate for myocardial infarction and pulmonary embolism than gastric banding or sleeve gastrectomy.

Internal hernia occurred more frequently after RYGB.[143] Although internal hernia (IH) can be a cause of short-term postoperative abdominal pain and obstruction, IH are, as discussed in 5.3.2, especially important to consider as a late potentially serious complication of RYGB.

A rare early, but serious complication increasingly reported in literature is the port-mesenteric splenic vein thrombosis (PMSVT) following MBS. A recent SR-MA analysed 41 studies, of which 13 studies that reported the total number of bariatric procedures (16 237patients) along with the number of PMSVTs (68 patients), representing an estimated incidence rate of 0.4% for PMSVT.[148] Sleeve gastrectomy (86/109 patients,78.9%) and gastric bypass (15/109 patients,13.8%) were the most common procedures before PMSVT. This uncommon complication can lead to some other serious consequences, such as bowel ischemia and death.

Another rare complication that can occur after MBS is rhabdomyolysis (which can cause acute kidney failure), the risk of which seems to be related to BMI and prolonged operation time (cf. systematic review by Chakravartty et al.).[149]

Key points - short-term complications that may be more likely to occur in function of the type of BS (SG vs. RYGB)

- **In general 30d mortality rate for RYGB and SG are in the same order of magnitude.**
- **Short term safety based on ≤30 day re-admission and re-operation rates improved over time, with especially a decrease in short-term reoperation rates.**
- **SG is reported to have an on average shorter mean operation time and possibly also a lower rate of blood loss requiring transfusion.**
- **In general, SG seems to be characterized by lower short-term serious morbidity (order of ca. 4% for SG vs. 6% for RYGB) and lower 30-day reoperation rate (order of 1.6% vs. 2.5%), but a higher rate of deep venous thrombosis (0.5% vs. 0.2%) compared to RYGB (US 2010-2013 data from the ACS-NSQIP database).**

5.3.5 *Safety in adolescents undergoing MBS*

Based on the (limited) evidence in literature, and most of the publications on this topic of bariatric surgery in adolescents, it seems that MBS in adolescents has a similar short-term surgico-medical safety profile when compared to the adult population.[36, 85, 86, 106-108, 150-161]

The only RCT on bariatric surgery in adolescents was conducted in Australia and enrolled 50 adolescents between 14 and 18 years with a BMI higher than 35 kg/m².[68] They were assigned either to a supervised lifestyle intervention or to undergo laparoscopic adjustable gastric banding (LAGB), and followed up for 2 years. Twenty-four of 25 patients in the LAGB group, and 18 of 25 in lifestyle group completed the study. Re-operations (33%) were required in 7 patients either for proximal pouch dilation or tubing injury.

Three observational studies on bariatric surgery in adolescents have received particular attention in recent scientific literature: Teen-LABS,[84] AMOS[85] and FABS-5+[86].

The Teen-LABS Consortium published a prospective observational study reporting on 228 severely obese adolescents (≤19 y) undergoing bariatric surgery (161 RYGB and 67 sleeve gastrectomy) at 5 US centres from 2007 to 2012.[84] At 3 years, low ferritin was found in 57% (95%CI: 50 to 65) of the participants (66% after RYGB and 32% after sleeve gastrectomy). Thirteen percent (95%CI: 9 to 18) of participants had undergone one or more additional intra-abdominal procedures. One participant with known type 1 diabetes died 3.3 years after RYGB from complications of a hypoglycaemic event.

In the Adolescent Morbid Obesity Surgery (AMOS) study, 81 adolescents (aged 13 to 18 years; mean age 16.5 years) with severe obesity underwent RYGB (2006-2009) at three specialised paediatric obesity treatment centres in Sweden.[85] Twenty (25%) patients underwent additional abdominal surgery for complications of surgery and 58 (72%) showed some type of nutritional deficiency, despite the prescription of nutritional supplements.

The Follow-up of Adolescent Bariatric Surgery (FABS-5+) study reports the 5-12 years outcomes of a cohort of 74 young people aged 13-21 (mean 17.1) years who underwent RYGB at one centre in the US between 2001 and 2007.[86] Of these, 58 (78%) were included in the long-term analysis (mean follow-up of 8.0 years. At follow-up, 25 (46%) of 58 patients had mild anaemia (i.e. not requiring intervention), 22 (45%) had hyperparathyroidism, and eight (16%) had low amounts of vitamin B12.

Based on the limited evidence in literature it seems that MBS in adolescents probably has a similar short-term 'surgical' safety profile when compared to the adult population (indirectness).

The data on the long-term safety are very scarce especially regarding nutritional and developmental complications in this growing population of patients. Points for particular attention are amongst others growth, nutrient deficiencies, psychological health effects and development, aspects of well-being, and adherence to the necessary lifelong life-style changes to be made, the dietary restrictions to be respected, and compliance with lifelong vitamin/micronutrient supplementation and medical (multi-disciplinary) follow-up.

Key points – safety considerations on MBS in the adolescent population

- **Based on the limited evidence in literature it seems that MBS in adolescents may have a similar short-term 'surgical' safety profile when compared to the adult population.**
- **Long-term solid outcome data on MBS in adolescents are virtully non-existing, and data are scarce especially regarding nutritional and developmental complications in this growing population of patients; points for particular clinical attention are amongst others growth, nutrient deficiencies, psychological health effects and development, and psychosocial aspects of well-being.**

5.4 Late adverse effects and complications

Literature data on the safety or possible untoward effects of MBS on the long-term (>5-10 years) are less well described and especially less well quantified. Real long-term safety data based on RCT are very sparse and almost non-existing, and most of the data are based upon observational research. Form this observational research few observational long-term safety data are based upon prospective cohort studies, and most are based upon respective cohort studies or registry studies. Therefore we opted to: 1st) roughly describe or estimate in a qualitative or semi-quantitative way the most frequently occurring possible long-term adverse effects, and 2nd) to advance specific clinical attention points deserving further consideration in the ongoing HSR project.

5.4.1 Effect on LT mortality risk and general reporting rates for late complications following MBS

The evidence from observational studies about the long-term effects on mortality are already presented in part 4.2.2.2, next to the RCT-based evidence (part 4.2.2.1). In this part, additional insights apart from mortality are presented.

Recent real life data on the LT effect of MBS vs. medical obesity treatment on medical complications, according to a Norwegian registry-based cohort study, were published by Jakobsen et al.[162] Primary outcomes included remission and new onset of hypertension based on drugs dispensed according to the Norwegian Prescription Database. Pre-specified secondary outcomes included changes in comorbidities. Adverse events included complications retrieved from the Norwegian Patient Registry and a local laboratory database. Mortality was not part of the primary outcomes investigated. The specific reason why this study is elaborated in more detail resides in the fact that it **gives insight on the absolute and relative risk for remission and new onset of co-morbidities and complications**, with their relative risk (or probability ratio) comparing surgery with specialized medical management.

As stipulated this registry-based cohort study was designed to compare changes in medical complications and obesity-related comorbidities among patients with severe obesity (BMI ≥40 or BMI ≥35 and at least 1 obesity-related comorbidity) undergoing bariatric surgery or specialized medical obesity treatment. The study consisted of an initial study and a FU-study. Baseline data were collected from the Registry- and Biobank (RB) study. The study contains complete clinical and laboratory information from all included patients at their first consultation at the centre. Linkage with the national prescription database allowed the (evolution) of use of drug categories over time. Patients were recruited and followed at the Morbid Obesity Centre, a tertiary care EASO-accredited centre. Physicians informed the patients about beneficial and detrimental effects of various treatment options and encouraged the patients to incorporate their own values and preferences in the decision-making process before the patient and physician agreed on the specific choice of therapy: medical therapy or bariatric surgery. Patients were offered clinical follow-up at the tertiary clinic for at least 2 years after finishing the surgical or medical treatment programs. Patients were enrolled between 2005/11 and 2010/07. Information on treatment choice was obtained from electronic patient records in 2015/07, and information on drugs was obtained from national prescription database in 2016/06, data on all-cause mortality from the National Registry. Anonymous data on medical complications and surgical procedures were obtained from the Norwegian Patient Registry from 2008 to 2015, and laboratory (FU-)data were obtained from the laboratory files of the medical centre. After checking for eligibility, 1888 patients were included in the pre-specified analyses. A total of 956 patients (51%) voluntarily opted for specialized medical treatment, while 932 patients (49%) voluntarily opted for bariatric surgery, mostly gastric bypass (92%) or sleeve gastrectomy (7%). At baseline, the patients had a mean (SD) age of 43.5 (12.3) years and mean BMI of 44.2 (66% were women). As compared with medical patients, surgically treated patients were younger with a higher BMI and earlier appearance of obesity: mean age 41.2 vs. 45.7 y, and mean BMI 45.4 vs.42.9. For the other demographic criteria, patients were relatively well balanced. The patients were followed up for a median of 6.5 years (range, 0.2-10.1 years) after the start of treatment, and the mean (SD) time from the first consultation to surgery was 23 months (SD 12 months). The total

median follow-up durations in the medical and surgical treatment groups were 7.1 years (range, 0.2-10.1 years) and 7.8 years (range, 2.5-10.0 years), respectively, and the median follow-up after the bariatric surgical procedure was 5.8 years (range, 0.6-9.2 years).

A total of 26 (2.8%) and 65 (6.8%) patients in the surgical and medical groups died respectively, with no significant (age, sex, and BMI-adjusted) differences in overall mortality risk (hazard ratio, 0.74; 95%CI: 0.45-1.19, NS). Overall short-term 30-day mortality after surgery was 0 (0/932). **Based on this observational study**, the authors reported that surgically treated patients had a **greater likelihood of hypertension remission and lesser likelihood for new-onset hypertension. Surgically treated patients also had a greater likelihood of diabetes remission, but also a greater risk of new-onset depression, treatment initiation with opioids, and greater risk of undergoing at least 1 additional gastrointestinal surgical procedure**. The proportion of patients with low ferritin levels was significantly greater in the surgical group (26%vs 12%, P <.001), which may point to a problem of Fe-deficiency due to malabsorption as a result of gastric bypass surgery. Table 19 shows the absolute and relative risk for remission and new onset of co-morbidities and complications, with as parameters their relative risk or probability ratio comparing undergoing surgical vs. specialized medical treatment therapy.

Table 19 – Absolute and relative risk/relative probability for remission and new onset of co-morbidities and complications comparing surgical vs. specialized medical treatment therapy, according to Jakobsen et al.2018

Condition	% (95% CI) Absolute Risk Surgical Group (n = 932)	Absolute Risk Medical Group (n = 956)	Risk Difference	Relative Risk (95% CI)
Hypertension[a]				
Remission	31.9 (28.4-35.4)	12.4 (9.5-15.3)	19.5 (15.8-23.2)	2.1 (2.0-2.2)
New onset	3.5 (2.2-4.9)	12.2 (9.3-15.1)	8.7 (6.7-10.7)	0.4 (0.3-0.5)
Diabetes[a]				
Remission	57.5 (53.8-61.2)	14.8 (11.7-17.9)	42.7 (35.8-49.7)	3.9 (2.8-5.4)
New onset	0.3 (0-0.7)	7.5 (5.2-9.8)	7.2 (5.3-9.1)	0.07 (0.03-0.11)
Dyslipidemia[a]				
Remission	43.0 (39.3-46.7)	13.2 (10.2-16.2)	29.8 (23.4-36.2)	2.6 (2.4-2.8)
New onset	1.1 (0.3-1.9)	6.4 (4.3-8.5)	5.3 (3.7-6.9)	0.3 (0.2-0.4)
Depression[a]				
Remission	26.7 (23.4-30.0)	27.4 (23.5-31.3)	1.1 (0.0-2.3)	1.2 (1.0-1.4)
New onset	8.9 (6.8-11.0)	6.5 (4.3-8.7)	2.4 (1.3-3.5)	1.5 (1.4-1.7)
Anxiety and sleep disorders[a]				
Remission	25.0 (21.8-28.2)	28.1 (24.2-32.0)	3.1 (0.7-5.5)	0.9 (0.8-1.1)
New onset	12.2 (9.8-14.6)	9.4 (6.8-11.9)	2.8 (1.6-4.0)	1.3 (1.2-1.5)
Opioid use[a]				
Remission	34.2 (28.8-39.6)	41.4 (35.8-46.9)	7.2 (3.6-10.8)	0.8 (0.7-0.9)
New onset	19.4 (16.5-22.3)	15.8 (13.1-18.5)	3.6 (2.3-4.9)	1.3 (1.2-1.4)
Complications				
Abdominal pain	26.1 (21.1-31.1)	13.5 (9.6-17.4)	12.6 (8.8-16.3)	1.9 (1.6-2.3)
Gastroduodenal ulcers	6.7 (3.9-9.5)	2.0 (1.0-3.0)	4.7 (3.1-6.3)	3.4 (2.0-5.6)
Iron deficiency anemia	6.8 (4.9-8.7)	2.8 (0.9-4.7)	4.0 (1.8-6.2)	2.4 (1.6-3.8)
Vitamin and mineral deficiency	1.7 (0.2-3.2)	1.6 (0.7-2.5)	0.2 (0-0.5)	1.1 (0.5-2.2)
Protein-energy malnutrition	2.3 (0.6-4.0)	1.9 (0.4-3.4)	0.4 (0.0-1.1)	1.2 (0.6-2.3)
Hypoglycemia	1.3 (0.5-2.1)	0.3 (0.0-0.7)	1.0 (0.3-1.7)	4.1 (1.2-14.6)
Nausea and vomiting	0.9 (0.0-2.1)	1.4 (0.0-2.7)	0.5 (0.0-1.3)	0.6 (0.3-1.5)
Surgical procedures				
Any gastrointestinal surgery	31.3 (26.0-36.5)	15.5 (12.8-18.2)	15.8 (13.1-18.5)	2.0 (1.7-2.4)
Operations for intestinal obstruction	8.7 (6.6-10.8)	0.8 (0.0-1.8)	7.9 (4.8-10.9)	10.5 (5.1-21.5)
Operations for abdominal pain	5.4 (2.8-8.0)	0.4 (0.0-0.9)	5.0 (3.4-6.6)	12.9 (4.7-35.7)
Operations on gallbladder	8.1 (5.0-11.2)	2.4 (0.7-4.1)	5.7 (3.1-8.3)	3.4 (2.1-5.3)
Operation of incisional hernia	2.8 (1.6-4.0)	1.3 (0.5-2.1)	1.4 (0.5-2.3)	2.1 (1.1-4.0)

[a] *Relative risk ratios were converted from adjusted odds ratios derived from multiple logistic regression models for repeated measurements. The analyses were adjusted for sex, age, and body mass index at baseline.*

Source: Jakobsen, G. et al., 2018, JAMA

They concluded that among patients with severe obesity followed up for a median of 6.5 years, bariatric surgery compared with medical treatment was associated with a clinically important increased risk for complications, as well as lower risks of obesity-related comorbidities, and that the risk for complications should be considered in the decision-making process. In the following paragraphs, several of these complications will be discussed in more details.

5.4.2 *Overview of complications that are (at least to some extent) more procedure-specific*

5.4.2.1 *Roux-en-Y gastric bypass (RYGB), essentially referring to the 'laparoscopic' RYGB*

Roux-en-Y gastric bypass (RYGB) restricts food intake by creating a small pouch (15-30 ml) at the top of the stomach. This pouch is the only part of the stomach that receives food, which greatly limits the amount of food a patient can comfortably eat and drink at one time. It is anastomosed to the Roux limb of jejunum. Food bypasses 95% of the stomach and the duodenum and part of the jejunum. As a consequence, fewer nutrients and calories are absorbed. RYGB also induces GI hormonal changes, contributing to its metabolic effects.

Complications of RYGB are diverse and may vary based upon the specific technique. The most important and more specific ones are underlined. They include among others: gastric remnant distension, stomal stenosis, stomal dilatation, marginal ulcer, cholelithiasis, ventral incisional hernias, internal hernias, small bowel obstructions, gastro-gastric fistulas; metabolic derangements, dumping, hypoglycaemia, and nutritional & micro-nutrient/vitamin deficiencies. Certain complications are mainly seen during the early postoperative periods, while others may present months to years following the surgery.[163] Note that some patients may develop deficiencies, despite 'correct' intake of supplements.

Gastric remnant distension is a rare but potentially lethal complication following RYGB. The gastric remnant is a blind pouch and may become distended if paralytic ileus or distal mechanical obstruction occurs postoperatively. Progressive distension can lead to rupture, spillage of massive gastric contents, and subsequent severe peritonitis. The combination of the large size of inoculum and the injurious contents (acid, bile, pancreatic enzymes, and bacteria) makes this complication more serious than leakage.[163] It is difficult to put a percentage on this adverse event (AE), though this complication has a high mortality, because of acute hypovolemic shock caused by the massive fluid shifts and sepsis.

Internal hernias (IH) are mesenteric defects that are created during a Roux-en-Y gastric bypass and include mesenteric defects at the jejunojejunostomy, a space between the transverse mesocolon and Roux-limb mesentery (Petersen's defect) or a defect in the transverse mesocolon in patients with a retrocolic Roux-limb.[163] After 2 years post-surgery, IH are the most important serious complication.[24] Although there is some debate as to whether systematic per-operative closure of all mesenteric defects should be realized, most data indicate that closure of all mesenteric defects with non-absorbable sutures may decrease the incidence (by ca. 50%) of small bowel obstruction/incarceration due to IH.[24, 163, 164] Although incidence rates for IH vary in literature, most clinical experts estimate life time risk of (sub)obstruction due to IH to be around 10% in case of non-closure of mesenteric defects. IH are an important cause of small bowel obstruction, and may also be one of the important causes of chronic abdominal pain. Note that presenting symptoms of small bowel (sub)obstruction may be more subtle during pregnancy in women that previously underwent RYGB.

Small bowel obstruction is most commonly caused by IH through one of the mesenteric defects, though alternatively small bowel obstruction can also be caused by adhesive disease, an incisional abdominal wall hernia or intussusception at the jejunojejunal anastomosis. Small bowel obstruction can present acutely, or can give chronic (intermittent) complaints of sub-obstruction.

Stomal stenosis (of the gastrojejunal anastomosis) has been described in ca. 5-25% of patients who have undergone RYGB. The aetiology is uncertain, although tissue ischemia, marginal ulcer, or increased tension on the gastrojejunal anastomosis may play a role. The stomal stenosis rate is higher in *laparoscopic* RYGB and may be related to the use of the small-

diameter circular staplers. Patients typically present several weeks after RYGB with nausea, vomiting, dysphagia, gastroesophageal reflux, and eventually an inability to tolerate oral intake, including liquids. The diagnosis is usually established by endoscopy or with an upper gastrointestinal X-ray series. Most of the patients with stomal stenosis can be treated endoscopically.[163]

As opposed to stomal stenosis, stomal dilation is characterized by de development of a wide open gastrojejunal stoma, allowing food to progress rapidly from the small gastric pouch into the small intestine. A possible 'anatomical' cause of weight regain is gastric pouch dilatation.

Marginal ulcers can occur at any time after RYGB, and can present with abdominal pain, nausea, GI blood loos/bleeding, stomal stenosis or perforation, but may also be asymptomatic. The incidence may vary and is estimated to range from ca. 1% to 35%.[163, 165] They occur at the gastrojejunal anastomosis and arise as a result of a number of factors. Sometimes they can be associated with a gastrogastric or rarely gastrocolic fistula. Factors that among others may increase the risk are H. pylori and use of NSAIDS. The prophylactic use of proton pump inhibitors during the initial post-surgical period might possibly reduce the risk. Although medical management of marginal ulcers is successful in 85 to 95% of patients, surgery may be indicated if marginal ulcers perforate or if persistent pain or recurrent bleeding occurs despite maximal medical therapy.[163, 165]

Leaks occurring in ca. 1% of the patients mostly present relatively shortly after surgery.[143].

Gastrogastric fistulas occur in approximately 1-2% percent of patients after RYGB and they may be a cause for weight regain.[163, 165] A gastrogastric fistulas is a channel that develops between the gastric pouch and the excluded stomach remnant, allowing ingested food to enter the bypassed foregut (stomach and duodenum).

Candy-cane-Roux-syndrome is a rare syndrome which refers to an excessively long blind Roux limb at the gastrojejunostomy causing postprandial pain often relieved by vomiting. It is believed that the blind afferent limb ("candy cane") acts as an obstructed loop when filled with food, and the distention of the loop causes pain until the food either spills into the Roux limb or is vomited back out. Patients have been reported presenting as early as 3 months after surgery and as late as 10 years after surgery. Typical symptoms include postprandial epigastric pain, nausea, vomiting, and reflux or food regurgitation. Diagnosis is made by endoscopy or upper GI-contrast studies, and treatment is revisional surgery, most commonly laparoscopic resection of the 'too long' blind afferent limb.

Anatomical changes induced by the surgical RYGB-construction imply that the excluded part of the duodenum and stomach is very difficult to examine endoscopically because they are beyond the reach of standard endoscopic access, which is an important inconvenience or consequence. The same applies for Endoscopic Retrograde Cholangio-Pancreaticography (ERCP), which might be desirable for certain diagnostic and therapeutic reasons. An example where ERCP may be indicated is the presence of a choledocholithiasis, a condition which more easily develops in patients with rapid weight loss due to MBS.[165]

Other symptoms such as early dumping and the postprandial hyperreactive hypoglycemic syndrome (previously called 'late dumping', sometimes characterized by severe postprandial hyperinsulinaemic hypoglycaemia) and cholelithiasis are discussed in 5.4.3 while nutritional deficiencies and nephrolithiasis are discussed in 5.4.4.

5.4.2.2 Sleeve Gastrectomy (SG), essentially referring to the 'laparoscopic' SG

Sleeve gastrectomy involves creating a "sleeve" of stomach over a bougie and removes a large portion of the greater curvature of the stomach leaving a small tube along the lesser curvature. This reduces stomach volume by 75-80%. SG also produces a decrease in ghrelin levels for up to a year, which may reduce the desire for food. Ghrelin is a gastrointestinal 'hunger' hormone. Significant advantages of SG include low complication rates (3 to 24 %) and low mortality rates, the relative ease of performing the procedure, preservation of the pylorus, maintenance of physiological route of food passage and the avoidance of foreign material.

SG complications include among others bleeding, narrowing or stenosis, fistula, leaks, and new onset or worsening gastro-oesophagal reflux (GORD), as well as some risk for nutrient deficiencies.

Leaks are one of the most serious complications after SG and seem to occur in 0.6-4% of the patients, with a contemporary average estimated to be around 1-2% of patients.[142, 147, 166] Most leaks occur in the early post-operative period. Cholelithiasis risk is also increased and most probably the increase in risk is mostly explained the rapid substantial weight loss. The risk of nutritional and micro-nutrient/vitamin deficiencies is also increased, though in general to a lesser extent than for purely or mixed malabsorptive interventions. Patients can also present with stenosis or narrowing of the gastric sleeve causing gastric outlet symptoms or obstruction [163]. Presentation varies depending on the severity of the obstruction and can include dysphagia, vomiting, dehydration and the inability to tolerate an oral diet. This may lead to nutrient deficiencies. Management of stenosis primarily consists of endoscopic dilation. If the area of stenosis is too long, surgical intervention may be necessary with conversion to a RYGB. Stricturoplasty, seromyotomy or resection with gastro-gastrostomy are less effective and are fraught with a high leak rate.

Worsening of gastro-oesophagal reflux disease (GORD) or new onset GORD is relatively high after SG, cf. 5.4.3. Gastro-oesophagal reflux may lead to Barrets oesophagus (potentially harbouring mucosal metaplasia being considered as a pre-cancerous risk factor).

5.4.2.3 Laparoscopic adjustable gastric banding (LAGB)

As mentioned before this HTA did not focus primarily on the LAGB, and the most important complications will be only briefly touched upon.

The LAGB intervention has largely fallen in disgrace, though is still being performed. The intervention has moderate efficacy and with less coherent effects on BMI-loss compared to the RYGB and the SG, and especially is characterized on the long-term by high rates of weight regain, complications, technical port-malfunction, and issues of intolerance.

Although LAGB is the procedure with the lowest short-term post-operative mortality, this procedure has been associated with several, potentially serious and life-threatening complications.[22, 24, 163] Among the most important complications are acute obstruction, band erosion and erosion into the stomach (gastric perforation), band slippage leading to gastric prolapse, port malfunction, oesophageal dilatation, esophagitis, and infection. It's estimated that ca. 40% of patients develop long-term complications, leading to a high rate of revisional surgery encompassing among others undo-surgery or removal of the adjustable gastric band (up to 40-50%), with or without conversion (in one or two steps) to another MBS procedure like SG or RYGB. In fact nowadays there are more gastric bands being removed than put in place (clnical expert feedback, indirect indications form literature:[22, 24]). Apart from a possible but debatable very limited place in rather young not extremely obese patients (who refuse SG or RYGB), this procedure seems to have been largely abandoned.

5.4.2.4 Biliopancreatic diversion with duodenal switch (BPD-DS)

As mentioned before this HTA did not focus primarily on the BPD-DS, and the most important complications will be only briefly touched upon.

The BPD-SD (sometimes briefly referred to as 'duodenal switch') is a purely malabsorptive intervention and is nowadays rarely performed. Due to its very interventional and drastic nature this intervention incurs a very high risk of nutritional and metabolic adverse effects/complications, and this is the main reason why it has been essentially replaced by the RYGB, and for the not superobese patients both by the SG and RYGB. The BPD-DS at present only might have a very limited place as a possible treatment option in the super-obese patients with a BMI ≥50, and as second stage revisional re-do surgery after a failed primary intervention.

Among the most important complications are significant protein and calorie malnutrition, anaemia, metabolic bone disease, and deficiencies of fat-soluble vitamins and other vitamins, as well as trace elements, which on itself might incur an exaggerated risk for haematological and neurological consequences.

5.4.2.5 *Comparing overall safety between RYGB and SG*

Based on a table from a recent 'narrative' review focussed on the question on how to choose the best metabolic procedure, the following approximate 30 days (early) and late (>30 days) complications rates are mentioned for the adjustable gastric band (LAGB), the SG, the RYGB and the BPD.[27], see Table 20 for the comparison between SG and RYGB. These figures come from a narrative review, and the authors did not provide details of the underlying causes for these complication categories, though it gives some idea of the overall relative reporting rates for SG and RYGB. **Given the narrative nature of the review caution should be applied regarding the numbers.**

Table 20 – Early and late complication rates for SG and RYGB according to Castagneto Gissey et al. 2016

	SG	RYGB
Early complications (%)	5.46	5.91
Late complications (%)	**7.70**	**17.54**

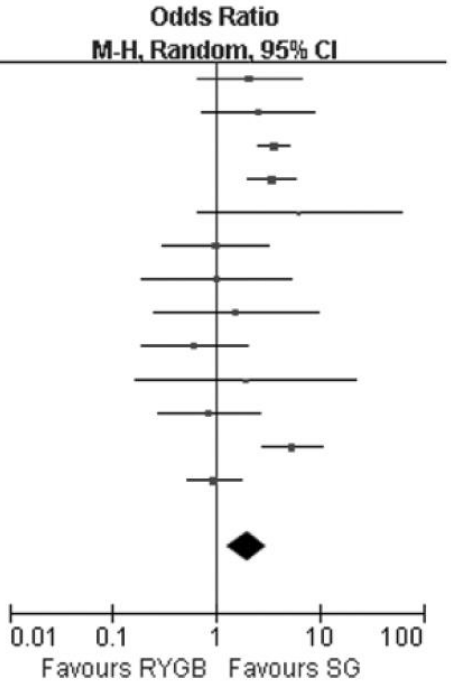
Li et al. reported on a SR-MA comparing the long-term results of RYGB vs. SG.[166]. 32 studies were deemed eligible and the minimal FU was at least 1 year, going up to 5 years. In total 6526 patients were included in the MA (3874 with RYGB; 2652 with SG). Six of the 32 studies were RCTs, 5 of them had a FU of 1 year, and 1 had a FU of 3 years. The RCTs included 302 patients out of total of 6526 patients. Although the overall results on weight loss were in general comparable for RYGB vs. SG, and overall resolution rates of obesity-related co-morbdities was comparable. However for some of the co-morbidites RYGB scored significantly better, like for resolutions of T2DM, hypertension, hypercholesterolemia, GERD, and arthritis. SG was also characterized by a shorter operation time. Regarding safety outcome, SG was a safer procedure with a reduced rate of complications and reoperations, cf. respectively Figure 22 and Figure 23.

Figure 22 – Meta-analysis of long-term FU postoperative complications, according to Li et al., Surg Laparosc Endosc Percutan Tech, 2014

Study or Subgroup	RYGB Events	RYGB Total	SG Events	SG Total	Weight	Odds Ratio M-H, Random, 95% CI
Benaiges 2011	16	95	4	45	7.4%	2.08 [0.65, 6.61]
Benaiges 2012	9	51	4	51	6.8%	2.52 [0.72, 8.78]
Boza 2012	152	786	51	811	13.9%	3.57 [2.56, 4.99]
Chouillard 2011	62	200	23	200	12.4%	3.46 [2.04, 5.86]
Cutolo 2012	5	16	1	15	3.0%	6.36 [0.65, 62.69]
Kasama 2008	16	105	4	26	7.2%	0.99 [0.30, 3.25]
Kehagias 2011	3	30	3	30	4.7%	1.00 [0.19, 5.40]
Lakdawala 2010	3	50	2	50	4.2%	1.53 [0.24, 9.59]
Leyba 2011	7	75	6	42	7.4%	0.62 [0.19, 1.98]
Nocca 2011	2	35	1	33	2.7%	1.94 [0.17, 22.46]
Paluszkiewicz 2012	28	36	29	36	7.5%	0.84 [0.27, 2.64]
Vidal 2012	55	135	13	114	11.2%	5.34 [2.73, 10.46]
Yaghoubian 2012	31	345	18	192	11.7%	0.95 [0.52, 1.76]
Total (95% CI)		**1959**		**1645**	**100.0%**	**1.96 [1.26, 3.04]**
Total events	389		159			

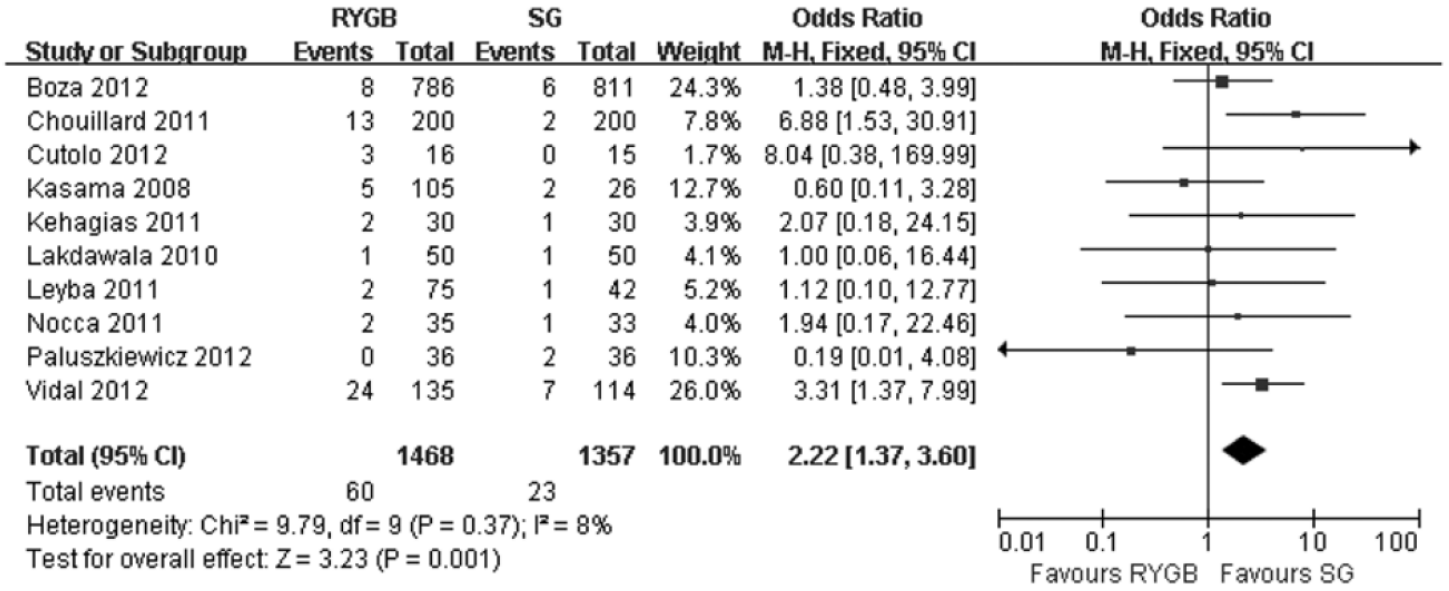
Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 33.87$, df = 12 (P = 0.0007); $I^2 = 65\%$

Test for overall effect: Z = 3.00 (P = 0.003)



CI, indicates confidence interval; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy
Source: Li,JF. et al., 2014, Surg Laparosc Endosc Percutan Tech

Figure 23 – Meta-analysis of re-operation, according to Li et al., Surg Laparosc Endosc Percutan Tech, 2014



CI, indicates confidence interval; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy
Source: Li,JF. et al., 2014, Surg Laparosc Endosc Percutan Tech

Note however that this meta-analysis predominantly captured both the relatively short-term surgico-abdominal complications and the more long-term 'medical' or 'metabolic' complications which were less represented.

Supporting references: [22, 24, 27, 47, 143, 145, 147, 166, 167]

Key points- on the relative safety of SG and RYGB (based on supporting references and 5.4.2.1, 5.4.2.2)

Observational data indicate that:

- **RYGB scored better than SG on the resolution of obesity-related comorbidities.**
- **SG scored better than RYGB on rate of complications and reoperations.**

This information from non-randomized observational data should be interpreted with caution.

The Sleeve Gastrectomy, SG:

- **is an intervention with a shorter operation time than the RYGB**
- **in general is a safe procedure, which on average might be somewhat safer than RYGB, with a reduced rate of 'short-term' abdomino-surgical complications and a lower rate of re-interventions for safety reasons; however this 'comparison' should be interpreted with caution given the narrative nature of the paper by Castagneto Gissey et al, and the relatively short-term time-horizon of the underlying studies in the paper of the SR-MA by Li et al.**
- **its most important serious complication are leaks; leak rate on average is relatively comparable with RYGB, though seems to be slightly higher than for RYGB**
- **is characterized by a higher risk of worsening of, or new onset gastro-oesophagal reflux (disease) or GOR(D), in contrast to the data observed with RYGB**
- **can cause long-term metabolic and nutritional deficiencies, though on average they are less prevalent than after RYGB (see also 5.4.4.2)**
- **might be characterized by somewhat higher rates of late weight regain (see also 5.4.14); note however that there is still less long-term experience with SG compared to RYGB;**

The Roux-en-Y Gastric Bypass, RYGB:

- **is the MBS intervention with the most extensive long-term experience, and as such often is considered the current "gold standard".**
- **is in general a relatively safe operation, though with general complication rates that are on average somewhat higher than for SG; however this 'comparison' should be interpreted with caution given the narrative nature of the paper by Castagneto Gissey et al, and the relatively short-term time-horizon of the underlying studies in the paper of the SR-MA by Li et al.**
- **its most important abdomino-surgical complication is internal hernias (IH) that seem to be a life-long risk; internal hernia can be an important cause of chronic (unexplained) abdominal pain complaints, and is an important cause of small bowel (sub)obstruction**
- **in general the average risk for long-term metabolic deregulation and macro- and micro-nutritional deficiencies (with possible important consequences) is definitely higher than for SG, which can be explained by its mixed restrictive/malabsorptive nature; this risk can be largely mitigated or avoided, by regular medical and nutritional follow-up and correct intake of supplements of vitamins and trace-elements**
- **has a verly low risk for new onset GOR(D), and on average a high resolution rate of pre-existing GORD**

5.4.3 Gastrointestinal late adverse effects (AE)

MBS implies anatomical and functional modifications of the gastrointestinal tract, and as such this may lead to a spectrum of late gastrointestinal adverse effects or symptoms.[21] Some of them have been discussed in 5.3. The other 'late' gastrointestinal AE may encompass (but are not limited to) gastro-oesophagal reflux disease (GORD), early dumping, postprandial hypoglycaemic reactive syndrome = PPHRS (previously called 'late dumping'), food intolerance, loose stool and diarrhoea, borborygmi, bloating, gall stones (cholecysto- and choledocholithiasis), problems related to bile reflux, unexplained abdominal pain, achalasia and pseudo-achalasia, formation of phytobezoar, acute liver injury. The most important ones, because of their frequency and/or severity, are underlined. Some gastrointestinal AE's may be (more) procedure specific. They will be briefly discussed.

Decreased intake and/or absorption of macro- and micro-nutrients, effects on alcohol absorption, and the potential for changed drug-PK (pharmacokinetics) are other (indirect) effects and they will be discussed in paragraph 5.4.4, 5.4.7 and 5.4.10.

5.4.3.1 Nutritional habits and change in food-tolerance

One of the intended effects and inherent consequences of MBS is to change eating habits and size of portions. Food intake is reduced by restricting the 'recipient' capacity of the stomach, limiting ingested volumes, inducing early satiety (via direct and/or indirect neuro-hormonal effects) etc. Therefore it is important that patients are compliant with dietary advice and instructions both with the aim of increasing the (long-term) effectiveness of the intervention and in limiting the occurrence of undesirable effects, symptoms of GI-nature and metabolic intolerance. Non-compliance with regard to meal frequency, volume, consistency and composition clearly may increase the probability of certain types of intolerance issues occurring.

As such are possible: (short-term) nausea and vomiting, dyspepsia, change in appetite (in general, of for certain foods), abdominal cramps, borborygmi, bloating, change in bowel frequency (loose stool and diarrhoea), early dumping symptoms, PPHRS.

Decreased food and nutrient intake may contribute to the increased risk for macronutrient and especially micro-nutrient deficiencies (part 5.4.4).

5.4.3.2 Gastro-oesophagal reflux

GOR(D) is a frequent problem in the general population, and is even more prevalent in (severely) obese patients. This is among others one of the reasons why most centres will perform an oesophago-gastro-duodenoscopy ('gastroscopy') before the intervention. GORD may lead to Barrett oesophagus, which (depending on the degree of dysplasia) may be a pre-cancerous condition. On average SG clearly appears to increase the probability for worsening of pre-existing GORD or cause new onset GORD. A few patients might (via their weight loss) experience less GOR. In contrast, RYGB (due to the anatomical changes) on average will improve GOR, so that many patients with pre-existing GORD may be cured after RYGB. Therefore, the presence of (severe) GORD or symptoms will be considered a (relative) contra-indication for SG, while the presence of Barrett oesophagus will often be considered an absolute contra-indication for SG. The International Sleeve Gastrectomy Expert Panel reported a postoperative GORD rate up to 31%.[90] Other trials have shown newly developed GORD in up to 22% of patients after SG at 1 year, while in other studies some patients also experienced improvement of symptoms at 2-3 years (because of weight loss).[90]

5.4.3.3 Gallstone formation (cholelithiasis: cholecysto- and choledocholithiasis)

Obesity on itself is a well-known risk factor for gallstone formation. The risk seems to be especially high in patients with the highest BMI, and is more common in women than man. The incidence of biliary tract disease (most often cholelithiasis) ranges from 25-45% in the morbidly obese, which is tree or four times higher than in the general population.[90] Most gall stones in obese subjects are cholesterol stones. During caloric restriction and substantial weight loss, secretion rate of bile acid pool decreases more than the secretion of cholesterol, resulting in an increase in the bile saturation, promoting the formation of crystals, bile sludge and finally gallstones

(cholelithiasis). Bariatric patients are at additional risk of gallstone formation, and this risk is maximal during the period of rapid weight loss, which is usually the first 6 months after the procedure. Risk subsequently wanes when the patient's weight stabilizes. Incidence figures on postoperative cholelithiasis in literature vary roughly from ca. 5-50%, and average rates up to 30-40% have been reported after RYGB, of which ca. 40% could be symptomatic.[90, 163]. Risk is increased after all types of MBS because of the period of rapid weight loss.

Key points – risk of cholelithiasis (gall stones)

- **Gallstones are prevalent in an obese population.**
- **During the period of rapid and substantial weight loss, the risk of gall stone formation is increased.**

5.4.3.4 Early dumping syndrome

Dumping or better 'early dumping syndrome' may occur after surgical procedures involving at least partial gastric resection or bypass, including RYGB and SG. The reported rates seem to be higher after RYGB, and are therefore might be more typical after this intervention, notwithstanding the fact that early dumping after SG might be more frequent than what is often percieved.[26, 168] Dumping syndrome is characterized by gastrointestinal symptoms (abdominal pain, diarrhoea, borborygmi, bloating and nausea) and vasomotor symptoms (flushing, palpitations, perspiration, tachycardia, hypotension, syncope).

Dumping is attributed to rapid gastric emptying or rapid exposure of the small intestine to nutrients. Symptoms are especially triggered after the ingestion of high levels of simple carbohydrates ('rapid sugars'). Early dumping presents within the first hour after a meal, often ≤15 minutes. On average 10-15% of patients report symptomatic early dumping symptoms, mostly after RYGB, however it also can occur after SG.[90, 163]. When more sensitive instruments like the Sigstad's scoring system are used, incidence rates are higher.[168] Symptoms are highest in the first 12 to 24 months after MBS. In most patients symptoms are self-limiting often resolving within 2-3 months with implementation of dietary measures (intake of smaller more frequent meals, avoidance of rapidly absorbed carbohydrates in favour of increased intake of dietary fibre, and postponing drinking to 30 minutes after meals).

Late postprandial reactive hypoglycaemia (previously called 'late dumping'), will be discussed in the chapter on metabolic and nutritional complications (cf. 5.4.4.1).

5.4.3.5 Chronic unexplained abdominal pain

After MBS up to 10% of patients report unexplained chronic abdominal pain that can be difficult to treat.[26] Expert questioning in the field confirm this. The issue is more prevalent after RYGB than after SG. Mild abdominal pain is reported by up to 95% of patients at some point in time after RYGB. Symptom severity varies from discomfort to severe cramping pain, nausea and vomiting.[26] Abdominal pain can be recurrent, and internal hernias occurring after RYGB should be considered since they can spontaneously reduce, causing intermittent pain. It can be expected that chronic (intermittent) abdominal pain may have a negative impact on QoL.[169]

5.4.3.6 Acute liver injury

Mechanical or thermic liver injury can occur and is mostly related to access, electrocoagulation devices and retractors used during surgery.

Although weight loss after bariatric surgery frequently induces an improvement of Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steato-Hepatitis (NASH) - even with a factor of possible regression of hepatic fibrosis when present - bariatric procedures have also been associated with rare cases of acute liver failure or of chronic liver disease evolving to cirrhosis.[170]

Most of these reports are historical and refer to older bariatric surgery techniques characterized by high malabsorption rates (like jejuno-ileal bypass), however there have also been reports mostly after biliopancreatic diversion with or without duodenal switch and more rarely after extended long-limb gastric bypass surgery. Cases of liver failure after LAGB and SG

should be very rare, as probably is the case after the nowadays performed 'classic' RYGB.[170] The possible underlying mechanism of this uncommon complication of liver failure is poorly understood. Very rapid weight loss, protein-calorie malnutrition, bacterial overgrowth, lipotoxicity (due to the release of large amounts of free fatty acids in the circulation), and genetic background are likely to play a central role in the physiopathology of hepatic injury. Concerning the 'phenotypic' expression of liver damage, there are two possible clinical patterns described: a rapid evolution to liver failure (within the first days) after surgery, and the development of a more 'insidious' form of chronic liver disease that may evolve into cirrhosis.[170]

Important to note in this context is that more and more patients with visceral obesity are diagnosed with significant or severe hepatic fibrosis or even cirrhosis as a result of end stage insidious fibrotic NASH. As such liver failure after surgery might have a link with pre-existing important liver disease (in a pre-cirrhotic stage). Reports of liver failure after SG or classic RYGB seem to occur very rarely, and in each case a differential diagnosis should be made with pre-existing liver disease, and/or other causes for concomitant liver disease after surgery (drug-related, alcohol, haemochromatosis, hepatitis B or C, etc.).[171]

Note however that the majority of literature data report improvements of NAFLD/NASH after contemporary MBS procedures such as RYGB and SG.

5.4.3.7 Other special GI adverse events of interest

Some rare less well known gastrointestinal AE that are reported in recent literature like e.g. case reports on phytobezoar formation or reports on achalasia and pseudo-achalasia, however these topics will not be further elaborated in this report giving the limited amount of literature reports available, and the safety review which is already very extensive.

Although data in general point to a lower risk of developing cancer after MBS (most prominently demonstrated for obesity related cancers), there is some controversy in recent literature as to whether MBS surgery might or might not be related to a higher risk for colorectal cancer.[172-177] Obesity related cancers include for instance cancer of the oesophagus, stomach, colon and rectum, breast, uterus and ovarium.[5] Some data in literature indicate a lower risk of colorectal cancer after MBS (as is the case for other obesity related cancers), while some other recent literature reports point to a potential increased risk of colorectal cancer. Moreover some of the controversy seem to focus on the RYGB procedure, with some hypothesis being made as to what concerns the potential underlying mechanism (presumed this risk is real). One of the hypothesis is that local mucosal changes can be induced secondary to the malabsorptive effects of the RYGB procedure potentially explaining an increased colorectal cancer risk, if present. One could speculate this could be due to increased mucosal bile salt exposure and/or changes in intestinal microbiota, which are both induced after gastric bypass surgery. However, all this remains speculative for several reasons such as e.g. that a potential increased risk observed in some observational research is contradicted by other studies showing a decreased risk, and where an increased risk is observed after MBS, no clear difference was found between different bariatric interventions.[174] This potential issue was identified lately during the HTA evaluation, and was not subject of more in depth research. As is clear from literature, the current data on this potential issue of increased risk for colorectal cancer are not conclusive, and will certainly be subject of further research being done in the field of MBS.

5.4.4 Metabolic and nutritional late AE

MBS involves major changes in anatomy and function of the GI-tract, and as such the intervention is not devoid of potential long-term late complications, such as LT-nutritional and metabolic effects or complications. Very often these late complications are less well quantified given the lack of good long-term data. In general they occur more frequently after purely malabsorptive and mixed restrictive/malabsorptive interventions, though some deficiencies and metabolic effects may also occur after purely restrictive interventions such as SG or a LAGB. As such their prevalence and nature may vary and depend on the type of MBS.

In addition many persons with obesity are already deficient in one or more vitamins, minerals or trace-elements before surgery.[168] Therefore, it is important to screen and if necessary correct deficiencies prior to surgery.[21, 178]

Also the fact whether or not a patient is fully compliant with postoperative dietary directives, or is poorly compliant, will clearly influence the prevalence and risk of nutritional deficiencies found after MBS. For all these reasons it is difficult to establish solid reliable prevalence rates.

Nutritional consequences may vary from micro-nutrient deficiencies (vitamins, minerals, trace elements), to macronutrient deficiencies and even to (rare) franc malnutrition. These deficiencies in turn, when not prevented, recognized and/or treated timely, may lead to other consequences or complications, such as haematological and neurological late adverse effects (cf. 5.4.5 and 5.4.6), some of which might not be fully reversible when not timely diagnosed and treated.

Metabolic changes and adverse effects may amongst other also encompass gall stone formation (cf. 5.4.3.3), increased risk for nephrolithiasis (due to hyperoxaluria) and may compromise bone health.

Losing too much lean mass (muscular mass) can occur in patients after MBS.[90] In these cases moderate to severe sarcopenia may develop, which is a status of a too low muscle mass.[179] The risk is especially high if there is not enough physical exercise and/or if protein intake is insufficient, and the risk will on average be higher in the elderly.

Note that fatigue is an often heard subjective and non-specific complaint after MBS (see 5.4.4.3). After MBS, many patients will ultimately feel more energetic, though others may express complaints of fatigue soon or later after surgery.

5.4.4.1 Late postprandial reactive hypoglycaemic syndrome (PPRHS), hypoglycaemia

The late postprandial (hypoglycaemic) reactive syndrome (PPRHS), (previously named 'late dumping') occurs between one and three hours after the meal and is characterized by (mild, moderate or franc) symptoms of hypoglycaemia. Associated symptoms may include perspiration, palpitations, hunger, weakness, confusion, tremor, syncope.

Late postprandial (hypoglycaemic) reactive syndrome is a consequence of the altered anatomy and food passage being a consequence of the MBS, and often arises when high content fast carbohydrate liquids or food is consumed. It shares this trigger with the 'early dumping symptoms' described above (5.4.3.4), however it also has a clear metabolic component and consequence as is apparent from inherent risk of hypoglycaemia.

Postprandial hypoglycaemia is a well-known and typical adverse effect of the RYGB, though it can also occur after SG.[26, 168]

The pathophysiology of postprandial hyper-reactive hypoglycaemia is not fully understood but likely includes alterations in multiple hormonal and glycaemic patterns (e.g. increase in incretin hormone levels), resulting in an exaggerated insulin secretion response, often triggered by the ingestion of rapidly absorbed carbohydrates. The incidence rates for symptomatic PPRHS are less than for early dumping, and is clearly more frequently reported after RYGB than after SG. Initial management consists again of the same dietary measures as for early dumping symptoms. If needed pharmacological therapy may provide relief, and very rarely, in case of rare therapy resistant important hypoglycaemia, the situation may require the 'undo' of the RYGB.

One important note is that hypoglycaemia as documented and defined after a modified oral glucose challenge test with 50g glucose is more prevalent than what is spontaneously reported based on the symptoms of 'late dumping'. Not all severe hypoglycaemic episodes are symptomatic (so that not all patients are aware of them).[180-182] Severe hypoglycaemia may be a possible underlying cause of falls and accidents.[94]

5.4.4.2 Vitamin and micronutrient deficiencies ('micronutrients')

The prevalence of vitamin and micronutrient deficiencies (grouped together as 'micro-nutrient' deficiency) is high after MBS, leading to potential serious adverse effects or complications. This kind of problems might arise after all types of metabolic and bariatric surgery, however the average risk varies in function of the type of intervention, with in rising order: lowest risk with the purely restrictive interventions (LAGB, SG), followed by mixed interventions like the classic RYGB, and highest with the purely malabsorptive interventions (BPD-DS, PBD or Scopinaro, and the gastro-jejunal

bypass…). Moreover the nature of the deficiencies may also vary according to the type of intervention.

Micronutrient deficiencies are typically categorized as late adverse events, but some can also present acutely and relatively shortly after intervention. Examples of the latter are Vit.B1 (thiamine) deficiency with potential serious and sometimes irreversible consequences (sometimes insidiously after restrictive interventions such as e.g. a SG followed by persistent vomiting).

Important to note is that the risk (prevalence and nature) of micronutrient deficiencies highly varies, and depends on other factors that modulate this risk, among others:

- Pre-existing deficiency of certain micronutrients (not corrected before intervention) will of course further increase the risk post-operatively. Examples are deficiencies in Vit.D, Fe, folic acid, Vit.B12, Vit.B1,Selenium (Se) etc.
- Unbalanced diet after the intervention
- Non- or suboptimal compliance with regard to the prescribed vitamin- and micronutrients supplements
- Poor compliance with regard to life-long medical monitoring and follow-up (important for early detection and correction of problems)

All these elements explain why it is difficult to find good reliable data in literature on the actual real prevalence of micro-nutrient deficiencies following surgery.

It is clear that the risk of micro-nutrient deficiencies seen after interventions like RYGB, SG and LAGB can be largely mitigated through strict compliance with life-long medical follow-up and correct intake of the recommended supplements. Note however that some patients still might develop micro-nutrient deficiencies despite the correct compliance with regard the intake of the recommended supplements.

Vit.D, Vit.B12 and iron (Fe) deficiencies are among the commonest deficiencies and are frequently encountered both after RYGB and SG. Folate deficiency is also frequent. Other deficiencies are more likely to occur with RYGB.

A meta-analysis by Kwon et al. evaluated the risk of Fe-deficiency, anaemia and Vit.B12 deficiency after SG vs. RYGB.[183] Only relevant studies with a follow-up >1 year were eligible. Of 36 potentially relevant studies, 9 met the inclusion criteria. This meta-analysis found an Odds ratio for the RYGB group vs. the SG of 3.55 (95%CI: 1.26-10.01) for postoperative Vit.B12 deficiency. When a subgroup with prophylactic Vit.B12 administration was analysed, the risk was still higher for the RYGB group, though this difference was no longer statistically significant. The OR for RYGB vs SG for the risk of anaemia and Fe-deficiency were greater for the RYGB group (and more pronounced in the group that received no prophylactic supplements vs. the group that received prophylactic supplements), though this increased OR did not reach statistical significance. The authors concluded that these results suggest that SG is more beneficial than RYGB with regard to postoperative Vit.B12 deficiency risk, whereas the two methods are comparable with regard to the risk of postoperative anaemia and Fe-deficiency. Based on the results of their MA, the authors recommended the postoperative use of Fe and Vit.B12 supplements in addition to the general multivitamin and mineral supplementation.

Another SR-MA was published by Weng et al. which evaluated the pre-existing prevalence and risk after surgery of anaemia and related nutritional deficiencies in patients undergoing RYGB.[184]. Articles with case numbers >100, follow-up period >12 months, and complete data from both before and after surgery were selected. Outcomes of interest were changes in baseline measurements of proportion of patients with anaemia, by haemoglobin, haematocrit, ferritin, iron, vitamin B12 and folate levels. Data from six prospective and nine retrospective studies with a total of 5909 patients were analysed. A random effect model with inverse variance weighting was used to calculate summary estimates of outcomes at 6, 12, 24 and 36 months postoperatively. Proportion of patients with anaemia was 12.2% at baseline, which, respectively, increased to 20.9% and 25.9% at 12 and 24 months follow-up, consistent with decreases in haemoglobin and haematocrit levels. Although the serum iron level did not change substantially after surgery, the frequency of patients with ferritin deficiency increased from 7.9% at baseline

to 13.4% and 23.0% at 12 and 24 months, respectively, post-operation. Vitamin B12 deficiency increased from 2.3% at baseline to 6.5% at 12 months after surgery in those subjects receiving RYGB. There was no obvious increase in folate deficiency. The authors conclude that RYGB surgery is associated with an increased risk of anaemia and deficiencies of iron and Vit.B12, but not folate.[184]

Vit.D deficiency is very prevalent before surgery, and compared to non-obese people, people with obesity are at higher risk (Vit.D is a fat soluble vitamin, stored in fat tissue, with a 'high distribution' volume in the obese). Vit.B12 needs intrinsic factor as a co-factor for intestinal absorption, a co-factor which is produced by the parietal cells of the stomach. Both SG and RYGB limit the production of and/or complexation with intrinsic factor. Iron (Fe) needs an acidic milieu for efficient absorption, which is decreased in patients after SG (due to resection of a large part of the gastric body) and in patients with RYGB (because ingested nutrients only are in contact with a small pouch of the stomach with low acidity, and in addition the duodenum is bypassed where in normal physiology most of the ingested Fe is absorbed). Also, many patients post LSG are chronically treated by PPIs, and subsequently present a highly reduced gastric acidity which further interferes with iron absorption.

Vitamin A, D, E and K are liposoluble vitamins and deficiencies in these vitamins may as such be more frequent after RYGB than after purely restrictive surgery because RYGB causes a relative malabsorption of fat.[185] Procedures with a malabsorptive component may alter to some or a larger extent the exposure of food to bile and pancreatic juices, as well as decrease the part of the small intestine that contributes to nutrient absorption.

Sites of micronutrient absorption within the GI-tract can be found in Table 21. A list of vitamins and deficiency syndrome can be found in Table 22.

Table 21 – Sites of micronutrient absorption within the gastrointestinal tract

Site of absorption	Micronutrients
Stomach	Copper, iodine
Duodenum	Iron, zinc, copper, selenium, vitamins A, E, and K, thiamin, riboflavin, folate, niacin, biotin, calcium
Jejunum	Zinc, selenium, iron, calcium, chromium, manganese, vitamins A, D, E, and K, thiamin, riboflavin, pyridoxine, folate, niacin, vitamin C, pantothenate
Ileum	Vitamins C, D, K, and B12, folate

Source: Shankar, P et al., 2010, Nutrition

Table 22 – Clinical symptoms of selected vitamin/micronutrient deficiencies

Vitamin / micro-nutrient	Key clinical manifestations of deficiency /deficiency syndrome	Procedure-related frequency	Additional risk factors	Pre-operative prevalence (rough risk estimate)	Post-operative prevalence (rough risk estimate)
Vit.B1 (thiamine)	Beri-beri; acute Wernicke's encephalopathy (and chronic Korsakoff syndrome), peripheral neuropathy, apathy, confusion, coma, nystagmus, ocular palsies, ataxia; nausea, vomiting, often triggered by IV-glucose administration in patients that are deficient; cardiac symptoms of congestive heart failure (wet Beri-beri)	SG+, RYGB+, BPD-DS+	pre-existing deficiency, persisted vomiting after intervention, excessive alcohol use, malnutrition	16-29% other source : 0-29% (mostly asymptomatic)[168]	1-49% other source: up to 30% (symptomatic)[168]
Vit.B6 (pyridoxine)	anaemia, weakness, insomnia, difficulty walking, nasolabial seborrheic dermatitis, cheilosis, stomatitis, peripheral neuropathy				
Folic acid **(Vit.B9)**	megaloblastic anaemia, (especially of consideration in women who become pregnant after MBS because of neural tube defects); additional symptoms might be loss of appetite, weight loss, weakness, sore tongue, headaches, irritability, and behavioural disorders		pre-existing deficiency ; reduced intake/absorption of raw vegetables	0-54%	Up to 65% after RYGB; 18% after SG other source: 9-38%[186]
Vit.B12 **(Cobalamin)**	megaloblastic anaemia (Pernicious anaemia), myelopathy, neuropathy	SG+, RYGB+(+), BPD-DS +++	l pre-existing deficiency; low meat intake, decreased acid production in the stomach, reduced	0-18%	33% after RYGB; 4-20% after SG other sources: - 4-62%[168]; - -the odds ratio for developing Vit12 deficiency after RYGB vs. SG has been at 3.55 (95%CI: 1.26-10.01)[183]

			availability of intrinsic factor		
Vit. ADEK (liposoluble vitamins)		more after RYGB+, and BPD-DS++			
Vit.A(1) **– Retinol or retinoic acid**	night blindness, xerophthalmia	idem		Up to 17%	8-11% after RYGB; 70% after BPD-DS
Vit.D **(cholecalciferol, ergocalciferol)**	skeletal health (osteopenia, osteoporosis, osteomalacia, secondary hyperparathyroidism, immune function, cancer prevention, cardiovascular health, influence on diabetes risk	idem; note however that this is also very prevalent in the general population, and especially in an obese population (high pre-surgery prevalence)	pre-existing deficiency	25-68%	25-80%
Vit.E (tocopherols)	symptomatic deficiency is uncommon; decrease in anti-oxidant capacity, anaemia, , peripheral sensory and motor neuropathy, ataxia, haemolytic anaemia, opthalmoplegia, retinal degeneration	idem		2.2%	Uncommon
Vit.K (phylloquinone, meaquinone, menadione)	affect clotting factors (bleeding tendency), possible effects on bone formation	idem		Uncommon	Uncommon
Calcium (Ca)	osteoporosis, muscular spasm (tetany), muscle weakness, paresthesia, arrhythmia, (hypocalcemia), secondary hyper-parathyroidia	BPD-DS ++, RYGB +, (SG)	pre-existing shortage, Hypovitaminose D, low dietary intake	1-10%	3.6% after MBS: 1.9% after RYGB, 9.3% after SG, 10% after BPD-DS
Iron (Fe)	microcytic anaemia, fatigue	SG ++, RYGB++ and BPD-DS +++	pre-existing shortage, GI-blood loss, menstruations+, low meat consumption, Cu-deficiency	0-58%	LAGB 14%, SG <18%, RYGB 20-55%, BPD 13-62%, BPD-DS 8-50%

Selenium (Se)	decrease in anti-oxidant capacity, cardiomyopathy and heart failure, muscle symptoms (weakness, cramps, myositis), loss of immunocompetence, thyroid dysfunction, fatigue, anemia, metabolic bone disease	RYGB +, BPD-DS ++		2%	14-22% after RYG and BPD-DS
Zinc (Zn)	dysgeusia, hair loss, impaired wound healing, glossitis, acrodermatitis enteropathica, nail dystrophy, diarrhoea, decrease immune response, intercurrent infection, emotional disorders, weight loss, bullous-pustular dermatitis, hypogonadism in men	RYGB +, BPD-DS ++ (SG)	pre-existing deficiency	24-28% overall; 9-74% seeking BPD-DS	70% after BPD-DS 40% after RYGB 19% after SG 34% after LAGB
Copper (Cu)	anaemia (microcytic), leucopenia, and neurological signs (neuropathy, myelopathy, ataxia) impaired wound healing, cardiac problems (Mitral valve prolapse)		too high intake of Zn	68% in women seeking BPD	90% after BPD-DS, 10-20% after RYGB

Adapted from UpToDate.com - [187]; Sources: Kushner et al., 2018[187] and Tack et al., 2014[168];
Note: the mentioned prevalence estimates should be read as 'indicative'

Most vitamin/micronutrient deficiencies develop insidiously and often only become apparent (clinically or in lab-analysis) 6 months or longer after MBS. Most vitamin deficiencies have 'reversible' consequences, while others may rarely lead to permanent damage or complications.

Some deficiencies may occur unexpectedly and sometimes surprisingly rapidly after surgery (even within <1 month or less) with acute possible devastating consequences like e.g. Wernicke encephalopathy and Korsakoff dementia and psychosis (Vit.B1 or thiamine deficiency). Vit.B1 deficiency (Beri-beri) can also be a cause of heart failure (wet Beri-beri).

Vigilance is required when patients are at risk of thiamine (Vit.B1) deficiency, electrolyte imbalances or dehydration, for instance when there is protracted vomiting after surgery with inadequate dietary intake and rapid weight loss. Important electrolyte disorders including potassium imbalances, especially hypo-kaliema, may lead to important potentially life-threatening cardiac arrhythmias.

Acute Wernicke's encephalopathy (due to Vit.B1 deficiency) typically presents with opthalmoplegia, ataxia, and mental alterations. If not recognized and treated promptly this may lead to Korsakoff's syndrome. Korsakoff's syndrome may also develop chronically and lead to dementia,

short-term memory failure (with confabulation) and apathetic mental confusion (Korsakoff's psychosis).

Other deficiencies like Vit.B12 and Cu deficiency might lead to haematological and neurological complications. Anaemia, leucopenia, thrombocytopenia are essentially reversible, though neurological syndromes are not always reversible.

Deficiency in folic acid may lead to megaloblastic anaemia (reversible), though the higher risk of folic acid deficiency after MBS mighty especially be very relevant for women wanting to become pregnant, as folic acid deficiency increases the risk of neural tube defects in their foetuses.

Vitamin A deficiency may result in xerophthalmia, retinopathy and night blindness. Since Vit.A is liposoluble, deficiency is a result of fat-mal absorption after malabsorptive interventions.

Vit.D plays an important role in bone health, however a part from bone health, severe hypo-vitaminosis D may cause chronic fatigue, muscle weakness and may have other consequences (like. e.g. increased risk of diabetes, effects on immune system).

Selenium deficiencies are frequent, also before MBS, and deficiencies have been reported in 14-22% of post-bariatric surgery patients.[186] Clinical manifestations may include cardiomyopathy and heart failure, muscle symptoms (weakness, cramps, myositis), loss of immune-competence, thyroid dysfunction, fatigue, metabolic bone disease and lower anti-oxidant capacity.

Zinc deficiency is prevalent before MBS (up to 30% of obese patients prior to surgery), and some reports suggest that incidence might increase with 6% per year after MBS.[168, 188] Zn deficiency may lead to hair loss, diarrhoea, poor wound healing, alteration of taste, alteration of immune response, bullous-pustular dermatitis, enteropathica-like acrodermatitis, nail dystrophy, emotional disorder, and possible sexual dysfunction in men.[189, 190]

For more information regarding the prevalence rates (pre- and post-surgery), risk factors and pathophysiology, clinical symptoms and consequences, and management of micronutrient deficiencies, readers are referred to specific literature on the topic.[21, 26, 168, 183, 186, 188-197]. Additional information is also available on UpToDate by Kushner et al.[187]

Some attention should be given to the possible toxicity of vitamin B6 (pyridoxin) and zinc when given higher amounts than needed. Vit.B6 intoxication may lead to neuropathy and a too high intake of zinc may lead to copper deficiency which may be cause of neurological and haematological complications.[168, 198]

Taken together the following vitamin-and micro-deficiencies which deserve most attention through routine screening and/or clinical alertness are:

- Vit.B12, Fe (iron), VitD.
- Folic acid
- Calcium (Ca-metabolism related parameters)
- Vit.B1
- Vit.A
- Selenium
- Zinc

Key points – Risk of vitamin and micronutrient deficiencies

- **The prevalence of vitamin and micronutrient deficiencies is high after MBS, which may lead to potential serious adverse effects or complications.**
- **The average risk varies in function of the type of intervention, with in rising order: lowest risk with the purely restrictive interventions (LAGB, SG), followed by mixed interventions (classic RYGB), and highest with the purely malabsorptive interventions (BPD-DS, PBD or Scopinaro, and the gastro-**

jejunal bypass).
The nature of the deficiencies may also vary according to the type of intervention.

- **Pre-existing deficiencies (prior to MBS) are frequent, and when not corrected, will further increase the risk post-MBS.**
- **Vit.D, Vit.B12 and iron (Fe) deficiencies are among the commonest deficiencies and are frequently encountered both after RYGB and SG. Folate deficiency is also frequent. Other deficiencies are on average more likely to occur with RYGB (and certainly even more with the more 'drastic' malabsorptive interventions).**
- **Most vitamin/micronutrient deficiencies develop insidiously and often only become apparent (clinically or in lab-analysis) 6 months or longer after MBS.**
- **Most vitamin deficiencies have 'reversible' consequences, while others may rarely lead to permanent damage or complications.**
- **Some deficiencies may occur unexpectedly and sometimes surprisingly rapidly after surgery with acute possible devastating consequences like e.g. Wernicke encephalopathy or acute congestive heart failure (wet Beri-beri).**
- **It is likely that the risk of micro-nutrient deficiencies can be largely mitigated through strict compliance with life-long medical follow-up and correct intake of the recommended supplements.**

5.4.4.3 Fatigue

Fatigue is an often heard subjective and non-specific complaint after MBS. A confounding factor is that fatigue is a frequent problem in the general population as well. Fatigue is a problem which may have numerous possible causes. After MBS, many patients will ultimately feel more energetic, though others do express complaints of fatigue soon or later after surgery.

Fatigue is often reported, especially during the initial period of rapid substantial weight loss following the surgical intervention, a period which is characterized by a 'catabolic' state.

Therefore patients need to respect the dietary instructions with regard to correct protein and caloric intake, and invest in sufficient exercise, in order to prevent or limit excessive loss of muscle mass and strength. Correct compliance with regard to the recommended intake of vitamin/micronutrient supplements is important as several vitamin/micro-nutrient deficiencies clearly also may be a cause of fatigue (such as e.g. Fe, severe vit.D deficiency, Vit.B12 deficiency, folic acid…). Another frequent cause of fatigue is sugar intake, and concomitant subsequent hypoglycaemia. In the absence of vitamin depletion, chronic hypoglycaemia related to dietary flaws must be ruled out (expert input).

Quantification of fatigue as a possible direct consequence of MBS is not possible, but the above mentioned considerations with regard to fatigue are important as clinical points for attention.

5.4.4.4 Malnutrition, with focus on protein malnutrition AND the risk of decrease in muscle mass and strength

Albeit less frequent than micro-nutrient deficiencies, macro-nutrient deficiencies resulting in malnutrition may occur after MBS, where the risk increases from purely restrictive interventions, to interventions with an important malabsorptive contribution, to purely malabsorptive interventions. Among macro-nutrient complications, protein malnutrition is the most severe complication. Protein malnutrition is defined by hypo-albuminemia (e.g. serum albumin <3.5 mg/dL) in the absence of other causes of protein loss (like e.g. nephrotic syndrome). Some papers report the condition in 13% of

patients two years after a 'distal' RYGB with a Roux-limb of ≥150 cm, in 3-18% of patients after BPD, and up to 5% in patients with classic RYGB.[194] When it occurs, protein malnutrition is usually observed at 3-6 months after MBS and is largely attributed to the development of food intolerance to protein rich foods and overall decreased food intake (not accompanied by a relative increased contribution of protein intake as percentage of overall food intake). Protein malnutrition may cause an annual hospitalization rate of 1% per year after purely malabsorptive MBS.[191]

A part from franc protein malnutrition, it is also important that there is a particular focus of attention on the prevention and early diagnosis and management of loss of muscle mass (called sarcopenia) and strength. Due to phenomena of unloading and decreased protein intake, there is an increased risk of loss of muscle mass and function. As food intake decreases post-surgery, and if patients are still consuming the same relative proportion of proteins, the total absolute intake of proteins may be too low. In the first months to 1.5 year after surgery, the patient may be in a 'catabolic' state, and when there is insufficient protein-intake, and/or not enough physical exercise, this might lead to a loss of muscle mass, strength and physical weakness. Prevention by consumption of food that is relatively protein-rich, and by sufficient muscular exercise and training is key. Taking a correct diet and implementation of sufficient physical exercise is important.[21]

In rare circumstances malnutrition might be that severe that (home) parenteral nutrition is indicated.[199]

5.4.4.5 *Effect on bone health*

One of the possible and best known long-term metabolic consequences of hypovitaminosis D are effects on bone health (risk of osteopenia, osteoporosis). Risk of Vit.D hypovitaminosis and insufficient Ca intake/absorption are high after RYGB but both problems are also very prevalent after SG (especially for hypovitaminosis D). Reports in literature on the effects on bone loss and fractures are variable, from no significant effect to reports of an increased rate of bone loss (based on BMD measurements and/or bone turnover markers) as well as an increased risk of fractures (MBS vs. no surgery, and mixed or mal-absorption MBS vs. restrictive MBS).

Severe Vit.D deficiency and/or a severe long-lasting negative calcium balance will lead to osteopenia and osteoporosis which might be a cause of osteoporotic fractures of the hip, lumber spine or wrist. Vit.D hypo-vitaminosis might result in secondary hyperparathyroidism, which if long-lasting may become 'permanent' tertiary hyperparathyroidism (autonomous hypersecretion of parathyroid hormone by the parathyroid glands), again a cause of osteoporosis and fractures

Note also that part of the initial bone loss following surgery might also be explained by 'weight-unloading' of the skeleton.

A SR-MA by Kalani et al. looked at the effect of barariatric surgery (RYGB, biliopancreatic diversion with or without duodenal switch) on 25-OH-vitamine D levels as a primary outcome, compared to non-surgical controls with obesity.[200] A total of 7 trials were eligible for inclusion and included 4282 bariatric surgical patients and 15 630 controls. For the meta-analysis a random effects model was implemented. The primary outcome examined was the change in 25-OH-D levels at 12 months post-surgery, and secondary outcomes included among others change in bone mineral density (BMD) measurements at 12 months post-surgery at the lumbar spine (LS) and total hip (TH). Data for Vit.D and BMD were also evaluated at 24 months, as was the incidence of self-reported fractures (any site) per patient at 24 month. The authors evaluated the risk of bias (RoB) for the 2 RCTs by the Cochrane Collaboration's tool for RoB and for the 5 controlled observation studies by the Newcastle Ottawa Scale. They evaluated the overall RoB as low with neither the RCTs nor the included observational studies being assigned a high RoB. The authors however did not describe how well the bariatric population matched with the non-surgical controls with obesity. At 12 months, there was no significant difference in 25-OH vitamin D in the surgical group compared to controls (weighted mean difference or WMD = 6.79%; 95% CI: -9.01, 22.59; p = 0.40; I^2 = 68%). A significant BMD reduction was however shown at the total hip (WMD, -7.33%, 95% CI = -8.70 to -5.97, p <.001, I^2 = 0%), and a trend towards decline was observed at the lumbar spine (WMD, -1.73%, 95% CI = -3.56 to 0.11, p = 0.06, I^2 =

0%). Changes at 24 months for applicable outcomes were similar to the results at 12 months. There was however a nearly statistically significant difference between fracture risk in the surgical population compared to controls (RR = 1.24; 95% CI: 0.99-1.56; *p = 0.06*; I^2 = 0%) at 2 years. Notwithstanding the fact that there has been inconsistency on the measure of self-reported fractures across studies (as some studies required radiographic confirmation and others not) and as there very likely might have been some under-reporting of fractures, this almost significant increase in the risk of fractures at 2 years after surgery, might be worrying because of possible underreporting, and because these data on fracture are only two year data, not providing data on the longer term. The authors of the article conclude that bariatric surgery may compromise metabolic bone health, but the paucity of high-quality literature limits conclusions.[200]

Another MA on the effects of MBS on fracture risk by Zang et al. found that the risk of any type of fracture was higher in the surgical group than in the non-surgical group (risk ratio [RR] 1.29, 95% confidence interval [CI] 1.18–1.42). After surgery, the fracture risk in non-vertebral sites was significantly increased, especially in the upper limbs (RR 1.42, 95% CI 1.08–1.87; and RR 1.68, 95% CI 1.15–2.45). Compared with those with restrictive procedures, subjects who underwent mixed restrictive and malabsorptive procedures tended to have an increased fracture risk (RR 1.54, 95% CI 0.96–2.46). The authors stated the all the included studies in the meta-analysis (1 RCT and 5 observational studies) were of high quality. The authors concluded that MBS is associated with an increased risk of total and non-vertebral fractures, especially in the upper limbs. Besides it seems that he reported risk of bone loss and increased risk of fractures may be more pronounced with malabsorptive interventions compared to purely restrictive interventions.[201]

In general it is difficult to observe and predict, from literature data, reliably the real-life risk of bone loss and osteoporotic fracture risk, as this risk depends on many variables (like pre-exiting deficiencies, correct intake of Vit.D and Ca supplements, the population studied, the type of bariatric procedure performed, etc.). Special clinical attention will be required in populations already at increased risk for osteoporosis.

For more information on the influence of MBS on bone metabolism and the risk of metabolic bone diseases, readers are referred to specific literature on the topic.[202-208]

5.4.4.6 Cholelithiasis (gall stone formation)

The increased risk of gall stone formation has been discussed in section 5.4.3.3.

5.4.4.7 Nephrolithiasis (kidney stones)

Bariatric surgery may increase the risk of hyperoxaluria, oxalate nephrolithiasis and oxalate nephropathy.

The risk is higher in patients with a history of nephrolithiasis, and in general the risk is higher after malabsorptive interventions than after purely restrictive interventions. Malabsorptive procedures may lead to malabsorption of bile acids and/or fatty acids. When fat is mal absorbed, Ca ions are saponified by intraluminal free fatty acids, subsequently leading to an increased free intestinal oxalate load, leading to a higher gut absorption. Besides, permeability of the GI tract to oxalate can be increased by exposure of unconjugated bile salts and long chain fatty acids. After absorption the majority of oxalate must be eliminated by the kidney, and under predisposing conditions, this oxalate may precipitate with urinary calcium to form insoluble Ca-oxalate complexes and eventually kidney stones. Other factors may increase this lithogenic risk.[209]

The MBS with the highest risk is the jejuno-ileal bypass, a procedure which has become obsolete due to unacceptable rates of complications. Although modern MBS are associated with lower risk, two- to threefold increases in urinary oxalate levels have been reported after RYGB.

In a retrospective matched case-control study of patients undergoing MBS (78% of whom underwent RYGB) the risk of kidney stones was more than double of the risk in the control group. Over a 6 year FU period new stone formation was 11% in the surgery group vs. 4.3% in the control group, whereas their risk at baseline was similar.[210] Those patients undergoing purely malabsorptive surgery had the highest relative risk (comorbidity

adjusted HR of 4.15, significant) vs. obese controls, whilst the standard RYGB had in intermediate risk (comorbidity adjusted HR of 2.13, significant). The risk of nephrolithiasis was not significantly changed for purely restrictive procedures. On average, patients with a history of prior nephrolithiasis were more at risk to form a new nephrolithiasis than those without a prior stone history (42% vs 14% at 10 years, HR=4.1, significant).[210]

A literature review by Canales et al., identified 24 eligible studies containing 6777 bariatric patients with kidney stone incidence, and 7089 non-stone forming controls. Of all MBS procedures, only RYGB was linked to post-operative kidney stone development, where stone incidence was increased two-fold in people with no prior history of nephrolithiasis (incidence of 8.5%), and four-fold in patients with previous stone history (incidence of 16.7%).[209] Urine analysis in a subset of 686 patients with 24h-urinary profiles, showed among others a 50% increase in urinary oxalate. Restrictive procedures and obese controls reported stone incidence rates from 1.3-4.7% during a similar 2 year time-frame.

A SR and meta-analysis by Thongpryoon et al., based on 4 eligible studies which reported RR, OR or HR on risk of kidney stone formation comparing bariatric surgery vs. no surgery (1 RCT and 3 cohort studies; 11 348 patients in analysis), resulted in a pooled RR of 1.22 (95%CI: 0.63-2.35, NS) for those undergoing MBS vs. those not undergoing surgery. The type of bariatric surgery subgroup analysis demonstrated an increased risk in patients undergoing RYGB with a pooled RR of 1.73 (95%CI: 1.30-2.30) and a decreased risk of kidney stones in patients that underwent restrictive procedures (including LAGB and SG), with a pooled RR of 0.37 (95%CI: 0.16-0.85).[211] The authors conclude that there is an association between RYGB and increased risk of nephrolithiasis, and that restrictive bariatric surgery on the other hand may decrease this risk, though that future studies with long-term follow-up are needed to confirm this potential benefit of restrictive bariatric surgery.

Another MA of 2015 by Upala et al. only published in abstract format, and based on a meta-analysis of observational studies of post-bariatric surgery and urinary tract stones and urinary stone chemistry profiles (10 270 patients included in the analysis) showed a pooled RR of 1.53 (95%CI: 0.26-9.16, NS) for urinary tract stone formation, and a significant increase in urinary oxalate concentration.[212]

Taken together, these data suggest that RYGB (and malabsorptive interventions in general), increases the risk of kidney stone formation, especially in patients with a history of nefrolithiasis.

Key points – Nephrolithiasis risk (kidney stone formation

- **Bariatric surgery may increase the risk of hyperoxaluria, oxalate nephrolithiasis and oxalate nephropathy.**
- **The risk of kidney stones is mostly present for RYGB where stone incidence may be increased by ca. a two-fold in people with no prior history of nephrolithiasis, and by ca. a four-fold in patients with previous stone history.**

5.4.5 Haematological late AE

Haematological consequences (microcytic and megaloblastic anaemia, leucopenia and prolonged bleeding time) can be a result of deficiencies in Fe, Vit.B12, folic acid, Cu, Se and/or Vit.K. Once treated correctly they are essentially reversible.

Fe-deficiency may be a result of low intake, low absorption, and/or chronic blood loss. The consequence may vary from slight to moderate microcytic anaemia to franc and severe anaemia sometimes requiring intravenous administration of Fe (via day-care clinic) or even blood transfusion.

Vit.B12 and folic acid deficiency may (apart from neurological symptoms) lead to slight or moderate chronic megaloblastic anaemia. Anaemia may also be a consequence of combined deficiencies in iron, Vit.B12 and/or folic acid deficiency.

Although copper deficiency is relatively uncommon, it might be a cause of anaemia and leucopenia. In addition it may cause important neurological problems (see 5.4.6).

Severe Vit.K deficiency (a liposoluble vitamin), which could be seen in case of fat-malabsorption as a consequence of malabsorptive interventions, may impair haemostasis through deficiency in certain coagulation-cascade factors.

Table 22 include most of the haematological symptoms or complications that are linked to micronutrient deficiencies (cf. 5.4.4.2).

5.4.6 Neurological late AE

Long-term neurological complications are mostly consequences of vitamin or mineral deficiencies like e.g. of Vit.B1, Vit.B12, folic acid, Cu. If not recognized and treated correctly they can leave the patient with irreversible consequences.

There are no systematic reviews and meta-analysis available describing and quantifying the risk of the neurological complications. Moreover the risk will vary substantially with the quality of the medical follow-up and monitoring and correct intake of the recommended micronutrient supplements.

Vit.B1 has important roles that regulate the heart, the GI tract, and the peripheral and central nervous system. Vit.B1 levels cannot be routinely measured via standard laboratory testing. Vit.B1 insufficiency probably is prevalent but under-recognized before MBS (because often asymptomatic). Vit.B1 deficiency can present with acute or chronic symptoms and consequences like e.g. Wernicke's encephalopathy, Korsakoff's syndrome and psychosis. Alcoholism increases the risk of Vit.B1 deficiency. Wernicke's encephalopathy might be easily triggered when glucose containing infusions or oral administration is not accompanied by sufficient Vit.B1 administration when there is a deficiency for this vitamin.

Vit.B12 deficiency may cause symptoms as tingling and numbness (paresthesia), ataxia, irreversible neuropathy and myelopathy, mood changes, and memory problems.

Folic acid deficiency can cause tiredness, weakness, and neural tube defects in foetuses of pregnant post-bariatric women. Copper deficiency can cause myelopathy, peripheral neuropathy, optic neuropathy (and myopathy) as well. Table 22 include most of the neurological symptoms or complications that are linked to micronutrient deficiencies (cf. 5.4.4.2).

5.4.7 Alcohol- and substance use disorder

5.4.7.1 Context

In recent years there has been an increase in literature reports pointing to an increased risk of alcohol use disorder and other substance use disorders post-bariatric surgery patients which deserves attention.

5.4.7.2 Alcohol use disorder (AUD)

Alcohol use disorder (AUD) is frequent in the general population with even higher prevalence rates of alcohol and other substance/drug use disorders being described in potential candidates for MBS, especially in those with (a history) of an eating disorder. Note that in general, people evaluated for MBS are (in Belgium) also seen by a clinical psychologist or psychiatrist and those with an active AUD ought to be contra-indicated.

Patients with obesity are at higher risk than the average population for 'food-addiction', addiction to sugar/fat and emotional 'binge eating', as a reward in response to emotional stress, and as such it has been suggested that some patients having undergone MBS might unconsciously search to replace one type of addiction with another type of emotional reward or addiction ('addiction transfer'). However the topic is more complex than this. It seems that the risk for AUD increases only as from ≥2 years after surgery, and seems to be limited mostly to gastric bypass surgery. So the theory of 'addiction transfer' as a valid or the only explanation is flawed and incomplete.

Risk factors identified in literature indicative for the development of post-operative AUD are: male gender, relatively young age at moment of surgery, smoking, regular alcohol use, AUD in history, use of recreational substances, and poor social network/support.[213-215] Reports of increased risk for AUD after MBS (de novo AUD and relapse after previous AUD) have been essentially reported after RYGB, while this risk has not been clearly

identified after LAGB or SG. A SR-MA by Azam et al. and a narrative review by Marien et al. have recently published in 2018 on the topic.[215, 216]. See infra.

The first reports date from almost 10 years ago.[217] This was confirmed in a prospective longitudinal study in 1945 patients that underwent MBS.[214] For all interventions combined the authors found that the prevalence was significantly higher as from the second year postoperatively (9.6%) vs. 1 year pre-operatively (7.6%), with no clear increase in the first year after the intervention. The adjusted odd rates (with LAGB as the reference group) was 2.07 (95%CI: 1.40-3.08) for the RYGB.

Svensson et al. reported in 2013, based on the important large prospective matched cohort SOS study, data on alcohol abuse diagnoses and self-reported alcohol consumption.[213] The SOS study enrolled 2010 obese patients who underwent bariatric surgery (68% vertical banded gastroplasty (VBG), 19% banding, and 13% gastric bypass) and 2037 matched controls. Patients were recruited between 1987 and 2001. Data on alcohol abuse diagnoses, self-reported alcohol consumption, and alcohol problems were obtained from the National Patient Register and questionnaires. Follow-up time was 8-22 years. During follow-up, 93.1% of the surgery patients and 96.0% of the controls reported alcohol consumption classified as low risk by the World Health Organization (WHO). However, compared to controls, the gastric bypass group had increased risk of alcohol abuse diagnoses (adjusted hazard ratio [adjHR] 4.97), alcohol consumption at least at the WHO medium risk level (adjHR=2.69), and alcohol problems (adjHR=5.91). Vertical banded gastroplasty (VBG) increased the risk of these conditions with adjHR's of 2.23, 1.52, and 2.30, respectively, while classic gastric banding was not different from controls. Alcohol consumption, alcohol problems, and alcohol abuse are increased after gastric bypass and VBG. The largest increase was seen after gastric bypass. The VBG has now become an obsolete procedure.

Data derived from a large US observational study on RYGB (LABS-2 study) and based on retrospective sub-group analysis (for reasons of complexity of assessments and financial limitations, the target limit was set at 300 patients in this sub-project), showed that in the 201 patients, who gave consent and provided data, 8% developed AUD during the first three years of follow-up, of whom 44% had no history of AUD.[218] The data collected were based on Structured Clinical Interviews for DSM-IV Axis I disorders, additional impulsive Control Disorder Modules, and various self-report measures, including the Alcohol Use Disorder Identification Test. Data on other behavioural addictive disorders indicated that 10% had a post-surgery disorder, of whom 32% had no history, however the authors conclude that for the understanding of these non-drug related addictive disorders more data are required from larger studies before conclusions can be drawn.[218]

The SR-MA by Azam et al. included 10 eligible studies measuring or reporting AUD before and after surgery.[216]. The main comparison was the prevalence of AUD after surgery vs. pre-surgery. The authors found no increase of AUD during the first two years following surgery, but found an increase three years post-operatively (pooled OR of 1.825 (95%CI: 1.53-2.178; p<0.004). Looking at individual underlying studies, the increased risk was present after gastric bypass surgery, but not after gastric banding. Evidence was mostly limited to cross-sectional prevalence data, rather than time-to-event or incidence data, which limits applicability of the results. Definition of AUD varied also from study to study, and other variables - like type of bariatric procedure, surgeon's skill and intervention volume - could not be accounted for. The majority of the included studies did not have a true control group, and therefore the authors could not fully exclude the possibility that AUD in these patient groups would have increased independently from bariatric surgery.

Obviously for the same quantity of alcohol intake, a decreased body weight will lead to a higher amount of alcohol per kg bodyweight, however even after correction for this, a faster alcohol absorption (shorter Tmax) and higher alcohol peak concentration (Cmax) was found in patients after RYGB.[219] In addition it also takes longer before the alcohol was completely eliminated from the body.[102, 220, 221] The changed anatomy created by the RYGB seems to be the most important explanation for the change in PK. The most important enzymes for alcohol metabolism are located in the liver and to a lesser extent in the small intestine and the stomach. After RYGB, ingested alcohol passes by only a small part/pouch of the stomach implying that only a small part of the stomach can contribute to the degradation of

alcohol, and subsequently after having bypassed the duodenum, it arrives further on in the small intestine where the ingested alcohol saturates the capacity of the alcohol-degrading enzymes leading to higher concentrations of absorbed alcohol in the portal circulation. The portal circulation takes the alcohol to the liver where alcohol degrading capacity might/will be exceeded leading to a faster and higher increases of alcohol concentration in the blood (systemic circulation). Men have higher liver alcohol degrading capacity than women, explaining why the effect of RYGB on changed alcohol PKs might be more pronounced in women.[215]. An increased 'exposure' to alcohol (due to more rapidly obtained and higher peak concentrations, plus a longer exposure due to a slower elimination of alcohol) for the same amount of alcohol ingested might (at least partially) explain why the risk of AUD could increase post-RYGB.[215]

A part from changes in alcohol PK after RYGB, other possible explanations have been advanced or suggested (like e.g. change in intestinal hormones or a shift/transfer from food to alcohol addiction) which however never have been proven. If a shift/transfer of addiction plays an important role, one would expect to observe a similar increased risk in alcohol use disorder both in patients after SG and RYGB bypass which is not the case.

Data on alcohol concentrations in patients after SG have been controversial. In these patients the stomach capacity and mucosal surface are reduced, however in the absence of a duodenal bypass the influence on alcohol absorption is likely to be less pronounced. One study found for the SG a difference between preoperative and postoperative Cmax and a longer time before complete alcohol clearance (disappearance from the body), however these findings could not be confirmed in another study.[222, 223]

Note that although most of the recent literature indicates a higher risk for AUD after RYGB, there still remains some controversy on the subject, as one study showed a decrease in alcohol ingestion in more than 50% of the patients with pre-exiting AUD during the first 2 years post-operatively, both in a group after RYGB and gastric banding.[224] Another studies showed no significant difference in alcohol drinking behaviour (pre- vs. post-operatively) after gastric banding or RYGB.[225]. However in both studies (Wee et al., Burgos et al.) follow-up was limited to 2 years, while other data indicate that the risk of AUD after RYGB only becomes apparent during follow-up periods exceeding 2 years. An important consideration and limiting factor in the objectification of alcohol abuse is the question method being used and the different scoring systems or questionnaires being used.

Taking all elements together, it seems as that the RYGB/gastric bypass probably increases the risk of AUD, especially in the period 2 years beyond surgery.

Also symptoms of alcohol intoxication may change after RYGB. Patients might sweat less and have less flushing, but might experience on the other hand more rapidly symptoms of dizziness, hot feeling and double vision.[215]

As AUD is prevalent in the general population and seems to be even more prevalent in obese subjects, a clear clinical point for attention is that candidates for bariatric surgery should be thoroughly screened for a history of, or for an active alcohol use disorder. Active alcohol use disorder is a contra-indication for MBS. Patients will need to be informed of the risk of AUD after MBS, especially after RYGB, the increased sensitivity to alcohol and the possible changed symptoms of alcohol intoxication.[215] They should also be aware that smaller amounts of alcohol could lead to faster and higher increases of blood alcohol concentrations with longer elimination time, which may have implications when driving a car, operating machines, or performing more complex tasks.

5.4.7.3 Other substance use disorders: focus on opioid use

Many candidates for MBS suffer from emotional problems and/or disordered eating behaviour, and a subset may suffer from 'food addiction' or binge eating disorder. In addition a considerable number of patients appear to use, on a chronic or intermittent basis, anxiolytics and pain killers, and some of them even may have evidence of some level of addiction. Moreover one type of 'addiction' like e.g. 'food addiction' might possibly lead to cross-addiction, and following surgery there might be a risk that one 'addiction' is replaced by another type of addiction.

Apart from the above described risk of AUD (mostly increased after RYGB >2 years after surgery), other types of substance use disorders have been

described in literature, in particular the risk of new (or recurrent) opioid use, and possibly analgesia medication in general.

Literature reports (mostly reports coming from the US) point to a possible increased risk of opioid use after MBS, especially in patients with a history of previous inappropriate opioid use, but an increased risk also seems to exist for patients without a history of pre-operative opioid use.[226-230] Risk factors encountered in literature that may entail a higher risk for post-operative opioid use are younge age, male gender, nicotine use, AUD and previous use of opioids analgesics. Other preoperative risk factors might be mood disorders, anxiety, preoperative pain disorders, and a history of previous hospitalisations for psychiatric disorders.[226, 227, 231]

One US multicentre observational cohort study (LABS-2) based on 2218 patients with eligible data (for this analysis) reported pre-surgery use of opioids in 14.7% (95%CI: 13.3-16.2) of the patients.[227] Usage was lower at 6 months post-surgery (12.9%, 95%CI: 11.-14.4%), but increased to 20.3% (95%CI: 18.2-22.5) at year seven. Among those without baseline opioid use, opioid use was 5.8% (95%CI: 4.7-6.9) at six months and increased to 14.2% (95%CI: 12.2-16.3) at year seven. In this study 71% underwent RYGB, 25% LAGB, and 4% underwent another procedure. Surgical procedure type was not significantly related to risk of new or continued opioid use after surgery, but more pain at baseline, worsening or less improvement of pain after surgery, and need for non-opioid analgesic use increased the risk for new or continued use of opioids.[227]

A retrospective cohort study across nine US health systems based on 10 643 patients undergoing MBS who did not use opioids on a chronic basis preoperatively, reported that overall 4% of them became chronic users 1 year after surgery.[226] The main outcome was chronic opioid use during the year post-surgery (excluding 30 post-operative days) defined as ≥10 dispensings over 90 days or ≥120 total days' supply. Pre-surgery opioid total day's supply was strongly associated with chronic use post-operatively: 1-29 days provides an adjusted OR of 1.89 (95%CI, 1.24-2.88); and 90-119 days provides an OR of 14.29 (95%CI, 6.94-29.42) for each compared with no days. Other factors associated with an increased likelihood of post-surgery chronic use included pre-surgery use of non-opioid analgesics, anti-anxiety medications, smoking and younger age. Several types of bariatric surgery were applied (among them 15.4% with LAGB and 65% with laparoscopic RYGB, the number of those with SG was only 2%). In contrast to the study by King et al., Raebel et al. reported a lower risk for chronic opioid use in those undergoing LAGB vs. those undergoing lap-RYGB: OR 0.42 (95%CI:0.25-0.7).[226, 227]

Interpretation of long-term use of opioids after different bariatric surgery types should be interpreted with caution as data are conflicting. On the other hand short-term post-operative use might be higher for procedures that are more invasive (like BPD-DS, vs. RYGG, vs LAGB).

Note that most of the data stem from the US, where opioid misuse in general may be more prevalent that in other regions.

Key points – Risk of Alcohol use disorder (AUD) and opioid use disorder

- **In general literature points to in increased risk of AUD. The risk seems to be mostly or essentially present after RYGB, and not (or to a far lesser extent) after SG or LAGB. The risk seems to increase especially as from beyond year 2 after MBS.**
- **The risk is higher in patients with a history of AUD before MBS. The risk of AUD might also be higher in males, relatively young age at moment of surgery, smoking, regular alcohol use, use of recreational substances, and poor social network/support, etc. Active AUD is in principal, a contra-indication for MBS.**
- **Apart from the higher risk for AUD after gastric bypass surgery, also the sensitivity for alcohol may be increased. This may for a large extent have a biological pharmacokinetic explanation. Alcohol is more rapidly absorbed, peak concentrations are higher and peaks are more rapidly reached. Also alcohol elimination time seems to be longer. The higher sensitivity for alcohol and alcohol intoxication after gastric bypass surgery is more pronounced in women than in men. Symptoms of alcohol**

intoxication might also change after gastric bypass surgery. This has implications when it comes to driving, alcohol testing, operating machines, or performing more complex tasks.

- **The risk of opioid use and opioid use disorder might also change. The risk for opioid use may be induced by early postoperative opioid pain management, especially in the presence of a history of previous opioid use/abuse**

5.4.8 Psychiatric adverse effects and psychological well being (LT)

5.4.8.1 Context and general overview

Psychiatric conditions or co-morbidities are frequent in the general population, and they are even more prevalent in obese subjects and this certainly also in those who are candidates for MBS.[21, 232-237]

Many obese subjects concomitantly experience mental and emotional problems or distress. Some suffer from one or even more psychiatric disorder(s). Often the link between obesity and psychopathology or psycho-emotional stress works in a two-way direction. Some psychopathology like depression, anxiety disorders etc. may increase the risk of emotional eating behaviour. Also some psychotrophic medications such some anti-depressants, and especially several antipsychotic medications do increase body weight, possibly with an associated increase of obesity associated comorbidities. Important psychopathology and psychosocial deprivation may increase the risk of eating problems or problematic eating. Some suffer from clear eating disorders such as bulimia nervosa or binge eating, which are psychiatric disorders. Many have (antecedents of) depression, anxiety disorder or even substance use disorder. On the other hand, obesity on itself often also may induce emotional and psychosocial suffering or even disease. Obese people often feel guilty and stigmatized by society. They often suffer from low self-esteem and have low self-confidence. This may lead to further social dysfunction and deprivation. This all makes that the implementation of lifestyle measures and the continuation of the necessary behavioural changes might at least be challenging, both in- and outside the context of bariatric surgery.

However as previously discussed in this document and as is apparent from an abundancy of literature on the topic, compliance with regard to lifestyle changes, healthy diet and dietary recommendations, the correct intake of the prescribed vitamin and micronutrient supplements following MBS, and the need for compliance with life-long follow-up is very important in order to increase the likelihood of long-term success, both in terms of durable weight loss as well as in terms of limiting the risks and consequences of complications.

Lack of compliance or poor compliance may have many causes which makes that adherence to follow-up and the continuation of necessary behavioural changes is being jeopardized or sub-optimal. Poor compliance might not be a deliberate choice of the patient. There might be individual reasons explaining why implementing durable lifestyle changes may be difficult, or why compliance with follow-up appointments is suboptimal or absent. Examples of reasons are people who experience loss of control during eating, or people who are in a difficult socio-economic situation which may (partly) explain why agreements made are not complied with, why appointments for further follow-up visits are not made or why people don't show up at visits, etc. (expert feedback from members of the "vzw Eetexpert.be")

For all the above mentioned reasons clinical psychological evaluation should be part of pre-surgery multi-disciplinary evaluation.[238] In Belgium clinical psychological evaluation is part of the pre-bariatric surgery evaluation. Notwithstanding this, there may still be under-recognition (under-detection) and/or under-treatment of mental illness before and after MBS.

RCT data show an improvement in several domains of QoL at 2-3 years after surgery. In the most relevant RCT (the STAMPEDE trial – type 2 diabetes population), the improvement at 5 years is observed in physical domain components only. Most of these data on QoL suffer from a number of methodological limitations such as a low number of patients involved and a substantial number of patients lost to follow-up. Note also that the

STAMPEDE trial was performed in a type 2 diabetic population which might be at higher risk of depression than the non-diabetic population.[13, 98] See also 4.2.3.

Based on non-RCT observational data, QoL and also psychopathology seems to improve in the short- and midterm after bariatric surgery, and also the prevalence of Axis I psychiatric disorders seem to be improved 2-3 years after surgery compared to pre-surgery.[239-241] While generally bariatric surgery may be beneficial for depression, there exists a subset of patients who might actually worsen following surgery. Also the average beneficial effect on depression symptomatology improvement may attenuate over time.[241]

Axis I disorders include all psychological diagnostic categories except mental retardation and personality disorder, and include conditions such as depression, anxiety disorders, bipolar disorder, anorexia nervosa, bulimia nervosa, and schizophrenia, post-traumatic stress disorder etc..

Based on literature reports, one might estimate that around 30-40% of bariatric surgery candidates have a current psychiatric disorder, and a risk of a life-time psychiatric condition in the range of 70-80%. The most prevalent or previous disorders in this population are mood and affective disorders (e.g. major depression, bipolar disorder), anxiety disorder, eating disorders and substance use disorders like alcohol abuse disorder, and self-harm. Many suffer from low self-esteem, and some might have a history of child maltreatment.[21, 232-235, 239, 242, 243]

As part of a 3-site sub-study of the Longitudinal Assessment of Bariatric Surgery study (LABS), 199 patients (LABS-3 participants) completed the Structured Clinical Interviews for DSM-IV prior to RYGB or LAGB.[239] At 2 or 3 years post-surgery 83% of patients in the sub-study completed a follow-up assessment. Linear mixed modelling was used to test change in prevalence of psychiatric disorders over time, report remission and incidence, and examine associations between psychiatric disorders and weight loss. Compared with status pre-surgery, the prevalence of any Axis I psychiatric disorder was significantly lower at 2 and 3 years post-surgery [30.2% vs. 16.8% (P=.003) and 18.4% (P=.012), respectively]. Adjusting for site, pre-surgery BMI, sex, age, race, surgical procedure and percent weight loss, having a mood disorder or an anxiety disorder at time of surgery greatly increased the risk of having the same disorder post-surgery (P for all <.01). Having a lifetime history of a, but not current, mood disorder at time of surgery also increased the risk of a post-surgery mood disorder. However, having a lifetime history of, but not current, anxiety disorder pre-surgery was not related to risk of a post-surgery anxiety disorder. There were significant interactions between age and pre-surgery mood disorder (P=.015) and anxiety disorder status (P=.007), such that the risk associated with pre-surgery status was greater among younger versus older individuals. Patients that (re-)developed an eating disorder 2-3 years after surgery had, as expected, ca. 7% less weight loss compared to those not developing and eating disorder. One of the conclusions by the authors was that in this LABS sub-study, bariatric surgery on average decreased psychiatric disorders through 3 years after surgery. The strength of this study is the use of standardized assessment of psychiatric disorders among a relatively large cohort. Limitations included potential bias associated with self-selection into the study or dropout from the study, as well as limited statistical power for some analyses. Another limitation is that the study did not allow to draw conclusions on the long-term.

As is clear from the chapter on QoL (4.2.3) and from the above paragraphs it seems that specific QoL domains and psychiatric disorders may improve in the short- and mid-term after MBS. However less is known on psychopathology outcome and QoL on the long-term. Moreover the short- to mid-term outcome improvements reported in literature are average outcomes, and one should be conscious that at the individual patient level some patients might experience important (relapse or new) depression or other important psychopathology following bariatric surgery. Possible explanations might be that they have to cope with the need for a changed lifestyle and accept important changes in physical function and appearance, as well as with the potential development of severe adverse effects after surgery. Furthermore pre-surgical psychologic distress could worsen if the results of the surgery were disappointing or failed to have the hoped improvements in QoL. Some patients might have unrealistic expectations of body appearance post-surgery. In addition insufficient effect on weight or weight regain, often a consequence of poor compliance with regard to

necessary lifestyle modifications and poor adherence to life-long follow-up and support, might increase the risk of important psychopathology.

The point of suicide risk will be further elaborated in 5.4.8.3 while the point of substance use disorder, and especially alcohol use disorder were discussed in 5.4.7. Although not definitely in the same category of suicide and suicide-attempts, deliberate self-harm may happen in the context of, or not be part of a suicide attempt.

5.4.8.2 Depressive disorder after MBS

Notwithstanding the fact that on average QoL and mood disorders may improve on the short- and mid-term after MBS, literature reports exist reporting an increased risk of depression and suicide after MBS. Therefore it is important that patients are well screened and informed pre-operatively and are compliant with the proposed lifelong medical follow-up after MBS.

A recent narrative review on this subject was published by Switzer et al.[241] The authors summarize their findings as follows. Obesity and depression share a complex relationship. More than half of patients with obesity who present for medical or surgical management meet the criteria for a psychiatric disorder, commonly a mood disorder. Studies generally report short-term overall reduction in depression rates between approximately 55 to 65% within the first two years following bariatric surgery. It appears that there is a dose response relationship between weight loss and resolution of depression. There are however some conflicting reports in the literature as to the maintenance of depression outcomes following bariatric surgery, with newer, long-term studies reporting the attenuation of depression symptomology improvement. While generally, bariatric surgery may (in the short-term) be beneficial for depression, there exists a cohort of patients who might actually worsen following surgery. This might be a consequence of multifactorial items like weight regain, unrealistic expectations or other stress-full life events; therefore this group needs to be monitored closely, as postoperative bariatric surgery patients surgery appear to be at an increased risk of suicide. A multidisciplinary team including psychiatrists, clinical psychologists or other mental health professionals is vital to optimize patient care in the depressed, obese bariatric surgery patient.[241]

A recent Taiwanese 12 year retrospective cohort study evaluated the risk of major depressive disorder (MDD) in 2302 patients who underwent MBS in 2001-2009, compared to a propensity score matched obese population of 6493 patients that did not receive MBS.[244] They excluded patients who had a prior diagnosis of depression before surgery. Patients were followed until death, a diagnosis of MDD or end date of 31 December 2012. The authors used Cox proportional hazard regression models to calculate the relative risk of MDD in those who received bariatric surgery. Overall, there was a 1.70-fold adjusted HR (95%CI: 1.27–2.27) for MDD in the surgical group. Subjects undergoing malabsorptive procedures showed a higher adjusted HR of MDD (3.01, 95%CI:1.78–5.09) than those receiving restrictive procedures (1.51, 95%CI: 1.10–2.07), and at time points more than four years after surgery compared with the risk in matched controls (adjusted HR: 2.92; CI: 1.75–4.88). The authors speculate that long-term malabsorption might be related to the incidence of MDD after BS, and state that a possible relationship between nutritional deficiencies after BS and MDD warrants further investigation.[244] With respect to other possible (putative) underlying mechanisms, Castaneda et al. point to possible role of variation in the absorption of psychotrophic medications and alcohol after RYGB, and possible alterations of GI hormone levels.[245]

5.4.8.3 Risk of suicide and deliberate self-harm after MBS

Evidence form long-term observational data and meta-analysis of these data indicate that long-term mortality is improved after MBS. However there are several reports suggesting that mortality from accidents and suicide might be increased vs. the general population and possibly also vs. the obese non-operated patients.

Deliberate self-harm may be part of a suicide attempt, though it might also occur independently of the willingness and purpose of committing suicide.

An initial historic US retrospective cohort study comparing 9949 patients who had undergone gastric bypass surgery with 9628 severely obese persons (7925 and 7925 patients were matched for age, sex and BMI) found, after a mean follow-up of 7.1 years, a decrease in all-cause adjusted long-term mortality of 40% in the surgery group compared to the non-surgery

group.[246] Cause specific mortality was decreased for coronary artery disease, diabetes and cancer related mortality, but found that mortality not caused by disease, such as accidents and suicide were 58% higher in the surgery group vs. the control group. This study is included in the SR-MA by Lim et al. and the SR-MA by Castenada et al. (see infra)

The same group by Adams and Hunt published an extensive narrative review in 2015 that aimed to evaluate all-cause and cause-specific long-term mortality among patients after bariatric surgery.[96] From the reviewed literature the authors conclude that bariatric surgical patients had: 1) a significantly reduced long-term all-cause mortality when compared to severely obese non-bariatric surgical control groups; 2) a greater mortality when compared to the general population; 3) a reduced cardiovascular-, stroke-, and cancer-related mortality when compared to severely obese non-operated controls; and 4) an increased risk for externally caused death such as suicide.[96]

Several other reports mention the risk of suicide in an obese population candidate for bariatric surgery and point to a possible increased risk of suicide after bariatric surgery, at least in a subset of patients for whom the exact aetiology is not always clear and often multi-factorial.[232, 235, 241, 242, 247-252]

A recent SR-MA by Lim et al. was published examining the prevalence of all-cause mortality and suicide among bariatric surgery patients.[243] After screening of 7614 published abstracts, 390 full articles were reviewed of which finally 61 studies were included that reported figures on suicide. These 61 studies provided a pooled cohort size of 142 356 patients for analysis in this systematic review and meta-analysis. There were a total of 43 prospective cohort studies, 14 retrospective cohort studies, one RCT and three case control studies. The pooled prevalence of all-cause mortality was 1.8% and the prevalence of suicide was 0.3% (3/1000). The MA revealed significant heterogeneity across the studies, but publication basis was not evident in the meta-analysis. Mean body mass index (BMI) and the duration of follow-up appeared to be significant moderators. The mean age as well as sex were not found to be moderators. The authors reported that there was no evidence of publication bias. The SR-MA only analysed all-cause mortality and suicide in a patients that underwent MBS, though no comparison was made with a non-operated obese control group. Apart from the strengths of this review, the authors recognize that their MA also has several inherent limitations: e.g. most studies failed to report how they managed to obtain information about deaths (such as whether they screened death records, etc.). Additionally, deaths from alcoholic cirrhosis, drug overdoses, poisonings, and accidents not explicitly stated as suicide were excluded from analysis. Most underlying studies listed low rates of long-term follow-up. Subgroup analysis was performed using the longest follow-up period recorded as most studies did not state clear default rates and average follow-up duration for extraction. It is possible that suicide and mortality occur amongst subjects lost to follow-up, which might possibly attenuate the results (and thus possibly could underestimate the real prevalence).

Another recent SR-MA by Castaneda et al. specifically evaluated the risk of suicide and suicide attempts/self-harm after bariatric surgery.[245] The primary outcome was the pooled event rate for suicide (rate, 95%CI), and secondary outcomes were suicide/self-harm attempts after bariatric surgery, both compared to the same population prior to surgery (mirror image analysis) and matched to control subjects (with the respective OR and 95%CI). In addition to the reported results, the authors also discussed on the possible pathophysiologic mechanisms and associated risk factors that could play a role. From the 227 screened citations, 32 studies encompassing 148 643 subjects were eligible for inclusion in this SR-MA. 77% were females (range 65-90%) and the RYGB was the most commonly performed procedure (59%). From the 32 studies, 14 were prospective cohort studies, 9 were retrospective or cross-sectional cohort studies, and 9 were case-control studies. No RCTs were available for analysis. Only one study specifically excluded patients with a history of pre-existing psychiatric diagnosis. Overall average follow-up was 3.85 years (range 0.85-35 y). From the included studies, 59% of these evaluated patients undergoing RYGB, 28% of these evaluated RYGB, LAGB or any restrictive procedure, 6% of these evaluated LAGB and 7% of these evaluated other restrictive procedures including SG and revision procedures. Post-bariatric suicide event rate was 2.7/1000 (95%CI: 2/1000-4/1000) with significant heterogeneity being reported. Heterogeneity was reduced when event rate per person-years of follow-up

was used, rather than events per person, thus accounting for the different lengths of FU in the studies. Mortality rate due to suicide expressed per 1000 patient-years (PY) was 0.25/1000 PY of follow-up. Suicide/self-harm attempt rate was 17/1000 (95%CI: 10/1000-30/1000). The self-harm/attempted suicide inpatient admission event rate was 3/1000 PY of follow-up (95%CI:2/1000-4.2/1000). The self-harm/suicide attempt risk was higher after bariatric surgery compared to rates before the procedure within the same population (mirror-image analysis), with an OR of 1.9 (95%CI: 1.23-2.95), based on 3 studies with a sample 43 406 subjects. Five case-control studies reported mortality from suicide compared to age, gender and BMI-matched controls and found an OR of 3.8 (95%CI: 2,19-6.59). Mortality rates from suicide were significantly greater by a 3-fold difference after RYGB compared to the population undergoing LABG. The reason for this is unclear, though might – according to the authors - potentially be explained by the anatomical alterations performed in each procedure, possible changes in pharmacodynamics and pharmacokinetics of various substances and medications, as well as changes in gut hormones (e.g. ghrelin). Limitations of this SR-MA include the fact that most data in this analysis are extracted from retrospective observational cohort studies or case-control studies entailing possible confounders and bias. Only a limited amount of underlying studies reported pre-surgical psychiatric diseases. Another weakness of this SR-MA analysis is the inability to differentiate between masked suicide events and accidental deaths. Hence a fraction of the latter could potentially represent some deaths linked to suicide, initially attributed to accidental deaths. Other limitations are that the included studies had diverse comparison groups, which could potentially explain the variability in outcome. Most of the control groups were age-, gender- and BMI-matched, though only few studies included control groups. Most studies did not provide data regarding post-surgical BMI. Based on this SR-MA, the authors conclude that bariatric surgery patients had a higher suicide risk compared to the general population and to matched controls (with an estimated OR 3.8; 95%CI: 2.2-6.6 vs. BMI- and age-matched controls). The subjects undergoing bariatric procedures have an almost 2-fold increased risk of self-harm/suicide attempts after surgery (compared to pre-surgery). Furthermore, the post-RYGB subjects had a higher suicide risk than the post-LAGB subjects, an association which might be related to other medical, psychiatric and socio-demographic factors. The authors state that further evaluation in future studies is needed on the possible modifiable factors in metabolic and bariatric surgery candidates and in the needs of post-bariatric populations, as well as investigating possible mechanistic explanations for difference in suicide rates by surgery type.

One US retrospective chart-review study looked at predictors of suicidality in bariatric surgery candidates and found that 16% of those seeking psychological clearance for MBS (out of 203 eligible charts reviewed) were classified as reporting suicidality.[253] The authors found that higher scores for depression were related to a higher risk of suicidality, and that both the higher scores for hopelessness and for current mood disorders each uniquely predicted suicidality above and beyond the predictive utility of depressive symptoms. Therefore the identification of each of these factors (depression, mood disorder and/or hopelessness) may contribute to the identification of patients who might be at risk for suicidality post-surgery.

In literature on the issue of self-harm is often addressed at the same time with a discussion or analysis on suicide and suicide attempts. However deliberate self-harm is definitely not completely the same (does not equal) suicide and suicide-attempts, as self-harm may be as well part of a suicide attempt, though it can also occur without the purpose of committing suicide (e.g. auto-mutilation).

Most literature reports mention the risk of self-harm in bariatric surgery patients to me more common than in the general population, though literature is less conclusive as to whether or not the risk of self-harm is increased post-surgery compared to pre-surgery.

An Australian 5 year retrospective, self-matched, longitudinal, multi-centre, population based cohort study evaluated all patients that underwent elective bariatric surgery in the state of Western Australia between 2007-2011 with a minimal FU of 12 months, and looked at hospitalisations for reasons of deliberate self-harm.[247]. All patients (n=12 062) were followed for an average of 30.4 months pre-operatively and an average of 40.6 months postoperatively. There were 0.9% of patients hospitalized for deliberate self-harm, which was more common than in the general population (incidence rate ratio, IRR=1.47, 95%CI: 1.11-1.94). Compared with before surgery,

there was no increase in deliberate self-harm hospitalizations (IRR=0.79, 95%CI: 0.54-1.16), and a reduction in overall mental illness related hospitalizations (IRR=0.76; 95%CI: 0.63-0.91) after surgery. There were three suicides during the FU period, a rate comparable to the general population during the same time period (IRR=0.61; 95%CI: 0.11-2.27).[247] Possible limitations of these study include the fact that it only recorded hospitalizations for self-harm, and that milder forms not requiring hospitalizations could not be analysed. Another limitation is that follow-up length was limited while longer observation periods may be desirable when studying events linked to chronic psychopathology.

A Canadian population-based, self-matched, retrospective longitudinal cohort analysis of patients living in Ontario and undergoing MBS, evaluated the incidence of self-harm emergencies in the 3 years after surgery compared to the incidence in the 3 years before surgery.[254] A total of 8815 patients underwent MBS in the 5 year enrolment interval between 2006-2011. The RYGB was the most predominant type of surgery performed (98.5%). Of all patients undergoing MBS, 64% had a mental health diagnosis of anxiety, and 8% of depression. The investigators categorized 4 distinct mechanism of self-harm behaviours: medications, alcohol, poisoning by toxic chemicals and physical trauma. Overall self-harm emergencies significantly increased after surgery (3.63 per 1000 patient-years) compared with before surgery (2.33 per 1000 patient-years), equalling a rate ratio (RR) of 1.54 (95%CI: 1.03-2.30). The most common self-harm mechanism was an intentional overdose (115 [72.8%]). A total of 147 events (93.0%) occurred in patients diagnosed as having a mental health disorder during the 5 years before the surgery. The use of ICD-10 codes may overestimate or underestimate self-harm behaviours because substance abuse, misuse or intoxications may have had a self-harming intent or not, and because determining intent is often problematic. Another limitation is that emergency visits as an outcome may well underestimate actual self-harm behaviours.

We refer to the literature for further information.[21, 232-235, 238-243, 247-252, 255-262]

Key points – Psychiatric adverse effects and aspects of psychological well-being

- **Despite a global decrease in mortality compared to severely obese non-operated patients and an (initial) improvement of psychiatric co-morbidities and QoL in patients that have undergone MBS, risk of suicide seems to be (slightly) elevated and this for currently unknown and possibly multifactorial reasons.**
- **Psychopathology and psychiatric disorders such as depressive disorders, anxiety disorders, eating disorders, self-harm and substance use disorders are prevalent among bariatric surgery candidates, and can persist or recur after surgery.**
- **Short- and mid-term observational data shows that patients may experience an improvement in QoL and show mood symptomatology improvement. Much less is known on the long-term, and the beneficial effect on psychological aspects of QoL may wane over time, with possibly the best long-term improvements being observed in the physical domain components of QoL. For the impact on QoL based on RCT data, we refer to part 4.2.3.**
- **Most patients seem to have an improvement of mood and depression scores in the first 1-2 years after surgery, though there might be a subset of patients where depression and mood disorders may actually worsen.**
- **Pre-surgical psychopathology may imply poor surgical outcomes in terms of weight loss, or weight regain, and incur a risk of recurrence or worsening of pre-existing/previous psychopathology; it is important that patients are informed to help them to create realistic expectations about the expected results and potential risk of MBS. Otherwise pre-surgical distress could worsen whenever the results of surgery are not**

meeting the patient's expectations or have not led to the hoped improvements in quality of life.

- **Suicide risk (ideation, attempts, completed suicide) seems to be higher in patients that have undergone MBS vs. the general population, though data are not completely consistent on whether or not the risk is increased in the period post-surgery vs. pre-surgery; a recent SR-MA on suicide and self-harm risk points to a possible doubling of the risk following surgery (vs. pre-surgery); several hypotheses point to factors as obesity itself, insufficient results on weight loss, but also and not to the least extent, to possible other causes that are independent of the surgical intervention like underlying but not sufficiently controlled psychiatric pathologies in a population at a higher risk of self-harm or suicide.**
  Reduced self-esteem may play a considerable role in the relationship between obesity and depressive disorders, thus potentially increasing the risk for suicidality.
  Depressive disorders may persist in bariatric surgery patients despite successful weight control after surgery.
  Also the risk of suicide might potentially be higher after RYGB (a mixed restrictive malabsorptive intervention), leading some authors to hypothesize on the role of nutrient deficiencies (like Vit.B12 and folate), possible hormonal effects, and change in drug-PK of psychotropic drugs.
- **The risk of depression, self-harm and suicide may be higher in patients who are candidates for and having undergone MBS; although the risk seems to be largely attributable to those with prior psychiatric diagnoses or problems, one needs to remain vigilant as problems might also occur in those without prior known history.**

5.4.9 (Re)emergence of maladaptive or problematic eating behaviours and eating disorders after MBS

There is some growing awareness about the (re)emergence of problematic eating behaviours (EB) and eating disorders (ED) in bariatric surgery patients, particularly the possibility of post-operative de novo problematic EB and ED.[237, 263-267]

Eating disorders often have a strong link to or can be part of psychopathology present before MBS. However one should be aware that ED or problematic EB may reoccur soon or later after MBS, while there are also other patients where new maladaptive and problematic eating behaviours may develop, that may possibly worsen and lead to an eating disorder.

The recurrence of pre-existing eating disorders like bulimia nervosa or binge eating disorder will not be further elaborated. These disorders are classified in DSM-5, and the reoccurrence of these can be an expression of pre-existing psychopathology or underlying factors becoming again more prominent.

De novo maladaptive or problematic eating behaviours and eating disorders may find their origin in a number or causes or reasons, such as for instance:

- Restrictive eating behaviour might be induced by post-operative symptoms like plugging (feeling that the small opening in the stomach becomes blocked or plugged), vomiting, dumping, dysphagia, constipation or abdominal pain. The resulting restrictive eating behaviour might arise in an attempt to compensate for the discomfort patients may experience when consuming difficult to digest meals or after 'over-eating'.
- Restrictive eating behaviour may also find its origin in a reaction to a subjective feeling of 'losing control'. These patients may confer a higher risk to develop a restrictive eating behaviour (which might give them a feeling of 'controlling'), which could as such result in anorexia nervosa (AN) or AN like symptoms.

- Restrictive EB or a restrictive ED might also develop insidiously when the patient is preoccupied or over-focussed as to what concerns the implementation of 'restrictive dietary recommendations' to limit portions, to masticate very well etc.. In this context these dietary recommendations might possibly become a trigger for the development of a restrictive ED in patients that are more susceptible to loose themselves in an eating pattern characterized by extreme control and rigid diet rules.
- Grazing (eating all day small quantities), as a cause of weight regain.
- Using energy dense, often in liquid or soft form, meals or foods (often rich in carbohydrates), as a cause of weight regain and dumping complaints.
- Binge eating, as a cause of weight regain.

Gastric restriction and dietary requirements after surgery might as such create conditions that trigger eating disorder (-like) symptoms regardless of the pre-operative status. Problematic eating behaviour does not equal an eating disorder, but might possibly evolve into an ED. Eating disorders are psychiatric pathologies and characterized by substantial emotional suffering and maladaptive behaviour.

Based on literature reports and expert feedback ("vzw Eetexpert.be"), it seems that some patients may develop eating disorders after MBS, particularly partial cases, and especially the risk of restrictive eating disorders seems not to be very well known by many stakeholders. Patient education about the danger of maintaining an overly restrictive diet, and the subsequent risk of developing an eating disorder may be important.

It's obvious that the development or re-emergence of problematic eating behaviours or eating disorders likely will affect the outcome and success of MBS. Also even when the weight result obtained after MBS is acceptably good, the psychopathologic features of eating disorders still may compromise patient's life.

This all demonstrates that bariatric patients and their health care professionals should be sensitive to this problematic, and moreover and again, it underscores the importance of life-long multidisciplinary follow-up with sufficient attention to the monitoring of eating habits and psychological/psychosocial aspects of wellbeing.

It is impossible at this stage to make reliable quantitative estimates on the risk of (re)emergence of eating disorders of problematic eating behaviour after MBS. We refer the reader to further supporting references.[237, 263-267]

Key points - risk of (re-)emergence of problematic eating behaviours (EB) and eating disorders (ED) post-bariatric surgery

- **Re-emergence and emergence of problematic eating behaviours or an eating disorders is possible after MBS.**
- **Eating disorders have a strong link with other psychopathology, or are part of the psychopathology which may be present before MBS. ED or problematic EB might reoccur after MBS, while there are also other patients in whom new maladaptive and problematic eating behaviours may develop, which can possibly worsen and lead to an eating disorder.**
- **Relatively well known problematic EB or ED that can (re)occur after MBS are e.g. grazing, using too much energy dense food, and binge eating. The occurrence of new restrictive problematic EB or restrictive ED is in general much less known.**

  Restrictive EB might be induced by post-operative symptoms like plugging, vomiting, dumping, dysphagia, constipation or abdominal pain, and this in an attempt to compensate for and cope with the discomfort patients may experience when consuming difficult to digest meals or after 'over-eating'.

- **Restrictive EB or a restrictive ED might also develop insidiously when the patient is preoccupied or over-focussed as to what concerns the implementation of 'restrictive dietary recommendations'. In this context these dietary recommendations might possibly become a trigger for the development of a restrictive ED in patients who are more susceptible to loose themselves in an eating pattern characterized by extreme control and rigid diet rules.**

5.4.10 *Potential for changes in drug pharmaco-kinetics*

The effects of MBS (with the related alterations of the gastrointestinal environment and function) on drug absorption are not always easy to predict.

Although relatively little is known about changes in drug PK after MBS, the potential risk seems on average to be higher after RYGB vs. SG. This is based on theoretical considerations (intervetions with a more mal-absorptive component may on average incur a higher risk) and on a concise non-systematic review of literature.[268-270]

Decreased or increased drug exposure have both been described. In a manner of demonstration some examples will be briefly mentioned or discussed, however literature is relatively scarce on the topic, and more specific prospective clinical trials evaluating changes in drug disposition are needed.

Changes in gastro-intestinal environment (anatomy and/or function, gut-microbiome) that may lead to an alteration in drug pharmacokinetics may be among others explained by:

- Changes in acid environment because large parts of the stomach are resected or bypassed (decrease in 'gastric' acidity); this is relevant for medications were absorption is influenced by pH.
- The fact that much less food is ingested, might also have an influence on drugs that depend on food-intake for better absorption.
- The fact that some drugs or substances are passed more rapidly to the small intestine (changes of transit time).
- The fact that certain drugs/nutrients are predominantly absorbed in some specific parts of the GI tract that may have been resected or bypassed (reduction of absorptive surface); this might partly be explained by the fact that specific gastro-intestinal transporters and/or P-glycoprotein efflux transporters important for drug absorption (or re-elimination) might be more specifically located in certain parts of the small intestine that might have been bypassed.
- The fact that some cytochrome enzymes (which are important for the metabolism and breakdown of certain drugs) are also present in specific parts of the duodenum/small intestine; resection or bypassing these parts might alter the rate and level of absorption of certain drugs.
- The enterohepatic recirculation of bile acids might be changed by some metabolic procedures, and this could change PK of drugs that undergo enterohepatic recycling.

On average the risk for changes in drug pharmacokinetics will be greater with higher levels of malabsorption induced by the MBS, with purely malabsorptive interventions incurring the highest risk, followed by the classic RYGB, and on average a lower risk with the purely restrictive interventions like the SG. However also purely restrictive interventions might entail a risk of changes in drug PK, e.g. due to the fact that some drugs may undergo some metabolism in the stomach and/or by the fact there might be changes in pH (intra-gastric and/or pH in the proximal of the small-intestine) that can either increase or decrease drug absorption.

Besides all this, significant weight reduction on itself may necessitate dose adaptations, for instance, because the person simply needs less because of lower body weight, or because of a change in distribution volume which is relevant for lipid soluble medications.

As such the patient that has undergone MBS might be at risk to changes in drug-PK for some drugs. There are examples where both drug absorption and disposition is decreased (lower extent of absorption and/or slower rate of absorption), though there are also examples where drug absorption is

increased (higher extent of absorption and/or faster absorption with higher peak concentrations being reached). This might be a fortiori relevant for drugs with a narrow therapeutic window. However in general knowledge on this topic sparse, and little is based on solid pharmacokinetic studies, while most is based on observational case-reports and other observational data.

People with obesity often take many drugs, for instance because of co-occurring psychopathology (psychotrophic drugs), and because of other medical co-morbidities (lipid lowering, anti-hypertensives, glucose lowering etc.). Use of some medication classes will be decreased or stopped (because of improving co-morbidities), while others will need to be continued. Besides, a large portion of people undergoing MBS are females who are in an age group of child-bearing potential. After MBS it is strongly advised that females avoid becoming pregnant in the first 18-24 months following surgery. Therefore it is important that these women use adequate contraceptive methods during this period, or after that period when pregnancy is not desired. As pharmacokinetics of oral contraceptives are likely to be changed, certainly after RYGB and even more after more extensive malabsorptive interventions, these women will be advised to use alternative contraceptive methods.

Drug classes that should be considered are those that are often used, and/or have a narrow therapeutic window. Even when no specific recommendations are available, specific attention and consideration is needed and the need for drug (dose)-adaptations through clinical monitoring needs to be considered. In addition, where available specific drug monitoring methods (e.g. measurement of drug concentrations, or e.g. coagulation test when using anti-coagulants) can be considered. This applies more specifically in cases where patients use critical drugs (e.g. anti-conception, statins, anti-hypertensives, anti-diabetes medication, thyroid medication, antibiotics, anti-tumoral drugs, psychotrophic drugs such as anti-depressants and anti-psychotics, opioid drugs, anti-retrovirals etc.) and/or drugs with a narrow therapeutic window (like anti-coagulants, anti-arrhythmic drugs, anti-epileptics, immune-suppressants etc.). It is noteworthy that patients taking lithium for bipolar disorder may experience increased absorption after SG, and may experience complications such as asystoly.[271] Conversely, duloxetine, sertraline, citalopram are usually fraught with reduced absorption after RYGB.[269]

Literature on the influence of MBS on pharmacokinetics of frequently used drugs is relatively scarce. Therefore a more in depth and specific discussion on the effects of MBS and the different techniques of MBS on the PK of specific drugs is out of scope for this HTA. Readers are referred to general overview articles on the topic as well as to some more drug-class specific literature.[194, 238, 268-270, 272-288]

Key points – potential for change in drug pharmacokinetics (PK)

- **The alterations of the gastrointestinal tract, environment and function caused by MBS may change pharmacokinetics of drugs, in particular the absorption characteristics (degree of absorption, rate of absorption into plasma, peak concentrations reached); some drugs are not or only slightly affected, while for other drugs changes might be clinically relevant.**
- **In general the risk for changes in drug pharmacokinetics will be greater with higher degrees of malabsorption induced by the MBS, with purely malabsorptive interventions incurring the highest average risk, followed by the RYGB, and on average a lower risk with the purely restrictive interventions like the SG; however relevant changes may also occur after purely restrictive surgery such as SG or LAGB.**
- **Intuitively one mainly thinks about the potential risk of decreased drug (and nutrient) absorption, however there are examples of both decreased and increased drug absorption and drug exposure following MBS.**
- **Literature in general is relatively limited on the topic, and more drug specific data and prospective clinical trials evaluating changes in drug disposition after MBS may be needed.**

- **Patients with obesity are often treated with multiple medications; some of them may be reduced or stopped after MBS because of improvement of obesity associated co-morbidities, while other drugs may need to be continued. As many bariatric surgery candidates have pre-existing psychopathology and are using psychotrophic medications which often need to be continued following MBS, particular clinical attention is needed regarding the possible need for dose or drug changes of psychotropic medications.**
- **As the absorption of oral anti-conceptive drugs might be impaired after MBS (certainly after interventions with a malabsorptive component), appropriate alternative contraceptive methods are needed in women of childbearing potential during periods where pregnancy is contra-indicated or not desired.**

5.4.11 *Pregnancy outcome related effects*

One needs to be aware that obese women might on average demonstrate higher levels of decreased fertility compared to the general population, and that as a consequence of weight loss following MBS average fertility improves. This means that when there is no pregnancy wish in females of child-bearing age, the continued use of appropriate methods of contraception needs to be considered.[21]

On the other hand, when there still is a pregnancy wish, women planning to undergo MBS need to be informed that they have to post-pone pregnancy by at least 12 to 18 months after surgery (many publications recommend 18-24 months or until stabilisation of weight loss after surgery).[21, 289] The reason for postponing pregnancy is that there might be short- and long-term consequences of rapid weight loss and potential (micro)nutritional deficiencies incurring a risk for the offspring.[289] In addition, the type of the MBS procedure to be chosen might be influenced by the presence or absence of a (possible) future pregnancy wish. For instance as internal herniation is a well-known risk after RYGB, which in addition may present less typically during pregnancy, the decision balance between SG and RYGB and eventually the shared informed decision on an individual patient basis might be in favour of SG if there is no specific contraindication for this intervention (clinical expert feedback). On the other hand, given that SG is a more recent type of intervention, and albeit becoming in the US the most frequently performed intervention, literature data on pregnancy outcome specifically after SG are limited. Notwithstanding the fact that the OAGB (or 'mini-gastric bypass') is not in the primary scope of this HTA review, an external expert drew attention to the fact that caution for protein malnutrition in pregnancy after OAGB is needed as it may be potentially accompanied by serious consequences.

Data on outcome of pregnancy after bariatric surgery show in general a lower risk of large-for-gestational-age (LGA) new born infants, no clear increase of pregnancy loss or congenital malformations, and a slight increase in the risk of small-for-gestational-age new born infants. In general the weight loss induced by MBS has many potential benefits compared to the situation of staying severely obese. Important is that patients are compliant with the prescribed vitamin and micronutrient supplementation, and that especially folic acid levels are normal and folic acid supplements are taken prior to conception and during pregnancy.[21]

A recent systematic review and meta-analysis by Kwong et al. included for analysis observational cohort trials (both from direct clinical charts or record data and from administrative databases) if they evaluated patients that underwent bariatric surgery, reported subsequent pregnancy outcomes and compared this outcomes with a control group.[290] This meta-analysis was unique because it looked both at studies that matched on pre-surgery BMI and at studies that matched at pre-pregnancy BMI. The first comparison (= primary analysis of this meta-analysis) matching on pre-surgery BMI is important to better describe the beneficial effects of surgery for weight loss and pregnancy outcome (effect of having undergone BS vs. not having undergone BS for severe or morbid obesity). Conversely, the second comparison (= secondary analysis) addressed a subset of studies with control subjects who had a pre-pregnancy BMI similar to the postoperative BMI of the patients. This approach helped at better describing the potential harm of bariatric surgery itself (=having undergone BS while pre-pregnancy

BMI was similar between the operated and non-operated group). After appropriate selection, 20 studies and ca. 2.8 million subjects (8364 of whom had BS) were included in the analysis. According to the primary analysis, patients who underwent BS showed reduced rates of gestational diabetes mellitus (odds ratio or OR=0.20; 95%CI:0.11-0.37, number needed to benefit/treat or NNT=5, large-for-gestational-age (LGA) infants (OR=0.31; 95%CI:0.17-0.59; NNT=6), gestational hypertension (OR=0.38; 95%-CI:0.19-0.76; NNT=11), all hypertensive disorders (OR=0.38; 95%CI:0.27-0.53; NNT=8), and caesarean delivery rates (OR=0.50; 95%CI:0.38-0.67; NNT=9); however, the group of patients that underwent BS showed an increase in small-for-gestational-age (SGA) infants (OR, 2.16; 95%CI:1.34-3.48; number needed to harm or NNH=21), intrauterine growth restriction or IUGR (OR=2.16; 95%CI:1.34-3.48; NNH=66), and preterm deliveries (OR=1.35; 95%CI:1.02-1.79; NNH=35) when compared with control subjects who were matched for pre-surgery BMI. There were no significant differences in rates of preeclampsia, neonatal intensive care unit admissions, stillbirths, malformations, and neonatal death. Malabsorptive surgeries resulted in a greater increase in SGA infants (P=0.0466) and a greater decrease in LGA infants (P<0.0001) compared with restrictive surgeries. However there were few studies that have looked specifically at pregnancy outcomes of patients who underwent sleeve gastrectomy. There were no differences in outcomes when the authors used administrative databases vs. clinical charts.

Table 23 provides a good insight both of beneficial pregnancy outcomes and harms associated with BS, based on all study outcomes as assessed in the SR-MA by Kwong et al.[290]

Table 23 – Beneficial pregnancy outcomes and harms associated with BS, based on all study outcomes as assessed in the SR-MA by Kwong et al.

Results for all study outcomes

Outcome	Studies, n	Events/ cases, n	Events/control subjects, n	Pooled odds ratio (95% confidence interval)	Number needed to benefit
Benefit					
Gestational diabetes mellitus	5	45/1111	335/2923	0.21 (0.12—0.36)	5
Large for gestational age	3	78/830	777/3094	0.31 (0.17—0.59)	6
Postpartum hemorrhage	2	8/424	25/486	0.32 (0.08—1.37)	21
Macrosomia	5	77/1123	338/2965	0.32 (0.11—0.89)	13
Large babies[a]	6	141/1280	882/3603	0.35 (0.19—0.62)	7
All hypertensive disorders	4	88/686	162/584	0.38 (0.27—0.53)	8
Gestational hypertension	3	14/179	50/283	0.39 (0.2—0.75)	11
Preeclampsia	3	17/179	42/283	0.59 (0.32—1.09)	21
Cesarean delivery	4	176/533	297/629	0.63 (0.39—1.02)	9
Harm					Number needed to harm
Neonatal intensive care unit admission	2	25/153	35/260	1.26 (0.37—4.26)	38
Malformations	4	61/1290	126/3925	1.29 (0.61—2.71)	97
Neonatal deaths	3	16/1451	15/2991	1.31 (0.37—4.71)	447
Preterm delivery	4	95/769	216/2627	1.33 (1.01—1.75)	35
Stillbirth	4	11/859	28/3776	1.4 (0.38—5.23)	370
Intrauterine growth restriction	2	21/533	8/324	1.6 (0.69—3.73)	66
Small for gestational age	6	183/1433	238/3558	2.18 (1.41—3.38)	21
Small babies[b]	6	183/1433	238/3558	2.18 (1.41—3.38)	21

[a] Composite of large for gestational age and macrosomia; [b] Composite of small for gestational age and intrauterine growth restriction.

Source: Kwong et al., Am J Obstet Gynecol, 2018

Strengths of this SR-MA are that: this SR-MA separated studies that matched on pre-surgery and on pre-pregnancy BMI; in addition the SR-MA also compared outcomes in function of the type of data sources that were used. Limitations are that: as with any meta-analysis the findings are limited by the design and results of the primary studies; none of the studies were randomized trials. All studies were observational cohort studies, with the potential for confounding by indication. Women who undergo MBS may be inherently different from women who do not undergo bariatric surgery, even if they are similar in BMI and other clinical variables. Specifically, there may be differences in certain social determinants of health. The studies that were synthesized attempted to address this issue by selection of appropriate control groups with matching BMI and the use of adjusted Odds ratios whenever possible. Other limitations are the inability to account for the amount of weight loss relative to the pre-surgical weight and the length of time between surgery and the pregnancy. Another weakness may come from the source of data, with differences in quality between administrative databases vs direct clinical data (from charts, office records). The additional subgroup analysis performed, however, did not reveal significant differences when the authors compared results from these 2 different sources. Finally several outcomes demonstrated substantial heterogeneity in the effect of bariatric surgery, for instance for the outcome of gestational diabetes mellitus, which makes the true risk reduction ess certain. However most of the outcomes studied showed effects going in the same direction. The authors conclude that although bariatric surgery is associated with a reduction in the risk of several adverse obstetric outcomes, there is a potential for an increased risk of other important outcomes that should be considered when bariatric surgery is discussed with women of reproductive age.

We refer to the literature for further supporting references.[289-297]

Key points – pregnancy outcome related effects or events (beneficial effects and potential risk)

- **Women with obesity on average demonstrate higher levels of decreased fertility compared to the general population; as a result of weight loss and improved metabolic and hormonal profile, women with obesity undergoing MBS on average become more fertile.**
- **Although MBS is associated with a reduction in the risk of several adverse obstetric outcomes (both for the pregnant women and the off-spring), there is a potential for an increased risk of other important outcomes that should be considered when MBS is discussed with women of reproductive age (women of child-bearing potential).**
- **Potential benefits of MBS regarding obstetric and pregnancy outcomes are: less gestational diabetes, less large for gestational age (LGA) infants, less pregnancy associated problems of hypertension, and probably lower rates of preeclampsia, post-partum hemorraghe and less need for caesarean section. Logic wise the risk for delivery-related traumata can be expected to be lower.**
- **Potential harms of MBS on obstetric and pregnancy outcomes are: a slightly higher risk for pre-term delivery, a higher risk for intra-uterine growth restriction and small-for-gestational age (SGA) infants. Comparison of malabsorptive surgeries with restrictive surgeries suggest that the risk for small-for-gestational-age infants might be higher with interventions that have a malabsorptive component.**
- **General advice/recommendation in literature is that women planning to undergo MBS need to be informed that they have to post-pone pregnancy by at least 12 to 18 months after surgery (some publications recommend 18-24 months or until stabilisation of weight loss after surgery).[289] The reason for**

postponing pregnancy is that there might be short- and long-term consequences of rapid weight loss and potential (micro)nutritional deficiencies incurring a risk for the offspring. This implies that when there is a contra-indication to become pregnant, or when there is no pregnancy wish in females of child-bearing age, the use of an appropriate effective contraceptive method is needed. As absorption of oral contraceptives may be impaired (especially after interventions with a malabsorptive component), other alternative anti-conceptive methods should be considered.

- **When considering MBS in women of child-bearing age who still might have a pregnancy wish, the type of surgery chosen with respect to contraception, pregnancy outcome/risk and the possible presence of other co-morbidities needs be considered and discussed including the risk associated with RYGB of internal hernia occurring during pregnancy, a complication which can present with atypical symptoms during pregnancy.**

5.4.12 *Dermatologic AE*

Dermatological adverse effects occurring post-bariatric surgery may incur medical and psychological problems. The purpose of this topic is not to provide an in depth analysis of all possible issues. Because an in depth discussion would lead us too far and beyond the scope of this HTA, we opted to provide a non-limitative list of these possible adverse effects or events without any further evaluation or discussion:

- The development of excessive skinfolds (mostly at level of abdomen, upper arms, thighs, breast) with possible aesthetic consequences and impact on body image and self-esteem. Excessive skin folds may also lead to maceration, intertrigo and infection. Plastic surgery might be necessary or desirable (e.g. abdominoplasty, brachioplasty, thigh lift, breast lift/mamma-reduction / body contouring).
- Hair loss, when occurring later on after surgery may be a consequence of micronutrient deficiencies such as Zinc deficiency.
- Acrodermatitis enteropathica, and nail dystrophy may also occur, often as a result of Zinc deficiency.

5.4.13 *Miscellaneous effects and new safety topics of potential interest*

Some other possible adverse effects/events gained attention in (recent) literature. Because an in depth discussion would be beyond the scope of this HTA, we opted to provide a non-limitative list of these possible adverse effects or events without further evaluation or discussion. Mentioning of these possible adverse effect in the list hereunder does not automatically imply that causality has been proven or demonstrated.

Among other these are:

- Achalasia and pseudo-achalasia
- Gastrobronchial fistula, especially after laparoscopic SG
- Ampullary achalasia
- Oesophagal cancer (as a consequence of Barrett's oesophagus, being on itself a possible consequence of GORD)
- Clostridium difficile infection (especially after RYGB > SG)
- Periodontal disease and dental carries
- Olfactory and gustative changes
- Red meat intolerance (after RYGB)
- Porto-mesenteric vein thrombosis (PMVT), especially after SG
- Guillain-Barré syndrome
- de novo inflammatory bowel disease
- …

5.4.14 Weight regain and need for revisional surgery

5.4.14.1 Context

Although this HTA does not have the aim of assessing the benefit risk balance of revisional re-do surgery itself, re-do bariatric surgery is a reality.

Revisional surgery (redo and/or undo surgery) might be necessary in some patients both for reason of insufficient weight loss and considerable weight regain, or for reasons of serious adverse effects or severe intolerance. Assessing the need for revisions after metabolic/bariatric procedures can be an important indicator of the success of the initial procedure.

While the majority of bariatric patients achieve successful durable weight loss after primary surgery, the patients who present with insufficient weight loss, or important weight regain represent a challenging population. Note however that most patients will experience some level of normal but limited weight regain after the initial substantial short-term weight loss realised in the first 1-2 years after surgery (honey-moon period).

Considerable weight regain is an outcome of long-term effectiveness, and revisional surgery for weight regain (or insufficient initial weight loss) should be considered an efficacy outcome, although being non-desirable. Revisional surgery performed for reasons of complications after primary bariatric surgery should be considered a safety outcome. Literature reports are in general not straightforward in distinguishing incidence rates of revisional surgery for reasons of lack of LT efficacy (insufficient weight loss/weight regain), versus revisional surgery for reasons of complications or severe intolerance. For practical reasons we opted to address revisional surgery very concisely in the safety chapter.

The topic of revisional surgery was addressed through a brief and non-systematic check of literature, and is mostly based on some recent topic articles, the scientific dissertation of Himpens J, and on recent data from a large New York (NY) state database study.[80, 137, 139, 298]

Importantly, as incidence rates for short-term (≤30 d) re-operations or re-interventions has been addressed as a short-term outcome in chapter 5.3.3, and although we do recognize that LT-complications may be a reason for revisional surgery, we opted to put most of the focus in this chapter on revisional surgery of the 'redo' type, performed for reasons of insufficient weight loss or weight regain. The reason is that substantial weight regain seems to a relatively more important cause for revisional surgery than for reasons of complications.

Rates of revisional surgery (redo and undo) described in literature vary greatly and range somewhere between 5 and 50%, depending on the populations and primary interventions studied.[139] The highest rates are described after LAGB and vertical banded gastroplasty (mostly because of serious complications), and the lowest rates associated with BPD or BPD-DS. These latter interventions are the most effective, but also the most drastic and they are nowadays only seldomly performed because the very high inherent risk of nutritional deficiencies and metabolic complications.

Redo-revisional surgery aims at the conversion of one type of MBS into another. Revisional surgery however also includes 'un-do' surgery, though this is not the focus and specific interest of this paragraph. Undo surgery might be necessary because of potentially life-threatening complications (like e.g. band slippage and erosion with perforation after LAGB), or because of severe side-effects and poor tolerance (like e.g. untreatable reactive hypoglycaemia after RYGB, severe GORD after SG, etc.). LAGB is characterized by high rates of undo-interventions because of serious complications (and to a lesser extent because of moderate efficacy), and this is the main reason why nowadays there are more LAGB's being removed than placed.

Importantly, a distinction should be made between inadequate weight loss and substantial weight regain on the one side, and the need for revision on the other side, as not all failures need to be revised.[138]

The most common indication is failure of the primary intervention to provide durable adequate weight loss. Adequate weight loss generally has been defined as an achieved excess weight loss (EWL) of at least 50%.[299] However, adequacy of weight loss must also be judged in the context or absence of comorbid disease or risk.

Before considering whether a particular patient is a candidate for a revision of the primary operation, it is important to determine whether 'the operation failed the patient', or whether 'the patient failed the operation'.[138] The reason is that in many circumstances, significant weight regain (after an initial period of weight loss) or insufficient initial weight loss (a less frequent problem), can be favoured or caused by poor-compliance with regard to the required life-long dietary adaptations and restrictions. In other words one should distinguish an anatomic cause for weight regain from weight regain which is primarily the result of behavioural discrepancies such as large portion sizes (hyperphagia), high caloric content food, frequent between meal snacking (polyphagia, grazing) and lack of exercise.

As mentioned in 5.4.8, it's important to note that poor compliance may have many causes which make that adherence to follow-up and the continuation of necessary behavioural changes is being jeopardized or sub-optimal. Often lack of compliance might not be a deliberate choice of the patient and there might be individual reasons explaining why implementing durable lifestyle changes can be difficult, or why compliance with follow-up appointments is suboptimal or absent.

Insufficient weight loss or weight regain can have an 'organic' cause (like e.g. gastro-gastric fistula, or a wide open gastro-jejunal anastomosis, …), however this probably is the case in a relative lesser part of patients. Some of these 'organic' causes of weight regain can be treated by endoscopic interventions, while for other patients, a new surgical intervention might be required.

The indications and outcomes of redo-bariatric surgery might be procedure-specific and motivated by the specific clinical situation of the patient. At a first glance, the current evidence and expert opinion in literature supports additional treatment for persistent or recurrent severe obesity, persistent co-morbidities and/or complications.[137] Besides, on the other hand, sometimes one also need to consider and accept that, as with many other diseases, not everyone can be cured of their obesity.

5.4.14.2 Re-do interventions

Redo revisional surgery can be performed in one- or two stages, depending on the clinical situation, the initial type of MBS performed previously, and the new bariatric configuration aimed at. A two stage approach often is comprised of an 'undo' intervention followed by a new metabolic and bariatric intervention. Example of a one stage redo intervention after a LAGB is a direct conversion to a RYGB, while an example of a two-stage redo operation after a LAGB could be first an undo followed by the performance of a SG.

The 'gold' standard (read: most frequent situation) revisional option is usually to laparoscopically convert a restrictive operation (LAGB or SG) into a RYGB, in order to have a good balance between long-term weight loss, resolutions of co-morbidities, the anatomic situation related to the primary procedure and an acceptable rate of peri-/post-operative complications.[139]

In general the most frequent redo bariatric surgeries are:

- from LAGB, conversion to → SG (often in two stages), or to RYGB (in one or two stages)
- from SG conversion to → (re-sleeve), RYGB, or duodenal switch
- from a RYGB to → Biliopancreatic diversion with DS, or to distal RYGB

Note that historically the sleeve gastrectomy was conceived as a first step (=being part of), followed in a second time by a duodenal switch to create a biliopancreatic diversion with duodenal switch.

A scheme on the most important possible revisional procedures for LAGB, SG and RYGB can be found in Figure 24. However other types of revisional procedures have been described.

One way of 'looking' at initial procedures is to consider their 'reversible character'. Some interventions are considered or described as 'reversible' while some are not. However this distinction often is a relative one. In theory a LABG can be completely removed, however in case of band slippage and erosion, some level of dysmotility or permanent lesion of the gastric wall/innervation may remain. In addition, the hyper-pression induced by the

band frequently disrupts the lower oesphagal sfincter mechanism. A SG is irreversible in the sense that a substantial part of the stomach is removed, though there have been no major anatomical changes with respect to the pylorus, duodenum, and no parts are being bypassed. In case of the mixed restrictive-malabsorptive RYGB, the stomach size is reduced by creating a small pouch and transition towards the jejunum is changed by bypassing the duodenum. The stomach is divided in two parts, the pouch and the 'excluded' part of the stomach. Hence none of the stomach parts is being removed, however the stomach is trans-sected so that stomach wall continuity is interrupted. Theoretically a RYGB can be 'undone', however re-configuring and re-connecting the original parts might not (completely) restore normal gastric motility.

Another way is looking at interventions by classifying them from 'less invasive' towards more invasive or 'more drastic', leaving the door open for a possible 'step-up' approach when considering redo-surgery for insufficient initial weight loss, or considerable weight regain.

MBS interventions can as such be 'ranked' from 'less invasive' towards 'more invasive' or even 'drastic'. The purely restrictive interventions like the SG are considered less invasive than the mixed (restrictive/malabsorptive) RYGB, being itself less drastic than the more extensive interventions causing important mal-absorption ('long-limb' RYGB, Scopinaro intervention and the BPD-DS).

Figure 24 – Overview revisional procedures after LAGB, SG and RYGB (non-exhaustive)

LAGB	→	Normal anatomy (band removal)		
	→	**RYGB**		
	→	**SG**	→	**BPD-DS** (duodenal switch)
SG	→	(Re-Sleeve)		
	→	**RYGB**		
	→	**BPD-DS (duodenal switch)**		
RYGB	→	'Normal anatomy'		
	→	**SG → BPD-DS (duodenal switch)**		
	→	Distal RYGB		
	→	Restriction (banding by Fobi-ring)		

LAGB: Laparoscopic Gastric Banding; (L)RYGB: laparoscopic Roux-en-Y Gastric Bypass; (L)SG: laparoscopic Sleeve Gastrectomy; DS: BPD-Duodenal Switch. Adapted from Himpens et al., 2013[80]

As to what concerns the most frequently performed contemporary primary interventions, the SG and the RYGB, subsequent re-do surgery for insufficient weight loss and weight regain might be possibly slightly more common after a purely restrictive internvention than after RYGB (expert feedback).[139] On average SG and RYGB lead to comparable degrees of weight loss, with an observed tendency for a slightly higher efficacy in favour of the RYGB.

A full in depth evaluation of the need for revisional surgery after the different types of primary bariatric procedures performed was not in the scope of this HTA.

General rates of revisional surgery after LAGB have been reported to be up to 40-50%. This is much lower for both the SG and RYGB were rates of revisional surgery have been reported to be up to 10-20%, with in general higher rates for revisional surgery after SG compared to RYGB.

Recent data from a large New York (NY) state database study looked at the rates for revision or conversion after LAGB, RYGB and SG.[298] This study estimated the rate for revision or conversion after LAGB to be 26% (after a FU period between 4-10 years) and the mean time (+/- SD) to the subsequent procedure was 3.8 +/-2.3 years. The rate for revision or conversion after RYGB was 5% (after a FU period between 4-10 years) and the mean time (+/- SD) to the subsequent procedure was 3.6 +/-2.9 years. The rate for revision or conversion after SG was 10% (after a FU period between 4-10 years) and the mean time (+/- SD) to subsequent procedure was 3 +/-2.2 years. LAGB is also the procedure with the highest rates of two or more revisional interventions following the initial primary surgery.[298] This administrative database study however did not allow to identify the indication for revisional surgery (weight loss issues vs. complications from surgery).

The most important reasons for revisional surgery associated with LAGB are: insufficient weight loss, weight regain, hardware problems causing clinical problems (band slippage, band erosion, stomach perforation, early band obstruction, port and tubing problems), motility problems (oesophagal dilation, gastric pouch dilation), band intolerance and gastro-oesophagal reflux. The type of the subsequent revisional procedure depends on its indication. The most frequently performed types of revisional surgery after primary LAGB are: band or port replacement, band removal, without or with conversion to another type of bariatric procedure. Apart from the cases with specific port-tubing malfunction, most experts nowadays mostly prefer to convert LAGB into RYGB or SG, rather than to replace the gastric band (expert feedback).[138]

In general, the most important reasons for revisional surgery associated with RYGB are: insufficient weight loss, weight regain, extreme weight loss, anatomical changes or complications, intolerance caused by dumping syndrome and severe reactive hypoglycaemia, other metabolic issues, bypass intolerance. Possibilities and types of revisional surgeries after RYGB are more limited (conversion to long-limb RYGB, BPD-DS or restriction of the existing RYGB by placement of a ring (Foby ring).

In general, the most important reasons for revisional surgery associated with SG are: insufficient weight loss, weight regain, severe gastro-oesophagal reflux (GORD), and technical/anatomical issues like anastomotic leaks, sleeve stricture and sleeve dilation. In general there are more options for revisional surgery after SG than after RYGB. The most frequently performed types of revisional surgery after primary SG are: conversion to RYGB, or to BPD-DS ('duodenal switch'), and in theory a 're-sleeve' in case of considerable dilation of the initial GS (though probably very rarely performed).

Revisional surgery is on average technically more challenging than primary MBS. Outcomes of re-operative bariatric interventions in general are inconsistently reported, though at a first look, it seems that mortality rates after revisional surgery and 30-day readmission rates are on average somewhat higher than after primary MBS.[137] Re-operative bariatric procedures need to be performed by experienced bariatric surgeons/teams in centres that have the resources to manage these challenging patients.[137]

Note that some anatomical/organic causes of weight regain can be treated endoscopically (via gastroscopic access). The decision to proceed with additional medical or surgical therapy should be based on this multidisciplinary assessment and the patient's specific risk/benefit profile for a re-operative procedure.

Some general and specific considerations based on what was found after a quick literature search,[137, 139, 298] has been directly reflected in the key-points (see hereunder).

Key points – on insufficient weight loss, important weight regain and linked to this, the need for revisional bariatric surgery

- **Some patients may need a revisional surgery (re-operation or conversion) after a primary metabolic and bariatric surgery. The most common reasons for revisional surgery are insufficient initial weight loss, significant weight regain after primary MBS, and because of complications or severe intolerance. Revisional re-do surgery because of insufficient weight loss or considerable weight regain was the focus of this chapter.**
- **While the majority of bariatric patients achieve successful durable weight loss after primary surgery, the patients who present with insufficient weight loss, or (more common) substantial weight regain represent a challenging population.**

  Some of these patient may benefit from additional bariatric surgery to manage their obesity. This is not surprising since obesity is a chronic disease, and consequently requires life-long medical follow-up and care, and patient support.
- **In order to limit patient factors of non- or suboptimal compliance with regard to the necessary long-term life-style changes bariatric patients need to make and sustain (in order to maximize the probability of durable success), life-long medical and para-medical follow-up and support is very important.**
- **<u>Revisional bariatric surgery encompasses both redo and undo surgery</u>.**

  <u>Undo surgery</u> is mostly performed for reasons of intolerance and safety, as is very often the case after LAGB. This is one of the main reasons why nowadays there are more LAGBs being removed than placed.

  In general, <u>redo surgery or re-operative bariatric procedures</u> are often performed for reasons of insufficient weight loss or considerable weight regain. However, as said, tolerance issues might also be a reason for re-do / re-operative bariatric surgery (LAGB → RYGB and SG).
- **It is difficult to obtain reliable estimates on the percentage of patients who need revisional redo-surgery for reasons of inadequate weight loss or considerable weight regain after the current two most commonly performed procedures (RYGB and SG).**
- **Redo surgery in most cases involves the 'conversion' of one type of intervention into another type of bariatric intervention (performed in one or two steps).**
- **Most reports and studies in literature involve single institution studies/data, and long-term data across many institutions seem to be very scarce. The rates of, and reasons for revisional bariatric surgery are different from procedure to procedure. LAGB seems to be the procedure with the highest rates of two or more revisional interventions following the initial primary surgery**

5.5 Safety of bariatric surgery – discussion

5.5.1 Context

No intervention is exempt from possible complications or adverse effects, and this is no different for metabolic and bariatric surgery (MBS).

The decision to opt for metabolic and bariatric surgery is an important decision which requires thoughtful consideration, given the invasive (and often irreversible) nature, the existence of a number of concerns that may relate to long-term effectiveness, and to possible long-term safety and tolerability considerations.

Although the list of potential adverse effects and consequences might be very long, this does not mean that the overall benefit-risk balance of MBS in general would be negative. In fact, today MBS offers the most effective and durable treatment for severe obesity. The extended safety review merely attracts attention to the fact that the choice for MBS is not a decision that can be taken lightly.

Given the observational nature of the majority of the underlying data, this clinical safety evaluation - where the focus is on long-term safety - aims to provide a qualitative assessment, and where possible, tries to provide a semi-quantitative indicative assessment. The clinical safety evaluation also aims to identify and provide clinical points for attention, on which the subsequent and ongoing HSR project will be able to build on. One of the most important objectives of this HSR project will be to do proposals that will aim at the improvement of the organisation of care for bariatric patients.

As this applies to all laparoscopic surgical interventions, there might be a small risk of peri-operative mortality and complications associated with MBS. However with the remarkable progress made over the last (two) decade(s), early post-operative mortality rates came down to ca. 0.1-0.3% for the current two most commonly performed interventions (the RYGB and the SG). As such peri-operative mortality of these bariatric procedures now seems to have become similar to the mortality rates observed for other commonly performed elective surgeries like for instance cholecystectomy, hysterectomy, and have mortality rates that are clearly lower than for knee or hip arthroplasty, or colorectal surgery. Once the first perioperative risk has been taken, the major focus of interest is on long-term clinical effectiveness and safety. The discussion and conclusions are focusing on and essentially do apply to the Sleeve gastrectomy (SG) and Roux-en-Y Gastric bypass (RYGB). Almost all interventions are nowadays being performed laparoscopically.

5.5.2 Evidence review – short-term clinical safety

Contemporary 30-day mortality seems to be in the order of 1-3/1000, with in literature rates that are on average very comparable for RYGB vs. SG.

Short-term complications are typically considered to happen within 30 days of the intervention. They can be surgical in nature (directly linked and caused by the surgical act), or medical in nature. Medical complications occurring within 30 days of intervention are often indirectly or directly linked to the recent surgery, and their incidence is also influenced by the overall condition of the patient, including the number and severity of co-morbidities and other risk factors. Many of them (but not all) have also been described with other abdominal surgical interventions. Others are more specific to occur in function of the type of metabolic and bariatric surgery performed. Note however that a time period of 30 days following the intervention still remains relatively short-term, explaining why some authors and clinicians may use a period of ≤90 days following the intervention, when considering short-term complications.

Short term complications based on ≤30 day re-admission and re-operation rates decreased over time, with especially a sharp fall in short-term reoperation rates over the last decade(s). On average 30 day re-admission rate is ca. 5%, of which halve occur within the first week after discharge.

Taken together among the most frequent important early complications occurring after bariatric surgery (surgical and medical combined) are infection, haemorrhage, leaks/perforation, obstruction, venous-thromboembolism and myocardial infarction.

In general, SG seems to be characterized by lower short-term serious morbidity (order of ca. 4% for SG vs. ca. 6% for RYGB) and lower 30-day reoperation rate (order of ca. 1.6% vs. ca. 2.5%) compared to RYGB (based on US 2010-2013 data).

Nausea, vomiting, dehydration and electrolyte imbalances were more commonly a reason for readmission after SG. Also venous thromboembolism and post-operative leaks are relatively more reported after SG, compared to RYGB. When leaks occur, they may present on average over a longer time span after surgery in case of SG compared to RYGB. Sleeve gastrectomy is reported to have an on average shorter mean operation time and possibly also a lower rate of blood loss requiring transfusion.

Post-operative pain, bleeding, intestinal obstructions, wound problems, infection, myocardial infarction was on average more commonly reported as reasons for readmission after RGYB.

Globally one could conclude that compared to laparoscopic RYGB, laparoscopic SG is associated with a slightly lower 30 day serious morbidity and a comparable 30-day mortality.

5.5.3 Evidence review – long-term clinical safety

Some long-term adverse effects (AE) or complications apply to bariatric surgery as such, though there are also long-term complications or adverse effects that are more specific and are more likely to occur in function of the type of the bariatric procedure performed.

Regarding the long-term complications or effects, we can essentially distinguish surgical complications, medical complications (including neurological) and psychiatric or psychological aspects.

One of the most prevalent problems after MBS is the issue of vitamin and micronutrient deficiencies, which on average are more common after RYGB than after SG.

The risk or prevalence of vitamin and micro-nutrient deficiencies can highly vary depending on the type of intervention, the prevalence of uncorrected pre-existing deficiencies, and the compliance of the patient both with regard to the correct intake of the recommended vitamin/micro-nutrient supplements and with the life-long medical follow-up. Also the level compliance may vary over time.

These deficiencies may be insidious, may or may not cause symptoms, and may be at the basis of other (possibly serious) complications.

Medical and neurological complications mostly occur beyond the initial 30 days, and they may actually present years after surgery, and **some of them are caused by the above mentioned vitamin- or mineral deficiencies**. For some of them the patient also may have an important role or contribution, e.g. when there is poor compliance with regard to the intake of vitamin/mineral/trace element supplements, non-respect regarding dietary restrictions, and/or non- or insufficient compliance with regard to required lifelong medical (multidisciplinary) follow-up. Note however that the possible issue of poor compliance is not always a deliberate choice, as obesity often is a complex disorder, often being accompanied by the presence of complex psycho-social aspects.

Although classically (and often from a surgeon's point of view) complications are considered 'late' when they happen post-operatively after day 30, in clinical medical practice however it certainly is also key to consider 'late' complications when occurring beyond 1 to 2 years after surgery, more than 5 years, or even more than 10 or 15 years after surgery. In fact some authors and professional societyies considered data to be long-term when available data are equal to or go beyond 5 years, [100] or even, and better, when available data are equal to or go beyond 10 years.

Although, and notwithstanding the fact that the number of articles on bariatric/metabolic surgery and medicine 'literally' explodes, good solid long-term safety data (>5-10 years) based on RCTs, evaluating the effect on long-term mortality and possible long-term untoward effects of bariatric or metabolic surgery, are very sparse and essentially non-existing. Therefore, as is the case for long-term mortality, other long-term safety data essentially do rely on systematic reviews and meta-analysis which are mostly based on observational data and research, as well as on primary individual observational studies (cohort and registry studies).

Apart from the fact that the risk and risk level may well vary for each type of bariatric surgery (LAGB, RYGB, SG; BPD-DS), the risk and frequency of occurrence of these AE may among others also clearly depend on the presence of pre-existing co-morbidities, pre-existing nutritional deficiencies, and also patient compliance (which may also vary over time). This all explains why it is difficult to establish an exact risk estimate at the level of the individual patient.

Metabolic and bariatric surgery aims at improving obesity related health outcomes (by improvement of cardiovascular and other risk factors, amelioration or resolution of obesity related comorbidities…), improving QoL, and of course and not at the least, aims at reducing premature death. Therefore the evaluation of long-term mortality as an outcome can both be considered from a safety and from an effectiveness point of view.

Data on the net results for long-term mortality risk are the result and are composed of the beneficial health effects (as aimed at by MBS), and the possible negative effects. Solid long-term mortality data from RCTs are virtually non-existing because truly randomized clinical trials in general do not have enough patients included that allow conclusions on mortality and/or because they are only short- or mid-term as to what concerns their controlled follow-up period. Therefore we had to rely on primary articles, review articles and systematic-reviews and meta-analyses reporting on the risk of mortality after bariatric surgery, compared to groups of obese patients that did not had bariatric surgery. Most of this meta-analyses are based on a mix of data, that to a very large extent come from observational research (prospective and retrospective cohort studies, registry based studies), and to a much lesser extent from randomized clinical trials.

As there were ample data (mostly of underlying observational nature) that were overall consistent with regard to the observed effects on long-term mortality, it is important to consider this type of evidence in the overall evaluation. There remains however an important caveat and remark to be made which is that observational data are inherently more prone to a risk of bias than RCT data.

As said, the observed effect size is large, and overall very consistent. However the risk of bias remains always a possibility in observational research. Notwithstanding this caveat, when looking at the SOS trial (a large historic, well controlled and matched long-term study with overall a low or limited risk of bias), and when considering different SR-MAs on the topic where researchers did sensitivity analysis (among others by excluding trials with moderate-high risk of bias), we can be (based on the quality of the data and the effect size) low-to-moderately confident that overall mortality (= risk of premature death) is reduced after MBS.

The data from these sources (four SR-MA, largely from observational research) and from some recent registry/cohort studies show overall a consistent effect with regard to long-term mortality risk. In general one observes an average relative reduction in premature mortality risk that may roughly vary between -30% to -40% (-45%). This is a net-effect on overall mortality risk. Observations made in some of these SR-MA's point to a decrease in cardiovascular disease (or CV-disease related mortality) and cancer (or cancer related mortality). However there is a signal that death due to suicide and accidents could be higher in the surgical group vs. the non-surgical group.

As mentioned the long-term adverse effects vary by procedure and include among others surgical complications (e.g. gastrointestinal bleeding, intestinal (sub-)obstruction, formation of fistula, etc.), dumping syndrome, late metabolic complications (e.g. mineral and vitamin deficiency, protein malnutrition, post-prandial hypoglycaemia, anaemia, …), risk of cholelithiasis (gall stone), risk of nephrolithiasis (kidney stones), gastro-eosophagal reflux, chronic unexplained abdominal pain, neurological complications (mostly as a consequence of vitamin and mineral deficiencies). Recurrence of, worsening of, or new onset psychological suffering and psychopathology (depression, anxiety, suicidal ideation, self-harm, problematic eating behaviour and eating disorders, or other mental health conditions) have been described. Patients who undergo MBS may be at increased risk for substance use, including alcohol use and opioid medicines. The risk for alcohol use disorder seems to be mostly present after RYGB, with

an increased risk especially as from beyond 2 years after the intervention.

MBS may also alter the pharmacokinetics (drug disposition) of medicines. The risk seems to be on average higher after RYGB than after SG. For some drugs there might be a decrease in drug absorption, while for other drugs there might even be an increased drug absorption. Some changes in drug disposition are not related to the MBS as such, but are only a consequence of the decrease in weight and adipose tissue after surgery. In general, for many drugs, relatively little is known about the potential effect of MBS on changes in pharmacokinetics. One example is the potential for diminished absorption of oral contraceptive pills after RYGB or after other malabsorptive interventions, which may mandate the use of other contraceptive methods. After MBS, many patients will be able to decrease their doses of antihypertensive drugs, lipid lowering drugs and diabetes medication. However a substantial part of very obese people are taking psychotropic drugs, which very often will need to be continued after MBS. In this case, the dose of some of these psychotropic medicines might need to be adapted. Given that in general there is a relative paucity of data available on the effect of MBS on drug PK and disposition, a high level of vigilance is needed both with regard to the potential for a decreased absorption and lower plasma levels of some drugs, and also for the risk of toxicity with some other drugs. This will be in particular important for drugs with a narrow therapeutic window and/or those of critical clinical importance. This vigilance needs to be based on a high level of clinical suspicion both for decrease and increased (toxic) drug effects.

There are also some notes to be made regarding **pregnancy and pregnancy outcome**. Patients undergoing MBS are advised to avoid and postpone pregnancy until at least (12-)18-(24) months after surgery. Obese women of childbearing potential become on average more fertile after MBS (because of weight loss and an improvement in hormonal status), so that effective contraception should be in place. In general, pregnancy outcome, both in terms or maternal outcome and in terms of foetal/offspring outcome, will be improved in severely obese women that have undergone MBS, compared to severely obese women not having undergone MBS (and with stable high BMI). Risk for (pre-)eclampsia, gestational diabetes will be lower, as is the risk for large-for-gestational-age infants. Accordingly the risk of birth-related traumata, post-partum hemorraghe and the need for caesarean delivery are estimated to be lower. However in terms of outcome for the off-spring there might also be some increase in the risk for small-for-gestational age infants, and prematurity, where the risk might be slightly higher after interventions with a malabsorptive component. Female bariatric patients desiring to become pregnant need to be well screened for nutritional deficiencies both before and during pregnancy, and they should be compliant with regard to correct intake of the proposed vitamin and micronutrient supplements. Besides, the choice for a specific type of metabolic and bariatric procedure to be performed might also be influenced by the existence of a (possible) future pregnancy wish. For instance the life-long risk for internal hernia associated with the RYGB, a complication which might present more atypically during pregnancy, might be a possible reason to choose or prefer a SG instead of a RYGB, provided there is no contraindication for the SG.

Despite a global decrease in long-term mortality compared to severely obese non-operated patients and despite an (initial) improvement of psychiatric co-morbidities and QoL in patients who have undergone MBS, the risk of suicide seems to be (slightly) elevated and this for currently unknown and possibly multifactorial reasons.

Psychopathology and psychiatric disorders such as depressive disorders, anxiety disorders, eating disorders, self-harm and substance use disorders are prevalent among bariatric surgery candidates, and can persist or recur after surgery. Several data suggest that the initial beneficial effect on mood disorders, depression and psychological aspects of QoL may wane over time ('post honey-moon period'), with possibly the best long-term improvements being observed in the physical domain components of QoL. Although most patients show an improvement of mood and depression scores in the years after surgery, there might be a subset of patients where depression and mood disorders may actually worsen. Reduced self-esteem may play a considerable role in the relationship between obesity and depressive disorders, thus increasing the risk for suicidality. Suicide risk (ideation, attempts, completed suicide) seems to be higher in patients that have undergone MBS vs. the general

population, though the data are not completely consistent on whether or not the risk is increased in the period post-surgery vs. pre-surgery. A recent SR-MA on suicide and self-harm risk points to a possible doubling of the risk following surgery (vs. pre-surgery). Several hypotheses point to factors as obesity itself, (perception of) insufficient results on weight loss, but also and not to the least extent, to possible other causes that are independent of the surgical intervention like underlying but not sufficiently controlled psychiatric pathologies in a population at a higher risk of suicide (attempts) or self-harm. Depressive disorders may persist in bariatric surgery patients despite successful weight control after surgery. Also it is not excluded that the risk may possibly be higher after RYGB (a mixed restrictive malabsorptive intervention), leading some authors to hypothesize on the role of nutrient deficiencies and possible hormonal effects. Patients should be informed about the risk of suicidality, and in general they need to be educated that it is normal to have an initial improvement in psychiatric illness and psychosocial functioning, which may be followed by a decline.

There **is some growing awareness about the (re)emergence of problematic eating behaviours (EB) and eating disorders (ED)** in bariatric surgery patients, particularly the possibility of post-operative de novo problematic restrictive EB and ED.

Eating disorders have a strong link with other psychopathology, or are part of the psychopathology which may be present before MBS. ED or problematic EB might reoccur after MBS, while there are also other patients in whom new maladaptive and problematic eating behaviours may develop, which can possibly worsen and lead to an eating disorder. Relatively well known problematic EB or ED that can (re)occur after MBS are e.g. grazing, using too much energy dense food, and binge eating. However the occurrence of new restrictive problematic EB or restrictive ED is in general much less known. Restrictive EB might be induced by post-operative symptoms like plugging, vomiting, dumping, dysphagia, constipation or abdominal pain, and this in an attempt to compensate for the discomfort patients may experience when consuming difficult to digest meals or after ‘over-eating’. Restrictive EB or a restrictive ED might also develop insidiously when the patient is preoccupied or over-focussed as to what concerns the implementation of ‘restrictive dietary recommendations’. In this context these recommendations might possibly become a trigger for the development of a restrictive ED in patients that are more susceptible to loose themselves in an eating pattern characterized by extreme control and rigid diet rules.

Dermatologic adverse effects may also occur after MBS, and they may incur further medical and psychological problems. **A frequently reported issue by patients is the development of excessive skinfolds (mostly at level of abdomen, upper arms, thighs, breasts**) with possible aesthetic consequences and impact on body image and self-esteem. Excessive skin folds may also lead to maceration, intertrigo and infection. Plastic surgery might be necessary or desirable in order to resolve these issues.

Revisional surgery (redo and/or undo surgery) might be necessary in some patients both for reasons of insufficient weight loss and for considerable weight regain, or for reasons of serious adverse effects or severe intolerance. While the majority of bariatric patients achieve successful durable weight loss after primary surgery, the patients who do present with insufficient weight loss or important weight regain represent a challenging population. Substantial weight regain is a relatively more important cause for revisional surgery than insufficient initial weight loss. Significant weight regain and insufficient initial weight loss can have diverse causes. There might be ‘organic’ cause (like e.g. gastro-gastric fistula, or a wide open gastro-jejunal anastomosis, …), however this probably is the case in a relative minority of patients. Some of these ‘organic’ causes of weight regain can be treated by endoscopic interventions, while for other patients, a new surgical intervention might be required. Before considering whether a particular patient is a candidate for a revision of the primary operation, it is important to determine ‘whether the operation failed the patient’, or ‘whether the patient failed the operation’. The reason is that in many circumstances, significant weight regain (after an initial period of weight loss) or insufficient weight loss, is favoured or can be caused by poor-compliance with regard to the required life-long dietary adaptations and restrictions. In other words one should distinguish an anatomic cause for weight regain from weight regain which is primarily the result of behavioural discrepancies such as large portion sizes (hyperphagia), high caloric content

food, frequent between meal snacking (polyphagia, grazing) and lack of exercise.

A distinction should be made between inadequate weight loss or substantial weight regain on the one side, and the need for revision on the other side, as importantly not all failures need to be revised.

As repeatedly mentioned, good compliance is necessary (but is not a guarantee) in order to maximise both the probability of durable success on weight loss, and to minimise the risk of long-term adverse effects, nutritional deficiencies and complications. Compliance includes the correct intake of the proposed vitamin/mineral/trace element supplements, respecting the dietary restrictions, and compliance with regard to the required lifelong medical (multidisciplinary) follow-up. This HTA did not have the aim to investigate the underlying causes for sub-optimal or poor patient compliance. Nevertheless it is important to state that the underlying reasons for suboptimal or poor compliance may be diverse and variable including amongst others a lack of sufficient information, understanding or knowledge, underestimation of the importance of compliance, negligence and nonchalance, but also factors such as financial constraints, psychosocial issues, psychopathology or the (re)occurrence of problematic eating behaviour and eating disorders. Factors influencing sub-optimal compliance and how to best deal with it in order to increase compliance will be a specific subject of attention in the ongoing HSR project on bariatric surgery.

6 OVERALL CONCLUSION ON CLINICAL EFFECTIVENESS AND SAFETY

Severe or morbid obesity is increasingly considered a chronic (complex) disorder or disease, needing long-term (multi-disciplinary) care, follow-up and self-care. **Based on the review of literature and this HTA evaluation, we can conclude that - at this moment - metabolic and bariatric surgery (MBS) offers by far the most effective durable treatment for morbid obesity (BMI ≥40) and for severe obesity (BMI ≥35) associated with important co-morbidities, this in terms of successful weight reduction and, overall can lead to better health status and outcomes. However no intervention is exempt from possible complications or adverse effects, and this is no different for metabolic and bariatric surgery (MBS).**

The focus and main conclusions of this HTA are on the Sleeve gastrectomy (SG) and the Roux-en-Y Gastric bypass (RYGB), as they are the two most commonly contemporary MBS procedures performed. Almost all of these interventions are now being performed laparoscopically. Therefore the conclusions of this HTA on MBS essentially only apply to the SG and RYGB.

The decision to opt for metabolic and bariatric surgery is an important decision which requires thoughtful consideration, given the invasive and often irreversible nature, and the existence of a number of concerns that may relate to long-term effectiveness and to possible long-term safety and tolerability issues or considerations.

The clinical benefit-risk balance of a treatment or intervention depends on its combined effects of the clinical effectiveness and the clinical safety (potential complications and adverse effects). **For MBS, the clinical benefits in terms of weight loss (and associated health benefits) are in general more easily to quantify, however the long-term clinical safety spectrum (of potential issues, complications or adverse effects) is very large and much more difficult to quantify. Therefore we opted to provide an extensive overview of the clinical safety spectrum of MBS, which is more of a qualitative or semi-quantitative nature.**

Notwithstanding the fact that the long-term clinical safety spectrum essentially is more of a qualitative or semi-quantitative nature and consideration, it remains an important part in the overall risk-benefit evaluation to be made, both in general and even so in particular, at the level of the individual patient. Moreover the extensive clinical safety description allowed the identification of clinical points for attention which will be further elaborated on in the ongoing and subsequent HSR project on bariatric surgery. One of the major aims of this HSR will be to come to proposals on how the organisation of care for bariatric patients can be optimised and improved.

Although the list of potential adverse effects and consequences may be very long, this does not imply that the overall benefit-risk balance of MBS in general would be negative. The extended safety review merely attracts attention to the fact that the choice for MBS is not a decision that can be taken lightly.

As this applies to all laparoscopic surgical interventions, there might be a small risk of perioperative mortality and complications associated with MBS. However with the remarkable progress made over the last (two) decade(s), early post-operative mortality rates after MBS came down to ca. 0.1-0.3% for the current two most commonly performed interventions (RYGB and SG). As such perioperative mortality of these bariatric procedures now seems to have become similar to the mortality rates observed for other commonly performed elective surgeries like for instance a cholecystectomy or a hysterectomy. Almost all SG and RYGB interventions are nowadays being performed laparoscopically, which improves short-term surgical risk and shortens recovery and hospitalisation duration. Once the first perioperative risk has been taken, the major focus of interest will be on long-term clinical effectiveness and safety.

Short-term and medium term clinical effectiveness have been evaluated and based on RCTs, except for the evaluation of effectiveness in adolescents where also observational studies were taken into account.

The effect on long-term mortality – a net effect which is a result of the aimed benefits and the possible risks – is essentially based on research which is based on studies of observational nature, as is also the evaluation of other long-term clinical safety or adverse effects. Solid long-term mortality data from RCTs are virtually non-existing because truly randomized clinical trials do not have enough patients included that allow conclusions on mortality and/or because they are only short- or mid-term as to what concerns their controlled follow-up period.

Therefore, we relied on systematic-reviews and meta-analyses reporting on the risk of mortality after bariatric surgery compared to groups of obese patients that did not had bariatric surgery. Most of this meta-analyses are based on a mix of data which to a very large extent come from observational research (prospective and retrospective cohort studies, registry based studies), and to a much lesser extent from randomized clinical trials. As there were ample data mostly of underlying observational nature which were overall consistent with regard to the observed effects on long-term mortality, it is important to consider this type of evidence in the overall evaluation.

The observed effect size on mortality risk reduction is relatively large and overall consistent, however with the important remark and caveat that an inherent risk of bias remains always possible in observational research. Notwithstanding this caveat, when looking at the historic SOS trial (a large and well controlled and matched long-term study) and when considering different SR-MAs on the topic where researchers relied on adjusted data and did sensitivity analysis (among others by excluding trials with moderate-high risk of bias), we can be (based on the quality of the data and the effect size) low-to-moderately confident that overall mortality (= risk of premature death) is reduced after MBS.

The data from these sources (four SR-MAs, the historically important SOS trial, and some recent registry/cohort studies) show overall a consistent effect with regard to long-term mortality risk. In general one observes an average relative reduction in premature mortality risk that may roughly vary between -30% to -40% (-45%). This is a net-effect on overall mortality risk. Observations made in some of these SR-MAs point to a decrease in cardiovascular disease (or CV-disease related mortality) and cancer (or

cancer related mortality). However there is a signal that death due to suicide and accidents could be higher in the surgical group vs. then non-surgical group.

Observational data normally imply a low grade or level of evidence because of the possible inherent risk of bias (RoB). However because of the large and consistent effect size and the fact that in several SR-MAs the risk of bias assessment indicated a relatively low-to-moderate RoB level (quality of the data), we decided to upgrade the evidence-strength and judged the overall GRADE level for long-term mortality risk reduction as being low-to-moderate, which is a reflexion of the confidence we have in the observed effect for this outcome. Therefore **we can be low-to-moderately confident that overall mortality (= risk of premature death) is reduced after MBS.**

Apart from the long-term mortality risk evaluation, most of the focus for the safety evaluation was on the long-term clinical safety aspects. Notwithstanding the fact that the number of articles on bariatric/metabolic surgery and medicine 'literally' explodes, good solid long-term safety data (>5-10 years) based on RCTs evaluating the effect possible long-term untoward effects of bariatric or metabolic surgery are very sparse and essentially non-existing. Therefore we essentially had to rely on systematic reviews and meta-analysis which are mostly based on observational data and research, as well as on primary individual observational studies (cohort and registry studies).

Based on this evaluation we conclude that:

- MBS currently is the most effective durable treatment for morbid obesity (BMI ≥40) and for severe obesity (BMI ≥35) associated with complications or important co-morbidities, this in terms of successful weight reduction. MBS overall can lead to better health status and outcomes.
- When patients are well screening and evaluated preoperatively, the overall benefit-risk balance is positive. However the benefit-risk-balance will vary from patient to patient.
- Based on the extended safety review, it is clear that the decision to opt for MBS is not a decision that can be taken lightly or loose-minded. MBS is not a miracle solution that will resolve everything or all aspects of obesity. The correct implementation of life-long life-style changes with regard to a correct adapted healthy diet and physical exercise remains crucial, as is the required compliance with lifelong medical follow-up.
- Most of the safety review was focussed on the possible long-term consequences, adverse effects or complications. These can be considered of surgical-anatomical nature, medical nature (including neurological) and psychiatric nature (aspects of psychological well-being).
- The quality of follow-up, compliance and self-care clearly can influence the outcome, both in terms of the probability of maintaining a durable long-term successful weight reduction as well in terms of limiting the risks and probability for the occurrence of adverse effects, intolerance or complications. Notwithstanding this, there are patients who - despite applying good self-care and are compliance on all aspects - will experience serious complications or severe intolerance after MBS.
- In severely obese patients with type 2 diabetes, MBS can induce (temporary) remission of their diabetes. Based on RCT data, ca. 55% of these patients will attain remission within 1-2 years after MBS, vs. ca. 8% in those not undergoing MBS. However 'remission' rates may decrease over time, with ca. half of those patients that obtained remission, relapsing within 5 years. An important note is that 'remission' in this context does not equal definitive cure. Even if patients do not show remission, most type 2 diabetes patients will show better glycaemic and metabolic control, often obtained with a less intensive pharmacological treatment.
- RCT evidence on the impact of bariatric surgery on hypertension is heterogeneous. In one RCT, remission of hypertension is observed in half of the patients after surgery. In other trials, no clear impact on remission was demonstrated, although there was a decrease in the number of antihypertensive drugs needed.

- In patients on lipid lowering drugs (RCT-data), at 5 years bariatric surgery is associated with significantly lower plasma lipids and lipid lowering drug use.
- Adverse effects of bariatric surgery may vary by procedure and include among others surgical complications (e.g. anastomotic or staple line leaks, gastrointestinal bleeding, intestinal obstruction, the need for re-operation), late metabolic complications (e.g. protein malnutrition, mineral deficiency, vitamin and micronutrient deficiencies, anaemia, hypoglycaemia), gall stones and gastroesophageal reflux.
- Patients who undergo metabolic surgery may be at risk for substance use, including drug and alcohol use.
- Pre-existing psychopathology and emotional disorders are prevalent in candidates for MBS. After MBS often a (transient) improvement can be observed especially in the emotional domains of QoL, however this effect may wane over time. There are some data potentially indicating that suicide risk, and the risk of self-harm and accidents may be increased post-surgery compared to pre-surgery.
- There is some growing awareness about the possible emergence or re-emergence of problematic eating behaviours (EB) and eating disorders (ED) in bariatric surgery patients, particularly the possibility of a de novo post-operative problematic restrictive EB and ED.
- MBS may influence the pharmacokinetics of drug absorption and disposition.
- MBS may both have beneficial effects on pregnancy and pregnancy outcome (for the mother and the off-spring), as well as carry some risks. There also might be implications in terms of a contra-indication to become pregnant in the first period (ca. 18 months) after MBS, the choice of the most appropriate contraceptive method to be used, and the choice for a particular type bariatric intervention in function of a possible future pregnancy wish.
- Dermatologic adverse effects may also occur after MBS, and they may incur further medical and psychological problems. A frequently reported issue by patients is the development of excessive skinfolds (mostly at level of abdomen, upper arms, thighs, breasts) with possible aesthetic consequences and impact on body image and self-esteem. Excessive skin folds may also lead to medical problems such as maceration, intertrigo and infection. Plastic surgery might be necessary or desirable in order to resolve these issues.
- Revisional surgery (redo and/or undo surgery) might be necessary in some patients both for reasons of insufficient weight loss and for considerable weight regain, or for reasons of serious adverse effects or severe intolerance.
  While the majority of bariatric patients achieve successful durable weight loss after primary surgery, the patients who do present with insufficient weight loss, or important weight regain represent a challenging population. Substantial weight regain is a relatively more important cause for revisional surgery than insufficient initial weight loss. Significant weight regain and insufficient initial weight loss can have diverse causes. There might be an ‘organic’ cause (like e.g. gastro-gastric fistula, or a wide open gastro-jejunal anastomosis, …). However often significant weight regain (after an initial period of weight loss) or insufficient weight loss, can be favoured or caused by poor-compliance with regard to the required life-long dietary adaptations and restrictions. Also a distinction should be made between inadequate weight loss or substantial weight regain on the one side, and the need for revision on the other side, as importantly not all failures need to be revised.

An important note on the importance of good compliance is that poor compliance may have many causes which makes that adherence to follow-up and the continuation of necessary behavioural changes is being jeopardized or sub-optimal. Poor compliance may not be a deliberate choice of the patient. There might be individual reasons explaining why implementing durable lifestyle changes may be difficult, or why compliance with follow-up appointments is suboptimal or absent. Examples of reasons are people who experience loss of control during eating, or people who are

in a difficult socio-economic situation which may (partly) explain why agreements made are not complied with, why appointments for further follow-up visits are not made or why people don't show up at visits, etc. (expert feedback from the "vzw Eetexpert.be")

One of the main purposes of the life-long medical (multidisciplinary) follow-up post-bariatric surgery is to monitor for and prevent complications and problems (including psychological problems), to diagnose them timely and manage these problems appropriately together with the patient. All of this will be subject of further research and subsequent proposals that will be made in the subsequent and ongoing HSR project, of which one of the major aims is to improve and optimize the care and organisation of care for bariatric patients.

Specific note on MBS in adolescents

The available evidence suggests that short-term effectiveness and safety outcomes of bariatric surgery in adolescents are comparable to those observed in adults. However, robust long-term data on the effectiveness and safety of bariatric surgery in adolescents are lacking. We refer to chapter 4.3 and 5.3.5 for more information on the context and results of MBS in adolescents.

Specific note on MBS in obese patients with type 2 diabetes and a BMI between 30-34.9 kg/m^2

RCT evidence on diabetes remission in patients with a BMI <35 kg/m^2 suggests that T2DM remission rates are similar to that observed in patients with a BMI >35 kg/m^2. Bariatric surgery may improve quality of life in diabetic patients with BMI between 30 and 35 kg/m^2. (Low level of evidence). Direct evidence on long term survival specifically for diabetic patients with BMI between 30 and 35kg/ m^2 is not available. We refer to chapter 4.4 for more information.

7 BARIATRIC SURGERY IN BELGIUM

7.1 Reimbursement criteria, length of stay and costs for bariatric surgery

7.1.1 Reimbursement criteria

Bariatric surgery is (partially – see part 7.1.3) reimbursed in Belgium since 2007. The RIZIV INAMI reimbursement requires the following criteria to be met (see Figure 49 in Appendix 6):

- Adults (≥18 years) with a BMI over 40 kg/m^2 or
- Adults (≥18 years) with a BMI between 35 and 40 kg/m^2 and one of the following co-morbidities or conditions:
  - Diabetes treated with medication
  - Therapy resistant hypertension (i.e. >140/90mmHg, despite treatment of at least 1 year with simultaneous use of at least 3 antihypertensive drugs)
  - Obstructive sleep apnea (OSAS)
  - Re-intervention after a complication or insufficient effect of the previous bariatric surgery intervention.

In addition:

- The patient must have followed a documented diet during at least 1 year which was not successful on the long-term;
- A multidisciplinary consultation in which besides the surgeon at least a physician specialized in internal medicine and a clinical psychologist or a psychiatrist participated. The report of this multidisciplinary consultation with a joint declaration about an indication for surgery is signed by at least the three of the above mentioned disciplines. This report is, together with the documented diet, to be found in the medical file of the patient.

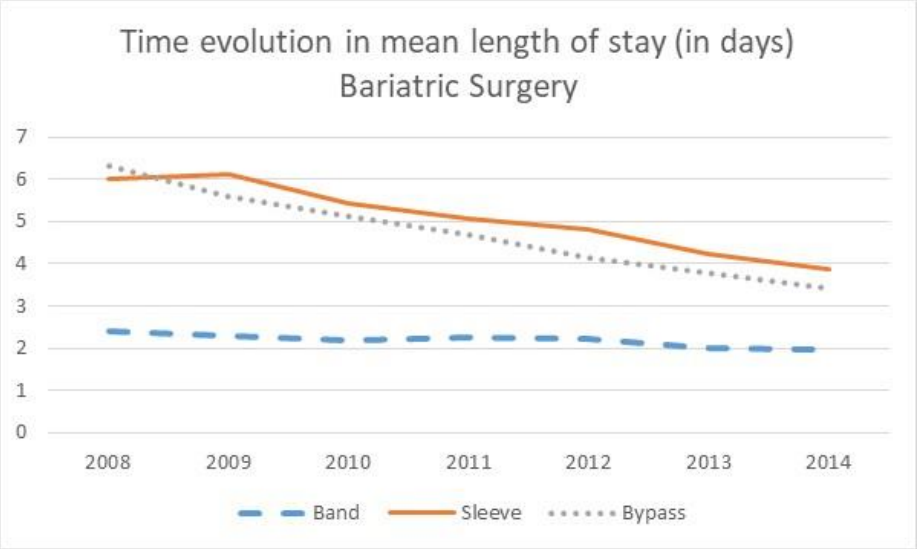
Key points

- **Bariatric surgery is (partially) reimbursed since 2007 in Belgium. To be eligible for reimbursement, a set of criteria have to be met : BMI ≥40 /or BMI 35-40 kg/m^2 in combination with either medicated diabetes, or therapy resistant hypertension or sleep apnea (or a previous unsuccessful bariatric surgery).**
- **In all cases a patient undergoing surgery must have been evaluated by a multidisciplinary consultation, and must have tried a diet for weight reduction for for more than 1 year without effect.**

7.1.2 Length of hospital stay

Figure 25 shows the mean hospital duration over time per type of bariatric surgery. In 2008 the average hospital stay was about 6 days for sleeve and bypass operations, and only 2-3 days for banding operations. In 2014 the average hospital stay has decreased to only 3-4 days for sleeve and bypass operations, and about 2 days for banding operations. Concluding, as an overall trend, hospital duration for bariatric surgery seems to shorten over time for sleeve and bypass operations, while remaining relatively stable for gastric banding. As a result, in the more recent years there is less difference in hospital duration for sleeve, bypass and banding surgery.

Figure 25 – Time evolution mean hospital duration by bariatric surgery type



Note: The corresponding table with numbers and a figure with more details on the natural variation of hospital stay duration (exit date – entry date) are presented in Table 52 and Figure 46 in Appendix 6.

7.1.3 *Financial costs: reimbursed costs & underlying cost components*

The **total cost for a bariatric surgery** consists of:

- the *reimbursed cost* (=the amount paid by the official convention health insurance fees RIZIV – INAMI)
- the *out-of-pocket amount paid by the patient*. The out-of-pocket cost consists of
    - the *co-payment* (NL "remgeld"/ FR "ticket modérateur")
    - + the *supplements* (e.g. for patients in a single room)

All bariatric **cost calculations** are based on RIZIV information. This allows a correct calculation of the *reimbursed cost* = part paid by the official health insurance. This variable can be found in the subsequent graphs & tables below.

Note: The *out-of-pocket amount* paid by the patient can be estimated based on previous studies by the Socialist Sickness Funds (2016)[300] and the Independent Sickness Funds (2018):[140]

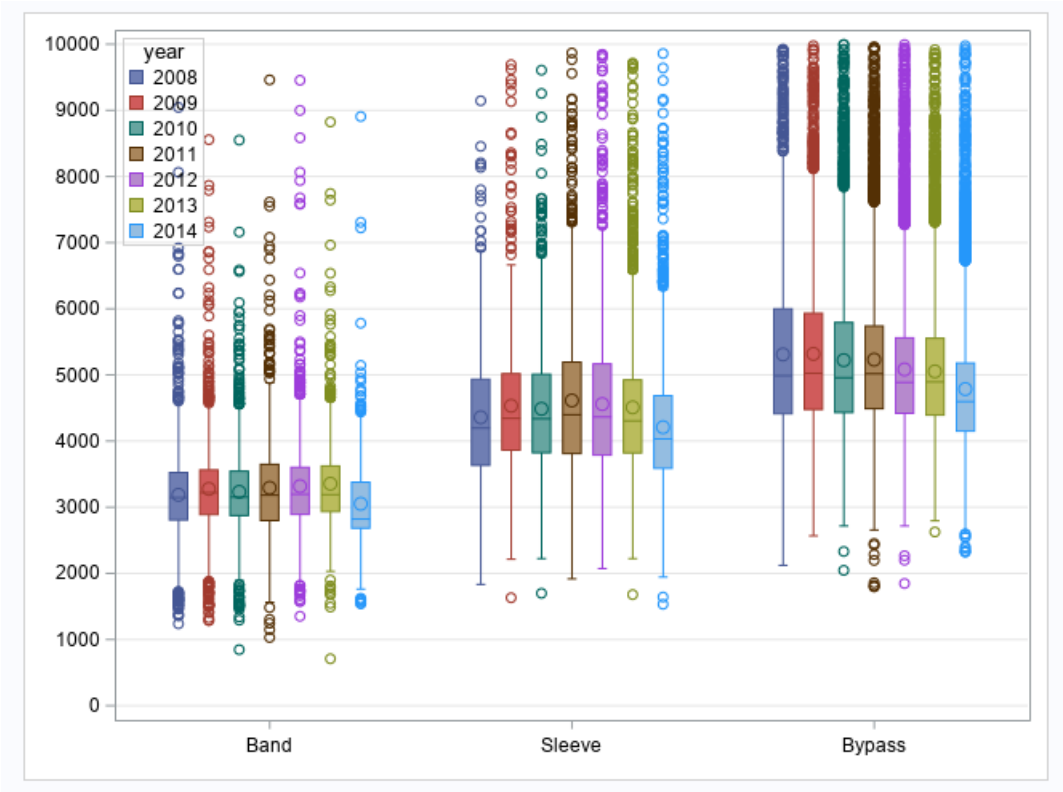
- ca. €1000 to €1200 for the co-payment part (NL "remgeld"/FR "ticket modérateur)[140, 300]
- ca. €1900 to €3700 extra in supplements for patients in a single room during hospital stay (of which about 83% was for additional surgeon fees).[140]

Calculations of reimbursed costs are based on the following selection criteria:

- Patients <u>not</u> covered by the official convention health insurance (RIZIV – INAMI) are excluded from calculations. This excludes patients who underwent surgery with only financial retribution from their complementary health insurance, as well as patients with foreign health insurance.
- Calculations are based on *all hospitalised patients with bariatric surgery*, excluding patients in day- hospitalisation.
- For the hospital stay cost the *100% per diem correction* [301] has been used correcting for additional hospital funding, specific to each hospital, so as not to underestimate the actual hospitalisation costs.
- A few patients (less than 10 each year cf. Appendix 6) were removed as it was impossible to classify them into the bypass/sleeve/gastric banding typology – because they had two different bariatric surgery types simultaneously within the same operation.
- No correction has been made to remove outliers (e.g. patients staying long due to complications or bad health conditions), in order to preserve information for both 'easy' and 'difficult' surgeries.

Figure 26 shows the RIZIV – INAMI reimbursed costs for bariatric surgery. The reimbursed bariatric cost is relatively consistent over time within each type of bariatric surgery, however there is a slight decreasing price evolution for **sleeve**, and especially **bypass** surgeries over the last years. Although bypass surgery becomes less expensive, with an average / mean reimbursed cost of about €5000 it remains the most expensive option at every moment in time.

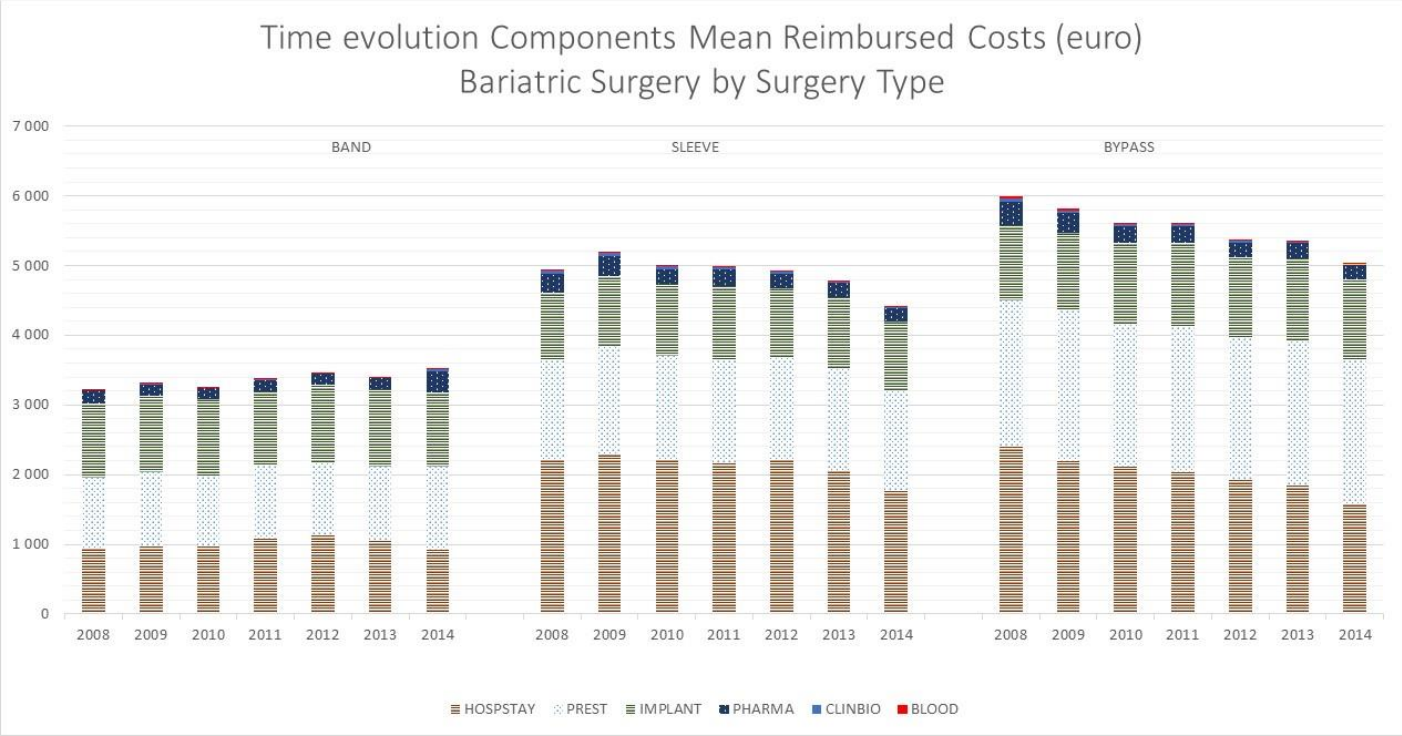
Figure 26 – Boxplot reimbursed bariatric cost by surgery type



*Note: Not all extremely outlying costs are graphically represented (max. 10 000 euro) in order to allow a clear focus on the main interquartile range (IQR) of the boxplots. Circles within the box represent the mean. Lower box border = 25th percentile. Middle straight line within box = median = 50th percentile. Upper box border = 75th percentile. Upper whisker = max observation below upper fence (red: upper fence equals 1.5*IQR above 75th percentile). Lower whisker = min observation below lower fence (red: lower fence equals 1.5*IQR under 25th percentile. Circles outside box and whiskers are outliers.*
Note that the mean costs will take into account the costs of outlying patients with higher values, and therefore will always render higher financial estimates than corresponding median costs. A table with further figure details is provided in Appendix 6 (Table 53).

The cost components contributing the most to the reimbursed bariatric costs (Figure 27) are the *hospital cost itself*, the *surgeon fees* and the *implant material costs*. Other components such as the cost of pharmaceuticals, the cost of clinical biology, and the cost of supplemented blood and plasma contribute relatively little to the reimbursed total costs. As such the earlier mentioned decrease in mean hospitalisation duration (reflected in hospital stay cost) is an important factor in the observed decrease of the total reimbursed hospitalisation costs; both tie strongly together (see Figure 47 in Appendix 6).

Figure 27 – Time evolution bariatric reimbursed cost components by surgery type



Note: Table 55 in Appendix 6 presents the underlying details for the above figure.

The specific detailed cost breakdown (cf. Table 55 in Appendix 6) further illustrates the reduced cost for *hospitalisation stay* over the years for **sleeve** and **bypass**.

It also illustrates that mean *surgeon fee costs* are different & typical for each type of bariatric surgery, and this remains relatively stable over the years: about €2100, €1400, and €1200 for bypass, sleeve and gastric banding, respectively. Mean *implant material costs* are about €1100 for all bariatric surgery types.

From a government point of view, despite the recent decrease in individual sleeve and bypass surgery costs, the annual spending goes up as the overall popularity of bariatric surgery in Belgium keeps growing (see part 7.2.2). In 2014, RIZIV – INAMI costs amount to about €60 million for primo implantations (see Table 24).

Table 24 – Estimated RIZIV – INAMI costs for primo implantation (bypass, sleeve or banding)

year	est. gov cost	Growth Year on Year
2008	€30 362 614	
2009	€39 684 236	1,31
2010	€44 325 721	1,12
2011	€55 354 960	1,25
2012	€57 909 072	1,05
2013	€60 017 961	1,04
2014	€60 105 438	1,00

Note: Table 55Estimations are based on government support for bariatric surgery (full surgery of type Bypass, Sleeve or Banding; without the derivated options : undo, post -op laparascopy or post -op adverse event surgery). The estimates take into account government funding through RIZIV nomenclature, as well as the 100% per diem correction. These estimations do not include patient out-of-pocket costs. As such, they form a conservative estimate for the bariatric surgery spending.

In 2014, as shown in Table 25, the government support for bariatric surgery mainly covers the expense for bypass (over 70% of the budget), and sleeve (about a quarter of the budget).

Table 25 – Estimated RIZIV – INAMI costs for primo implantation in 2014 per type of surgery (bypass, sleeve or banding)

Type	est gov cost 2014	Budget %
Bypass	€43 266 361	72%
Sleeve	€15 062 548	25%
Band	€1 764 271	3%
Multiple Bariatric	€12 258	0%
Total	**€60 105 438**	**100%**

Key points

- **Evolution of mean hospital duration for bariatric surgery over the years (2008-2014): Decreasing trend especially for bypass (from about 6 to about 3-4 days), and for sleeve (from about 6 to about 4 days). The hospital duration for banding remained relatively stable at about 2 days.**
- **Bypass remains the most expensive bariatric option over all years, followed by sleeve. Banding is the least expensive option.**
- **The total bariatric cost consists of:**
  - **The RIZIV – INAMI reimbursed cost (for band ca. €3500, for sleeve ca. €4400, and for bypass ca. €5000)**
  - **add ca. + €1000 to €1200 as co -payment (=consisting mostly of implant material costs) to be paid by the patient** [140, 300]

- **and, in case of a single room, add an extra €1900 to €3700 in supplements (=consisting mostly of surgeon fee costs)** [140]

- **The reimbursed cost is mainly composed of costcomponents 'hospital stay', 'surgeon fees' and 'implant material'. The cost components associated with clinical biology, pharmaceuticals, and supplementation of blood and plasma contribute little to the overall costs.**
- **The highest surgeon fee is associated with bypass operations (€2100), followed by sleeve operations (€1400) and banding (€1200) (year 2014).**

7.2 Bariatric Surgery: number of operations

7.2.1 Data selection

The first data source for this study –pertaining to demographics, medication use, adverse effects, reoperations and mortality-, is **administrative data from the Intermutualistic Agency (IMA)**. The Intermutualistic Agency integrates all data obtained from 7 separate Belgian health insurance funds, into one database. The result reflects the legal health insurance claims of all residents insured within the Belgian obligatory health insurance system. As the data are based on the invoices of all obligatorily health insured individuals in Belgium, the data does **not** include patients who underwent surgeries with only financial retribution from their complementary health insurance, **nor** does it include patients with foreign health insurance.

Patients were identified if they had at least one bariatric surgical procedure within the period 2009 until - 2014 (inclusive). Surgical procedures are coded using the RIZIV – INAMI-code classification system (codes cf. Table 50 in Appendix 6), and were considered when invoiced as the main act during a certain day. Patients were excluded from the main analysis if they had an earlier surgery in 2007-2008 (cf. specific coding exists since 2007): For the main analysis only the *first bariatric surgeries* were selected. Subsequent bariatric operations ("second" operations for the same patient) were classified as "*redo*" and will be considered in part 7.6.

Note: However 1. Before autumn 2007 bariatric surgery was not specifically coded, 2. Databases only go back to 2006 so anything before that period is unknown, and 3. Patients may also have been surgically treated without reimbursement in the past. As such, it is possible that a few patients in the pool may have had an earlier bariatric intervention.

Note: As a result of the patient-based selection (cf. exclusion of redo-surgery), the corresponding numbers in the main analysis below will be slightly lower than in operation-based selections.

The RIZIV – INAMI -coding allows to distinguish 3 types of bariatric surgeries: gastric bypass, gastric banding and gastric sleeves, a typology which will be used in subsequent analysis. To complement the bariatric procedure information, additional patient-related information was retrieved: a) data was extracted from the GZSS-database (Données Soins de Santé / Gezondheidszorg data) which contains all legally reimbursed medical acts in primary and secondary care; b) data was extracted from the FARMANET database (Données Pharmanet/ Farmanet data), which contains all reimbursed medication purchases; and c) data was obtained from the POPU-database (Données Population / Populatiedata), which contains additional socio-demographic information.

In addition, this study used **MZG – RHM data** as a second data source – pertaining to demographics, medical diagnosis of comorbidities, BMI, and costs. This is considered to reflect population data: Twice a year, all general, non-psychiatric, Belgian hospitals are legally bound to submit a large, standardized dataset of all 'inpatient hospital stays' (= hospitalisation of minimum one night) and 'day-care hospital stays' (=admission and discharge occurring the same day), as well as emergency room contacts to the Federal Public Service for Health, Food Chain Safety and Environment (FPS Public Health). This results in the Minimal Hospital Data or 'Minimale Ziekenhuis Gegevens' – 'Résumé Hospitalier Minimum' (MZG – RHM).

KCE has access to the MZG – RHM within the Technical Cell (TCT) data. The 'Technische Cel – Cellule Technique' (https://tct.fgov.be), created in the Law of 29 April 1996, is a common service of the RIZIV– INAMI and FPS, that has as its mission to collect, link, validate and anonymize data relating to hospital information.

In this study the following MZG – RHM data was used:

- Patient demographics, such as age and gender.
- Bariatric procedure(s) -and respective type (sleeve, bypass and banding), with all underlying cost components.
- Medical data of interest were principal and secondary diagnoses of the patient recorded for the hospital stay, as well as patient Body Mass Index (BMI). All diagnoses were coded according to the ICD-9-CM classification (International Classification of Diseases-9th Revision-Clinical Modification). The MZG-RHM codification system uses a (non-convertible) paediatric BMI equivalent for individuals of 20 years and younger instead of the standard (adult) BMI, so these data are missing for BMI classification.

The selection of TCT data was endeavoured to be as similar as possible to the IMA data; however small differences may occur.

7.2.2 *Trends*

Bariatric surgery has systematically gained popularity in Belgium over the last decade with an increase from 7500 bariatric patients in 2009 to up to more than 13 000 patients in 2016 (Table 26). However, despite the overall increase in the number of bariatric patients, different evolutions can be observed for the different types of bariatric surgery (see Table 26 and Figure 28):

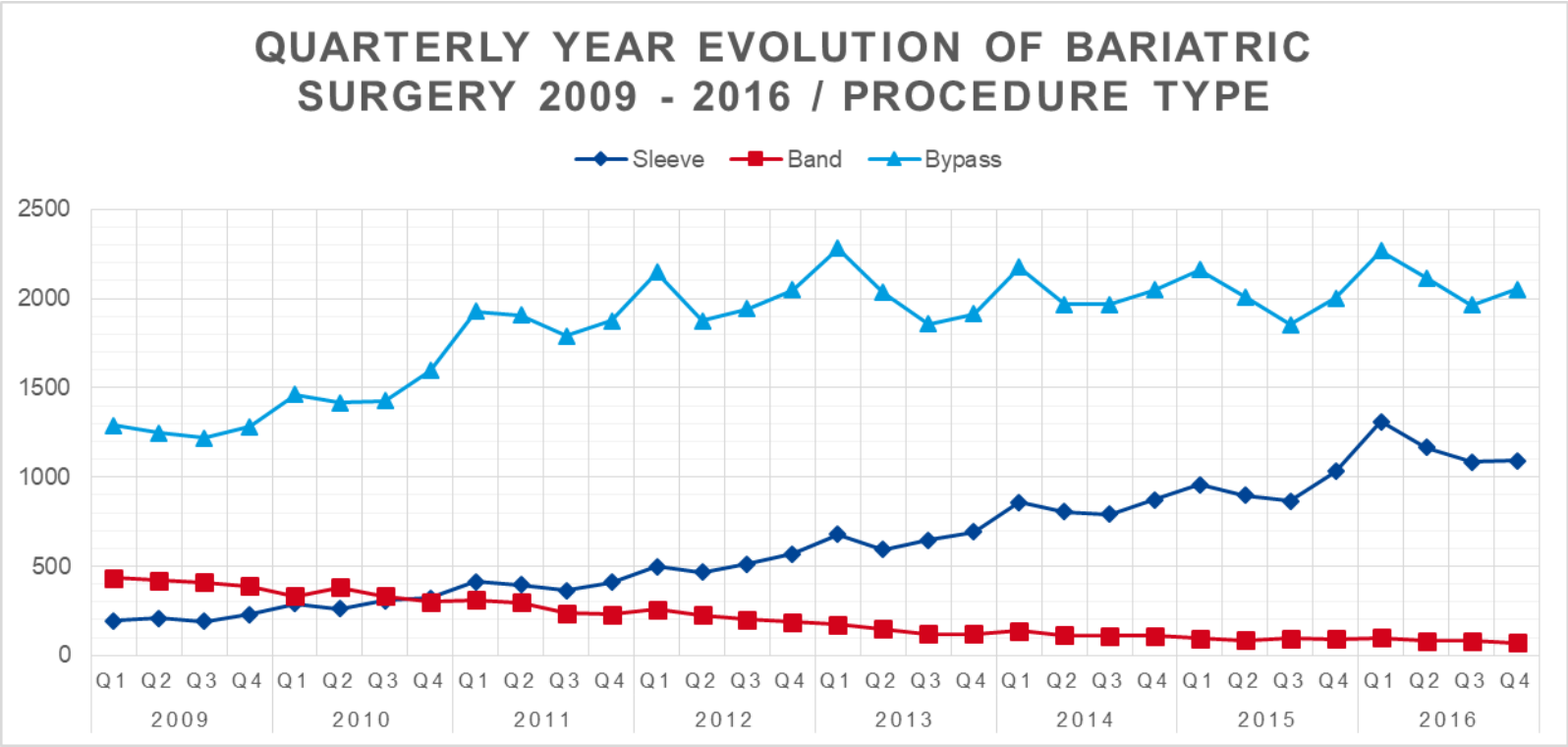
- The most frequently chosen option, **bypass** surgery, has become gradually more popular from 2009 onwards, until it reached a plateau in later years at somewhat more than 8000 operations yearly.
- **Gastric banding** surgery has systematically lost popularity from 2009 until 2016. The lowest level of yearly operations was reached in 2016 with 332 gastric banding interventions – it used to be more than 1600 in 2009.
- The third option, **sleeve** operations**,** have gained in popularity: Originally in 2009 sleeve operations were less prevalent than banding operations. This pattern is fully reversed in later years. Sleeve operations have increased from about 800 interventions in 2009 up to more than 4600 procedures in 2016.

Table 26 – Evolution of bariatric surgery in Belgium (2009 – 2016) by surgery type

First bariatric surgery				
Year	**Sleeve**	**Banding**	**Bypass**	**Total**
2009	821	1649	5036	7506
2010	1183	1346	5901	8430
2011	1583	1072	7499	10154
2012	2046	873	8012	10931
2013	2616	563	8092	11271
2014	3327	469	8158	11954
2015	3751	366	8027	12144
2016	4648	332	8402	13382

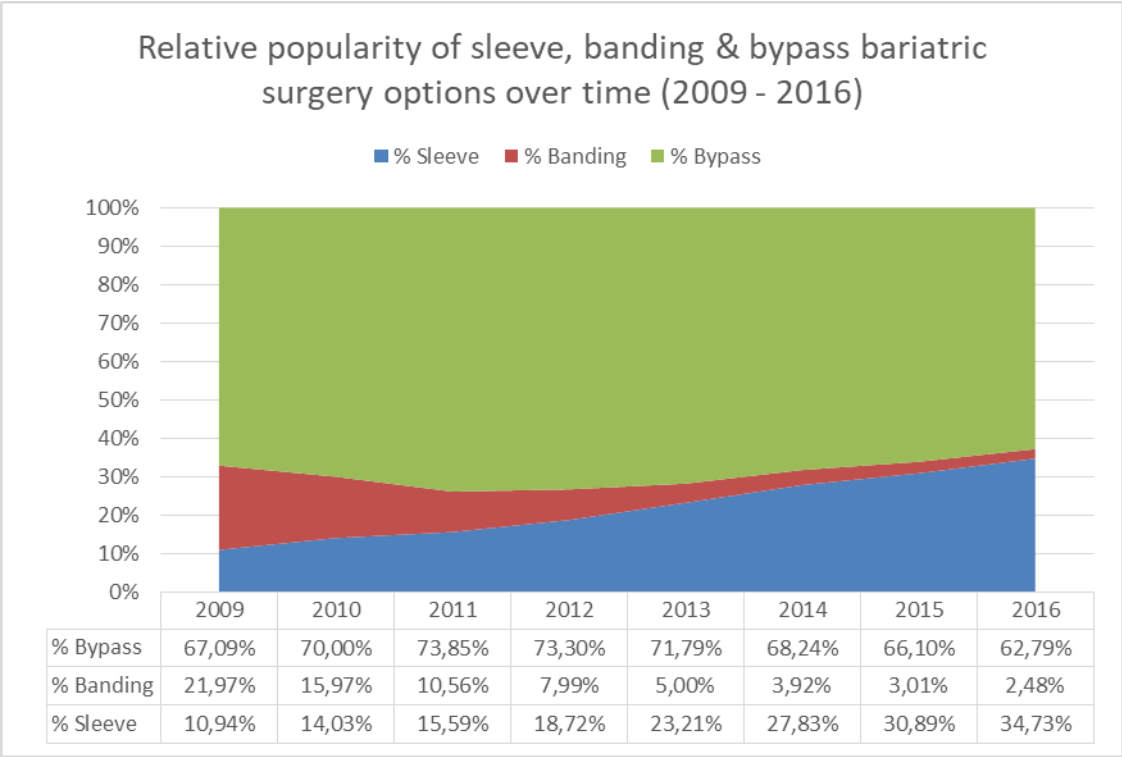
Seasonal (quarterly) fluctuations are noticeable for the bypass and sleeve operations: In the first yearly quarter there is a peak for both sleeve and bypass operations (Figure 28).

Figure 28 – Quarterly year evolution of bariatric surgery (2009 – 2016) by type



As a result of the enduring differential evolutions for different types of bariatric surgery, the proportional composition of the population of patients undergoing bariatric surgery is different every year (Figure 29). This impedes generalizations based on total numbers over consecutive calendar years in cases where changes are associated with different types of bariatric surgery; thus it is more accurate to look at information coming directly from the specific type of bariatric surgery of interest.

Figure 29 – Relative share of sleeve, banding & bypass surgery per year



	2009	2010	2011	2012	2013	2014	2015	2016
% Bypass	67,09%	70,00%	73,85%	73,30%	71,79%	68,24%	66,10%	62,79%
% Banding	21,97%	15,97%	10,56%	7,99%	5,00%	3,92%	3,01%	2,48%
% Sleeve	10,94%	14,03%	15,59%	18,72%	23,21%	27,83%	30,89%	34,73%

Key points

- **In 2016 over 13 000 bariatric surgery interventions were performed in Belgium. Over the last 8 years there has been a steady yearly increase in the amount of surgeries.**
- **Types of bariatric surgery : *Gastric bypass* is the most commonly performed procedure among bariatric operations, as in 2016 more than 6 out of 10 operations were of this type. *Sleeve operations* are rapidly gaining in popularity in more recent years, amounting to a third of all bariatric operations in 2016. The use of *gastric banding* is strongly decreasing and is only used in 2,5 % of all cases in 2016.**

7.3 Bariatric Surgery: Patient background

Different types of bariatric surgery have quite different consequences in terms of invasiveness, cost structure, possible side effects and whether they are reversible or not. Patients with different profiles may end up with a different type of bariatric surgery. As a result, the patient groups associated with the three different types of bariatric surgery (sleeve, banding and bypass) can be quite different.

Therefore, the following analyses will consequently look separately at patient cohorts associated with sleeve, banding, and bypass operations. The resulting cohorts are selected to allow for a minimal 5 year follow-up period after the procedure; which corresponds to initial operations in 2009, 2010 or 2011, see Table 27 for cohort size information. *Unless specified otherwise, all subsequent analyses refer to this patient selection.*

Table 27 – Cohort (2009 - 2011) size by gender and surgery type

	SLEEVE		BANDING		BYPASS	
	male	female	male	female	male	female
18-19	27	81	36	117	83	315
20-24	89	230	93	417	267	1116
25-29	84	257	94	430	347	1334
30-34	133	300	97	484	441	1662
35-39	174	332	134	502	673	1921
40-44	200	296	133	404	791	1945
45-49	185	273	128	334	785	1707
50-54	164	218	76	211	697	1460
55-59	124	146	65	135	529	1028
60-64	75	99	37	86	338	544
65-69	34	35	12	22	121	236
70-74	8	8	***	7	27	40
75-79	***	***	***	***	***	***
80-84	***	***	***	***	***	***
85-89	***				***	
90-94						
95-99						
100+						
SUBTOTAL	1303	2279	909	3152	5102	13314
GRAND TOTAL		3582		4061		18416

*Note: cellcounts under 5 are censored by ***. Only patients of 18 years and older are selected.*

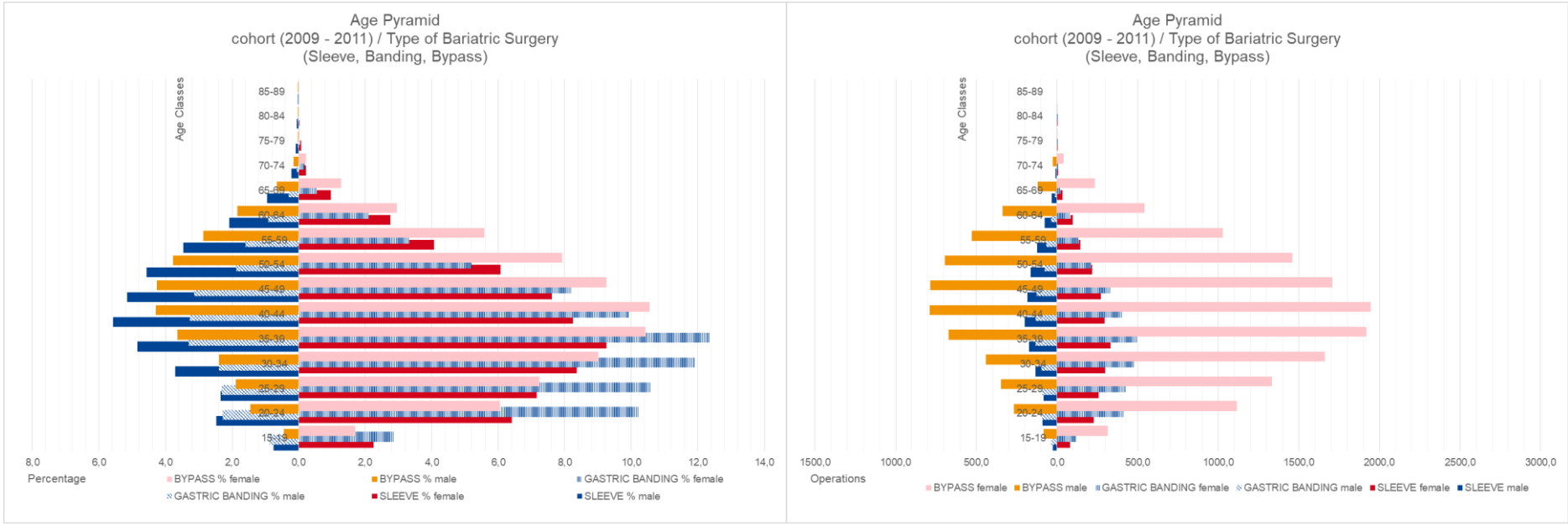
7.3.1 *Age & Gender*

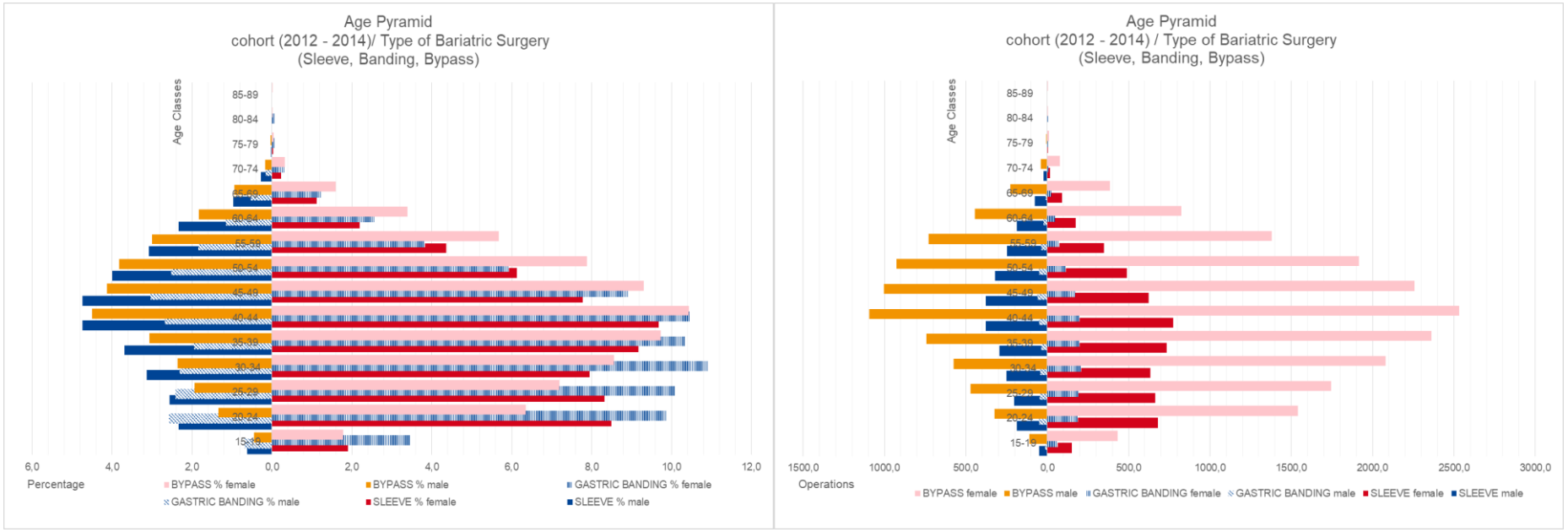
The resulting patient cohorts for sleeve, bypass, and gastric banding effectively differ in age and gender distribution.The **left panel** of Figure 30 looks at **proportional distribution patterns - every cohort population (sleeve, banding, bypass) equals 100%.** As such, the results are controlled for absolute numbers. The corresponding graph with **absolute numbers** is provided in the **right panel** of Figure 30 and illustrates the overwhelming proportion of bypass surgery. The proportional distribution patterns illustrate the underlying differences in patient cohorts (sleeve, banding, bypass) that will be used further in 7.4 and 7.5

When looking at **proportional results** for patient cohorts (Figure 30, left panel):

- Sleeves are relatively popular in the male population.
- Banding seems quite popular with a younger female audience
- Bypass procedures are relatively more selected than sleeves in the 40 -60 year female age group

Figure 30 – Comparative age pyramid (by surgery type: sleeve, banding, bypass), in cohort percentages & in absolute numbers

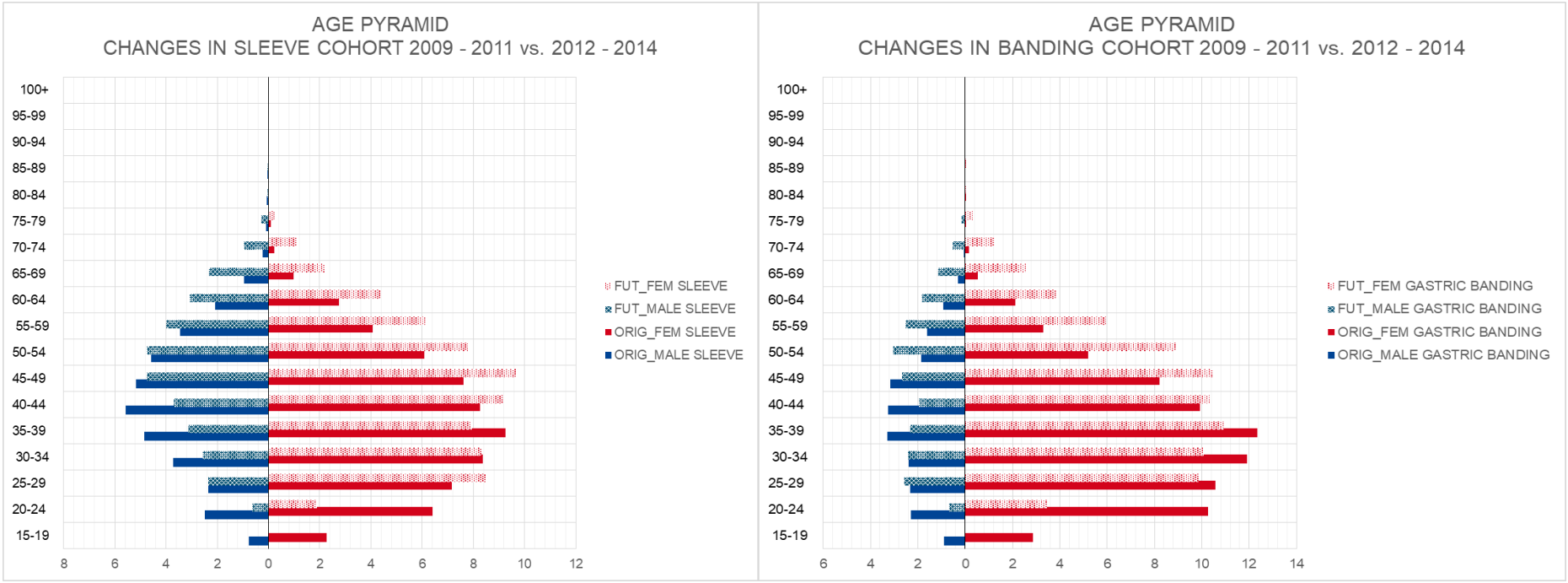




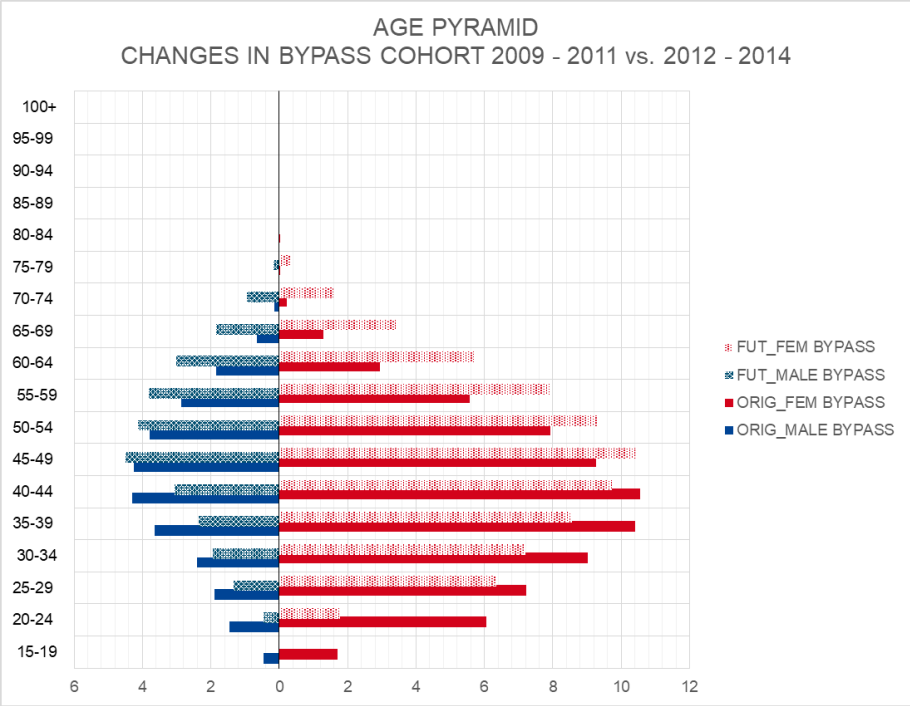
Note: the underlying patient selection is based on a 18 year cut-off – even though classical labelling for age pyramids comes in 5 year age groups

The main difference between the first cohort (2009-2011) and the subsequent cohort (2012-2014) is that the patients in the more recent cohort tend to be somewhat older when they undergo surgery (see Figure 31), and that the relative popularity of the different types of bariatric surgery has shifted (see Figure 29 above).

Figure 31 – Change in age pyramid from cohort 2009-2011 and cohort 2012-2014, by surgery type



Note: ORIG_FEM = female patients from cohort 2009-2011; FUT_FEM= female patients from cohort 2012-2014; ORIG_MALE = male patients from cohort 2009-2011; FUT_MALE= male patients from cohort 2012-2014



Note: ORIG_FEM = female patients from cohort 2009-2011; FUT_FEM= female patients from cohort 2012-2014; ORIG_MALE = male patients from cohort 2009-2011; FUT_MALE= male patients from cohort 2012-2014

7.3.2 BMI

The patient cohorts for sleeve, bypass, and gastric banding seem relatively similar when it comes to BMI typology. All three types of surgery have:

- A few rare cases have an extremely low body weight, seemingly patients with an earlier bariatric operation
- A minority (2%) of patients with a normal - to slightly overweight disposition (BMI 25 – 34 kg/m^2), possibly patients with issues from previous operations.
- About the same proportion (ca. 16 %) of patients with a BMI between 35 and 39 kg/m^2 – those patients are reimbursed upon fulfilment of additional criteria (see part 7.1).
- A relatively large proportion (around 74 %) of patients with a high BMI (over 40 kg/m^2). However, whereas the gastric banding cohort has a lower percentage (68 %) of patients with known BMI of ≥40 kg/m^2 than the other 2 cohorts, it simultaneously has a much higher percentage of 'missing' BMI that makes up for difference with the other two groups. As a result it is difficult to form a decisive conclusion for the banding cohort.

Table 28 – BMI class distribution, by bariatric surgery type

	Sleeve	Banding	Bypass
1.BMI <25	2	0	1
	0.06	0.00	0.01
2.BMI 25-34	50	94	270
	1.51	2.43	1.64
3.BMI 35-39	539	648	2654
	16.25	16.72	16.11
4.BMI ≥40	2464	2632	12 212
	74.31	67.92	74.11
Missing	261	501	1341
	7.87	12.93	8.14
Total n	3316	3875	16 478
%	100	100	100

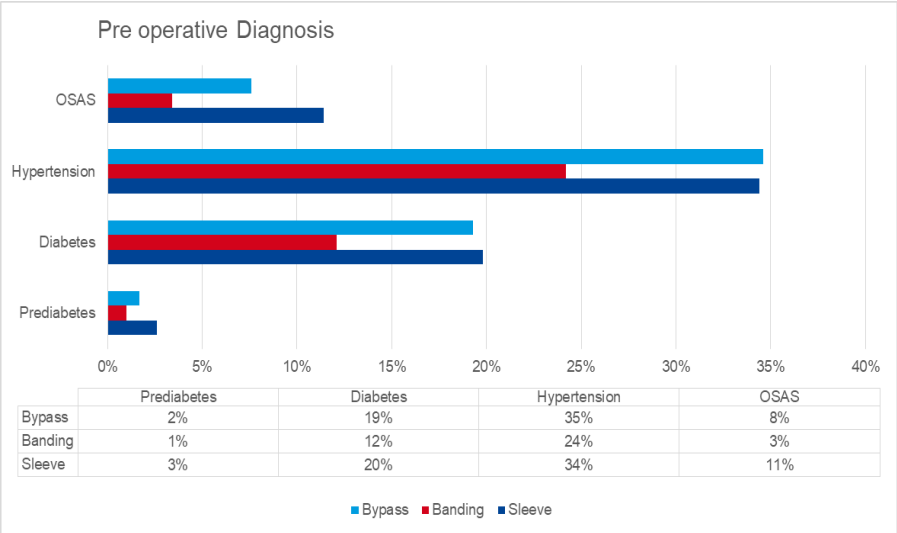
Note: As mentioned earlier in part 7.2.1., younger patients (-21 years) may be coded with a paediatric BMI equivalent, which is non- convertible to the adult BMI in kg/m², and are consequently recoded as part of the 'missing' category.

7.3.3 Patient pre-operative medication use & diagnosis of comorbidities

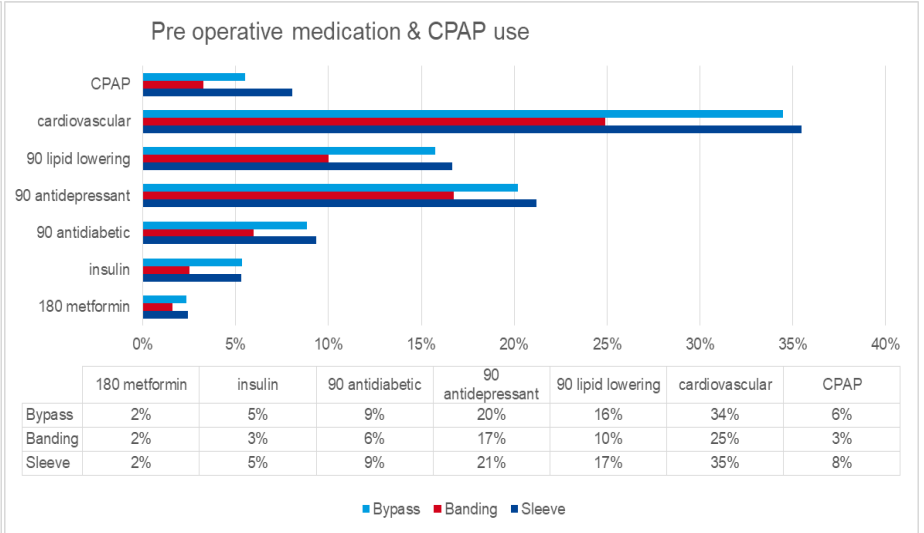
Apart from differences in general background variables such as age, gender, and BMI, pre -existing differences in medication use before the surgery are also possible. This would be in line with the assumption that the propensity for a particular type of bariatric surgery is associated with the severity of illness of the patient: It is possible that among the more invasive bariatric procedures, a patient group characterised by a more intensive medication use is more prevalent.

Differences in existing pre-operative medication use for the different types of bariatric research is shown in Figure 32. Systematic elevated medication use was more likely in the **bypass** and **sleeve** patient groups than in the **gastric banding** group. This pattern was observed for all investigated medication options; be it single metformin use, insulin use, overall antidiabetic medication use, antidepressant use, lipid lowering medication use or cardiovascular medication use. These differences were statistically significant (test results are provided in Table 60 in Appendix 6).

Figure 32 – Preoperative diagnosis vs preoperative medication use and CPAP convention adherence by bariatric surgery type



	Prediabetes	Diabetes	Hypertension	OSAS
Bypass	2%	19%	35%	8%
Banding	1%	12%	24%	3%
Sleeve	3%	20%	34%	11%



	180 metformin	insulin	90 antidiabetic	90 antidepressant	90 lipid lowering	cardiovascular	CPAP
Bypass	2%	5%	9%	20%	16%	34%	6%
Banding	2%	3%	6%	17%	10%	25%	3%
Sleeve	2%	5%	9%	21%	17%	35%	8%

Systematic typical medication is used as a proxy for medical diagnosis, as this is the only information readily available for patient follow up later on (see part 7.4 and 7.5). When comparing the *pre- operative medication use* results (right panel in Figure 32, based on IMA data), with the *medical diagnosis at time of operation* (left panel in Figure 32, based on TCT/ MZG-RHM data), quite similar patterns occur.

When using the utilization of a Continuous Positive Airway Pressure (CPAP) apparatus by patients as a proxy for Obstructive Sleep Apnea (OSAS) diagnosis, there is a 3% CPAP prevalence in the banding cohort - which is an exact match for the 3% OSAS medical diagnosis. When using CPAP as an OSAS proxy in the bypass and in the sleeve cohort, there is resp. a 6% and 8% CPAP prevalence. This is similar –yet slightly lower- to the actual 8% and 11% diagnosed patients in these cohorts. The small discrepancy seems plausible, as not all patients with an OSAS diagnosis choose CPAP as treatment.

> *Expert comment: In theory a patient has OSAS starting from an Apneu - Hypopneu Index >5; however the need for a CPAP-mask starts from an AHI 15 or 20.*

When using the medication definition for cardiovascular issues, the observed prevalence of 34%, 25%, and 35% for the bypass, banding and sleeve cohorts match the diagnosed prevalence of hypertension of resp. 35%, 24% and 34% for these cohorts. Note that the analysis operationalisations may generate somewhat higher figures than the reimbursement criteria (see text box below).

The *financial reimbursement rules* for bariatric surgery do not simply coincide with *the simple ICD - 9 diagnoses for hypertension and diabetes.* They add extra conditions to be fulfilled

*Therapy resistant Hypertension
(i.e. >140/90mmHg, despite treatment of at least 1 year with simultaneous use of at least 3 antihypertensive drugs

*Diabetes
treated with medication

Note: As data analysis in this study is based on RIZIV – INAMI reimbursed cases, for patients in weight class BMI 35-39 kg/m^2 with hypertension or diabetes as single comorbidity it seems very likely that they fulfil the stricter criteria for financial reimbursement. For patients with BMI 35-39 kg/m^2 that have hypertension or diabetes as a second (or third) comorbidity, or for patients with a BMI above 40 kg/m^2, it is possible that they fit the single ICD-9 diagnose, but not the stricter financial requirements -as they already received financial reimbursement based on their other characteristics.

For diabetes, using insulin and non-insulin based antidiabetic medication as a proxy, gives a similar prevalence pattern in the medication data (14%, 9%, and 14%) and in the diagnosis data (19%, 12%, and 20%) for resp. the bypass, banding, and sleeve cohorts. However, the diagnosed numbers are, for all three cohorts, about a quarter higher than estimates based on medication use.

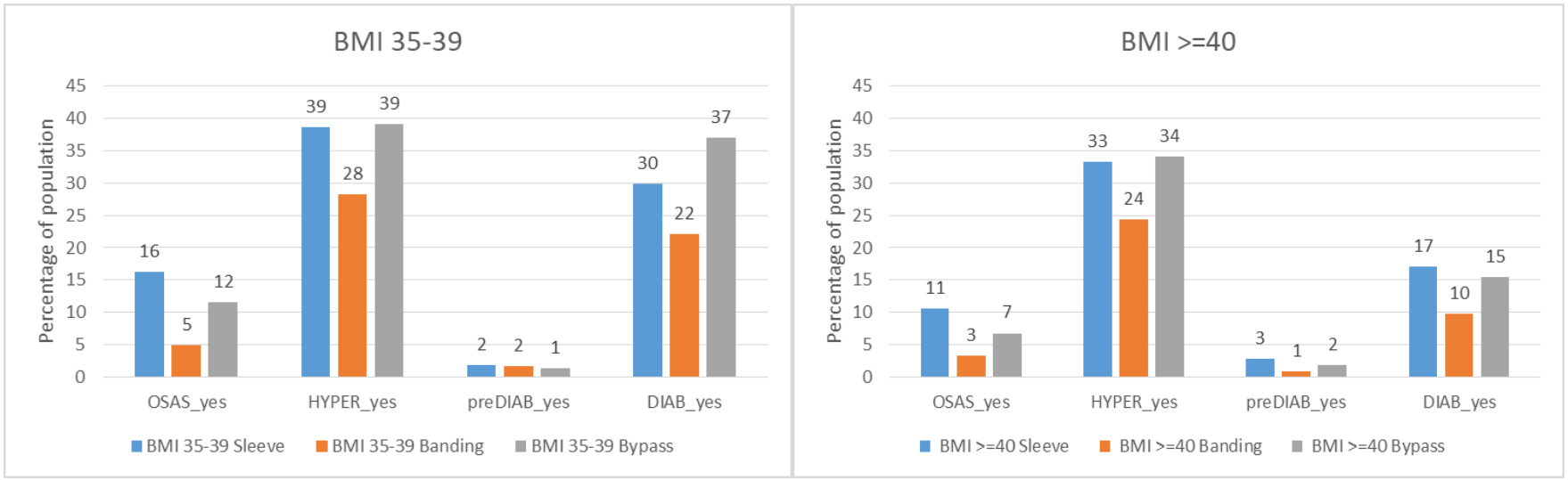
Note that the operationalisation of diabetes via hospital diagnosis may generate a slightly higher figure than the exact reimbursement criteria – due to patients that are diagnosed as diabetic but take low levels of medication.

Note that there is also a small discrepancy in the time frame used for measuring the hospital diagnosis (=at the time of admission in hospital for surgery), and medication (=the year preceding the operation). So a late diagnosis of a comorbidity will show up in the hospital diagnosis, even if it may not have been evident by the medication use the year before.

For single metformin use and prediabetes the relationship is less evident: probably because a high level of single metformin consumption can also be consistent with a diabetes diagnosis (instead of a prediabetes diagnosis), and because there is also a chance for metformin off label use not related to prediabetes.

In order to look at *prevalence of pre -existing comorbidities* for bariatric surgery in more detail, *BMI weight class* is taken into account: As the admission rules for financial reimbursement depend on the combination of comorbidity occurrence and BMI weight class (see part 7.1.1), this *selection system* has an impact on the presence of these comorbidities in the patient sample. Figure 33 presents the comorbidity prevalence per type of bariatric surgery for the two weight classes (BMI 35-39 kg/m^2; BMI ≥40 kg/m^2). The occurrence of all comorbidities is higher in the patient group with a BMI 35-39 kg/m^2. The difference in prevalence is most marked for the occurrence of diabetes. For example, in the patient group with a BMI 35-39 kg/m^2, 30% of the patients opting for a sleeve surgery have diabetes according to the hospital diagnosis, while this is only 17% in the group with a BMI ≥40 kg/m^2.

Figure 33 – Prevalence of comorbidities (Obstructive sleep apnea syndrome (OSAS), hypertension and diabetes) in sleeve, banding and bypass cohorts by BMI class based on hospital diagnosis



In Figure 33 all comorbidities were considered on their own, irrespective of whether a patient had more than one comorbidity or not. Most patients with comorbidities have only one comorbidity (see Table 29), which is the case for both patients in the BMI 35-39 kg/m^2 and the BMI ≥40 kg/m^2 group.

Table 29 – Number of comorbidities by BMI class (BMI 35-39 kg/m²; BMI ≥40 kg/m²) based on hospital diagnosis

Comorbidities		0	1	2	3	Total
Cohort 1						
BMI 35-39	**n**	1629	1361	772	79	3841
	%	7.7	6.44	3.65	0.37	18.16
BMI ≥40	**n**	10365	4807	1854	282	17308
	%	49.01	22.73	8.77	1.33	81.84
Total	***n***	***11994***	***6168***	***2626***	***361***	***21149***
	%	***56.71***	***29.16***	***12.42***	***1.71***	***100***
Cohort 2						
BMI 35-39	**n**	2361	2896	1496	263	7016
	%	8.23	10.09	5.21	0.92	24.45
BMI ≥40	**n**	13124	5647	2429	479	21679
	%	45.74	19.68	8.46	1.67	75.55
Total	***n***	***15485***	***8543***	***3925***	***742***	***28695***
	%	***53.96***	***29.77***	***13.68***	***2.59***	***100***

Note: Cohort 1 refers to bariatric operations in 2009-2011; Cohort 2 pertains to bariatric operations in 2012-2014.

As shown in Table 29, almost half of the bariatric patients (49% and 46% in the first and second cohort, respectively) are morbidly obese patients (BMI ≥40 kg/m²) and have no diagnosed associated comorbidity of OSAS, diabetes or hypertension. A much smaller percentage of bariatric patients have a BMI between 35 and 39 kg/m² together with at least one of the three comorbidities (10.46% (=6.44%+3.65%+0.37%)) and 16.22% (=10.09% + 5.21% + 0.92%) in the 1st and 2nd cohort, respectively). A third group has a *mixed profile*, as this group has both an elevated weight (BMI ≥40 kg/m²) as well as one or more of the three comorbidities. A small fraction are severely obese patients (BMI 35-39 kg/m²) with none of the three comorbidities. This contradicts reimbursement criteria and is most likely due to coding errors or redo procedures of early bariatric surgery.

Key points

- **Patient groups with a sleeve, banding or bypass operation differ in profile, both in terms of demographics (age & gender) as well as in terms of pre-operative medication use.**
- **The patient group associated with the reversible gastric banding surgery has the lowest pre-operative medication use (encompassing diabetes medication, antidepressants, lipid lowering agents or cardiovascular medication), and tends to be slightly younger in comparison to the patient groups choosing a non/less readily-reversible bariatric procedure (sleeve/bypass).**
- **Pre-operative medication use is relatively similar for the sleeve and bypass patient groups, although their respective demographic distribution is somewhat distinctive. When looking from a relative distibution point (irrespective of the actual total numbers): relatively more older women have a bypass, relatively more younger men have a sleeve. When taking actual total numbers into account, as bypass is by far the most popular bariatric option, bypass is prevalent in almost every gender and agegroup.**

- **The largest group of bariatric patients (around 3 out of 4) are morbidly obese patients (BMI ≥40 kg/m²). A much smaller group of patients are severely obese patients (BMI 35-39 kg/m²), with one or more of the comorbities (OSAS, medicated diabetes, resistant hypertension) that entitle financial reimbursement.**
- **Of the three comorbidities associated with financial reimbursement (OSAS, diabetes and hypertension), hypertension and diabetes occur most often. Hypertension is evident in about 1 in 3 morbidly or severely obese individuals (BMI weight classes 35 -39 kg/m² and +40 kg/m²).**

7.4 Bariatric Surgery: post-operative medication use

For patients with a specific illness, progress after operation was monitored by assessing their post-operative medication use. In each cohort (sleeve, banding, bypass) the patients taking more than a pre-specified dose of specific medication 1 year pre-operatively were selected for a 5 year post operative follow up. Table 61 in Appendix 6 provides a description of the pre-specified dose specifications. For each post-operative year, patient medication use was calculated to determine whether it surpassed the fixed threshold. These systematic yearly assessments were chosen in order to be able to detect possible cases of renewed medication use after an initial decline.

This method was applied to five issues thought to be associated with obesity: diabetes, depression, obstructive sleep apnea syndrome (OSAS), cardiovascular issues and cholesterol.

This results in 6 post-operative research questions ('RQ'), applicable to the population with the respective issues:

- Diabetes Medication: Is there a (sustained) decrease in diabetes medication after bariatric surgery? (RQ_1: Insulin; RQ_2: Overall use predictor)
- Antidepressants: Is there a (sustained) decrease in antidepressants after bariatric surgery? (RQ_3)
- Lipid lowering agents/ cholesterol: Is there a (sustained) decrease in use of lipid lowering agents after bariatric surgery? (RQ_4)
- Cardiovascular medication: Is there a (sustained) decrease in the use of cardiovascular medication after bariatric surgery? (RQ_5)
- Sleep apnea: Is there a (sustained) decrease in adherence to a CPAP convention after bariatric surgery? (RQ_6)

GENERAL NOTE FOR ALL POST–OP MEDICATION FOLLOW-UP CALULATIONS:

- **A direct comparison between the different types of bariatric surgery regarding their effectiveness in reducing post-operative patient medication use is not possible, as the outcomes are based on existing non-equivalent patient groups before surgery. Additionally, concrete data concerning the obtained post-operative yearly weight loss are not available in the database.**
- **Note that in bariatric surgery the stomach is targeted, which can impact the digestive process and alter nutrient absorption. As some of the studied medication is administered in pillform – not via parenteral administration –, these medications can be differently processed before and after surgery**

7.4.1 Insulin use post op (RQ_1)

For diabetes medication, both sole use of insulin as well as an indicator of overall use of diabetes medication (excluding insulin) (see part 7.4.2) was observed. For details: see Appendix 6 Table 51 & Table 61. The first analysis concerns insulin use is described in this part.

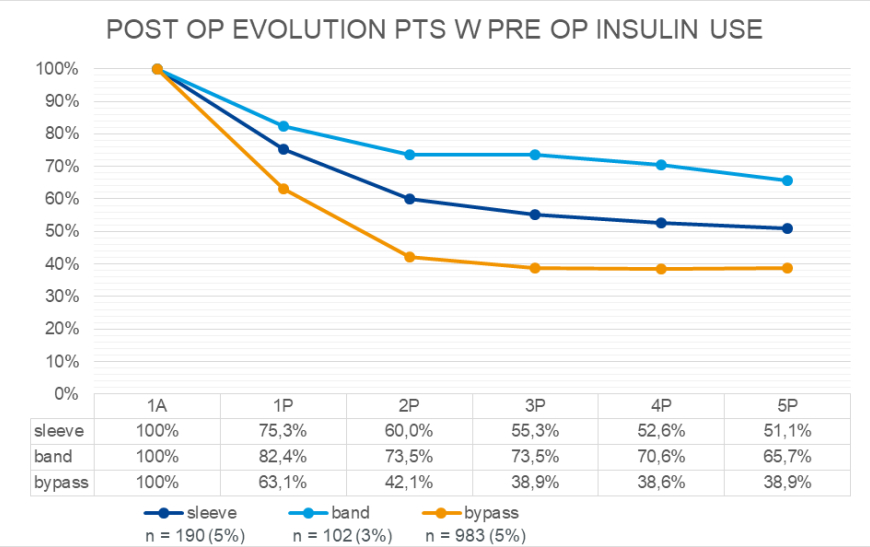
In each of the cohorts (sleeve, banding, bypass) the subsequent post-operative medication use of all individuals taking insulin 1 year pre-operation was analysed. The initial prevalence of pre-operative insulin use in bariatric patients varied from ca. 3% (banding cohort) to ca.5 % (sleeve and bypass cohort), generating a sample of respectively 102, 190 and 983 patients for follow up for the banding, the sleeve and the bypass cohort.

In all three cohorts the number of patients taking insulin decreased throughout the first and second post-operative year (see Figure 34). After the second post-operative year the number of patients taking insulin stabilized. In none of the three cohorts was there any evidence that the number of patients requiring insulin was on the rise in the next 3 years after the initial decline. In all three cohorts a large number of patients continued their insulin use 5 years after surgery (39%, 51% and 66% for bypass, sleeve and banding, respectively).

Medication disadvantages, remissions or coincidences may sometimes lead patients to discontinue their medication use, irrespective of whether their underlying condition is resolved. To counterbalance this issue in follow up, a matched control condition assessed the churn rate[f] of the medication under study in the general population.

This allows for a baseline against which to establish the pattern observed in bariatric patients. Subsequently, for each selected bariatric patient using insulin, several control patients were randomly drawn from a pool of patients not in a bariatric trajectory that also use insulin, each matched on gender, age and EPR-status to the bariatric patient. BMI of control patients was unknown. For the controls as well as for the bariatric patients, calculations were performed to assess their insulin use pattern over an equally long timeframe (see Table 62 in Appendix 6). After a 5-year follow-up period, about 89% of the matched controls still used insulin as specified above. For the bariatric patients this percentage is lower (see Figure 34).

Figure 34 – Follow up of insulin therapy patients postoperatively



	1A	1P	2P	3P	4P	5P
sleeve	100%	75,3%	60,0%	55,3%	52,6%	51,1%
band	100%	82,4%	73,5%	73,5%	70,6%	65,7%
bypass	100%	63,1%	42,1%	38,9%	38,6%	38,9%

Note: 1A: 1 year pre-operative; xP: x year post-operative.

Key points

- **In all three cohorts a similar pattern was observed. The number of patients previously using insulin medication decreased in the first two years immediately after surgery, after which it stabilizes. After the two years post surgery, none of the three cohorts showed a noticeable renewed increase in the number of patients using insulin medication up to 5 years of follow-up.**

[f] Note: Churn rate (also called attrition rate), is in its broadest sense, a measure of the number of individuals moving out of a collective group over a specific period of time.

7.4.2 *Overall diabetes post op (RQ_2)*

A similar analysis was performed for overall use of diabetes medication (without insulin component) (see definition in Table 61 in Appendix 6). In each of the cohorts (sleeve, banding, bypass) post-operative medication use of all patients pre-operatively procuring diabetes medication was monitored.

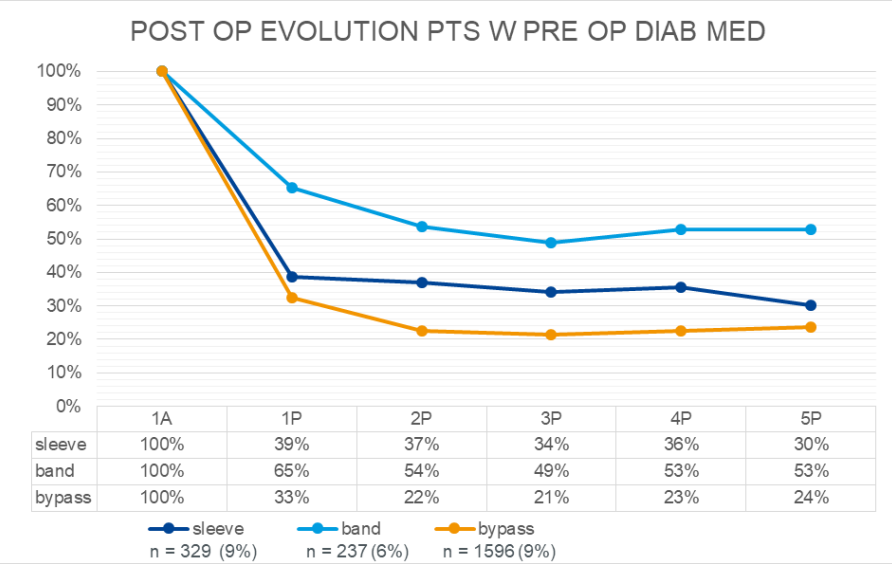
Initial prevalence of use in bariatric patients varied from about 6% (banding cohort) to about 9% (sleeve and bypass cohort), generating a sample of respectively 237, 329 and 1596 patients for follow up for the banding, the sleeve and the bypass cohort.

Again, as shown in Figure 35, in all three cohorts the number of patients taking diabetes medication decreased throughout the first and second post-operative year – although in the *sleeve cohort* the change seemed to occur mostly in the first post-operative year. After the initial transformative phase, again a sort of stabilization phase seems to be reached.

In all three cohorts, a large number of patients decreased their systematic diabetes medication use 2 years after bariatric surgery. After 5 years, 24%, 30% and 53% remained above the pre-specified threshold of medication use for the bypass, sleeve and banding group, respectively.

Also in this analysis, several control patients were randomly drawn from a pool of patients not in a bariatric trajectory that also use diabetes medication, each matched on gender, age and EPR- status to the bariatric patient. BMI of control patients was unknown. For the controls as well as for the bariatric patients, calculations were performed to assess their diabetes medication use pattern over an equally long timeframe. After 5 years of follow-up, about 70% of the matched controls still used diabetes medication as specified above (see Table 62 in Appendix 6). For the bariatric patients this percentage is lower (see Figure 35).

Figure 35 – Follow up of diabetes therapy patients postoperatively



	1A	1P	2P	3P	4P	5P
sleeve	100%	39%	37%	34%	36%	30%
band	100%	65%	54%	49%	53%	53%
bypass	100%	33%	22%	21%	23%	24%

1A: 1 year pre-operative; xP: x year post-operative.

7.4.3 *Antidepressants post op (RQ_3)*

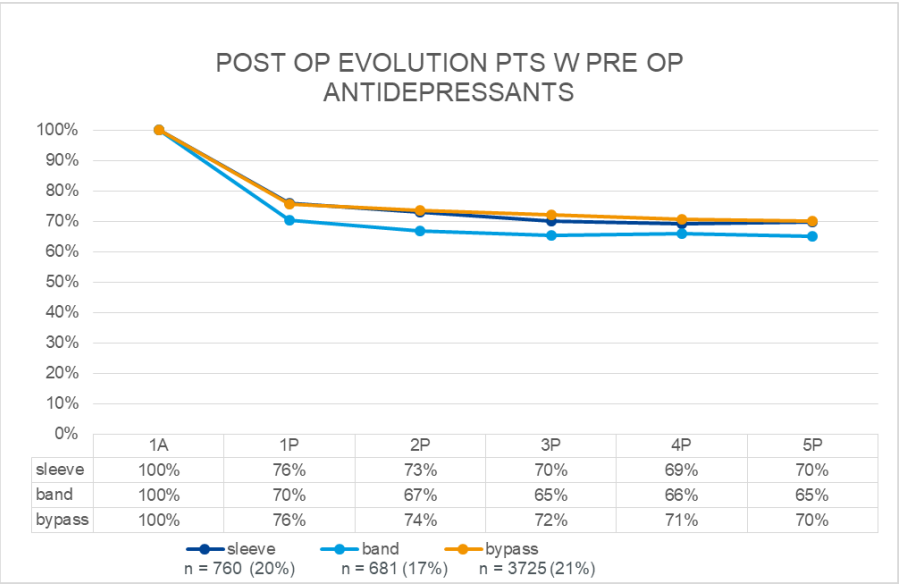
Analogously as for diabetes, the analysis was run for bariatric patients who were depressive, and systematically taking antidepressant medication (see Table 61 in Appendix 6 for the applied definition). Note that this research question is somewhat more associated with psychological wellbeing than the other more physiological/medically oriented research questions.

In each of the cohorts (sleeve, banding, bypass) post-operative antidepressant use of all patients pre-operatively taking antidepressant medication was monitored. Initial prevalence of antidepressant use in bariatric patients varied from about 17% (banding cohort) to about 20-21% (sleeve and bypass cohort), generating a sample of respectively 681, 760 and 3725 patients for follow up for the banding, the sleeve and the bypass cohort.

In all cohorts there was a limited drop in the number of patients taking antidepressants in the first post-operative year (see Figure 36). However, between the 2nd and 5th year, antidepressant use was relatively stable for all three cohorts. The findings are very similar for all types of bariatric patients. In all three cohorts, almost 7 out of 10 patients did uphold their consumption of antidepressants up to five years after their bariatric operation.

Similar as for the previous analysis, for each selected bariatric patient using antidepressants, several control patients were randomly drawn from a pool of patients not in a bariatric trajectory that also use antidepressants, each matched on gender, age and EPR-status to the bariatric patient. In this case, about 62% of the matched controls still used antidepressants. This is quite similar to the bariatric patients (see Figure 36 and Table 62 in Appendix 6).

Figure 36 – Follow up of antidepressant therapy patients postoperatively



	1A	1P	2P	3P	4P	5P
sleeve	100%	76%	73%	70%	69%	70%
band	100%	70%	67%	65%	66%	65%
bypass	100%	76%	74%	72%	71%	70%

1A: 1 year pre-operative; xP: x year post-operative.

7.4.4 *Lipid modifying agents/ cholesterol medication post op (RQ_4)*

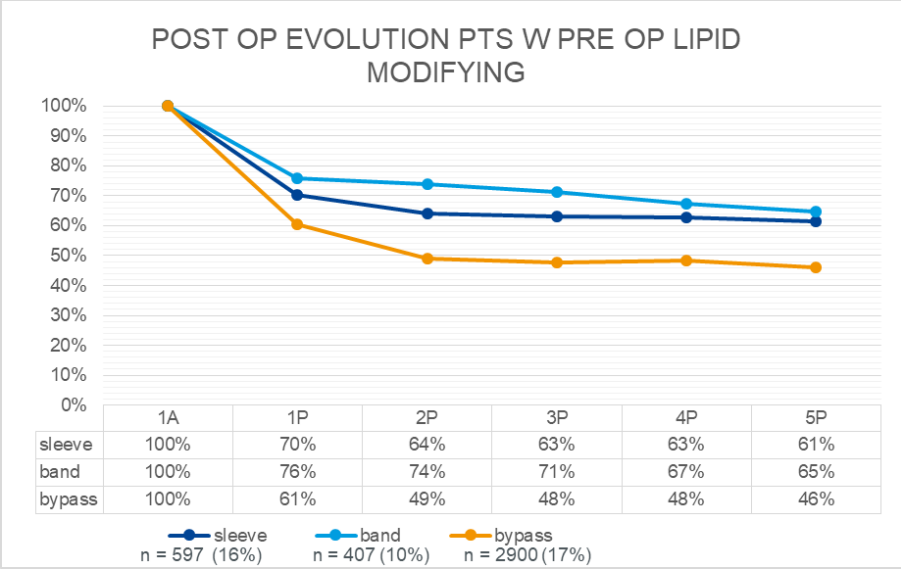
A similar analysis looked at the use of lipid modifying agents (ATC C10) in bariatric patients (see definition in Table 61 in Appendix 6). In each of the cohorts (sleeve, banding, bypass) post-operative medication use of all patients pre-operatively taking lipid lowering medication was monitored.

Initial pre-operative prevalence of lipid modifying agents in bariatric patients varied from about 10% (banding cohort) to about 16-17% (sleeve and bypass cohort), generating a sample of respectively 407, 597 and 2900 patients for follow up for the banding, the sleeve and the bypass cohort.

In all cohorts there was a drop in the number of patients systematically taking lipid modifying agents in the first two post-operative years (see Figure 37). After this, there seems to be a stabilization (sleeve & bypass cohort), or a slight further decrease (banding cohort) up to five years post-operative.

In this case, the analysis of a cohort of matched controls shows that after five years of follow up, about 79% of the matched controls still used lipid modifying agents. For the bariatric patients this percentage was lower (see Figure 37 and Table 62 in Appendix 6).

Figure 37 – Follow up of lipid modifying agent therapy patients postoperatively



	1A	1P	2P	3P	4P	5P
sleeve	100%	70%	64%	63%	63%	61%
band	100%	76%	74%	71%	67%	65%
bypass	100%	61%	49%	48%	48%	46%

1A: 1 year pre-operative; xP: x year post-operative.

7.4.5 *Cardiovascular medication post op (RQ_5)*

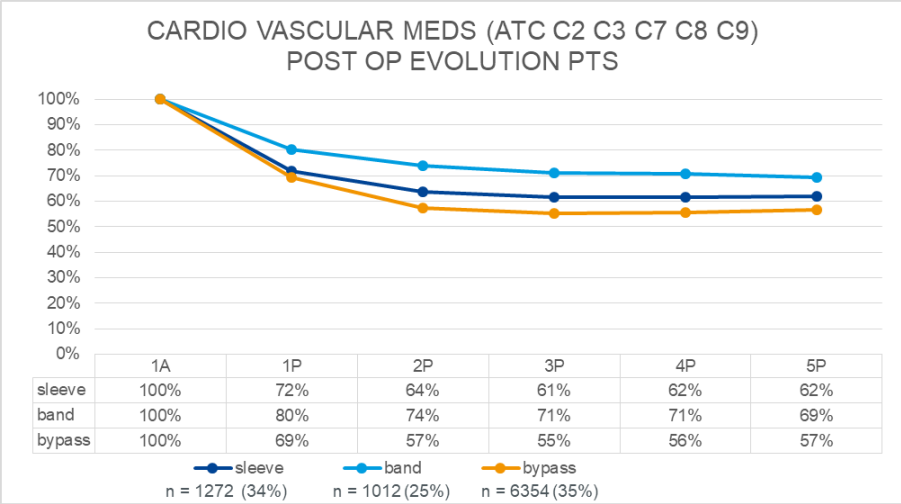
In order to capture patients with cardiovascular issues, patients were selected for follow-up if 1 year before bariatric operation they systematically took medication from at least one (more is possible) of the following medication groups: anti-hypertensives, beta blocking agents, calcium channel blockers, diuretics and/ or renin angiotension agents (see Table 61 in Appendix 6 for the applied definitions).

Initial prevalence of cardiovascular associated medication use in bariatric patients varied from about 25% (banding cohort) to about 34-35% (sleeve and bypass cohort), generating a sample of respectively 1012, 1272 and 6354 patients for follow up for the banding, the sleeve and the bypass cohort. This is a relatively high initial prevalence (i.e. the highest of all considered research questions), signalling that the results of the cardiovascular medication evolution after surgery affects a lot of bariatric patients.

In all cohorts there was a drop in the number of patients systematically taking cardiovascular-associated medication in the first two post-operative years, after which patient numbers remained very stable for all three cohorts for the subsequent three years of follow up (see Figure 38).

The analysis of the matched controls showed that after five years of follow-up, about 85% of these patients still used cardiovascular medication as specified above. For the bariatric patients this percentage is somewhat lower (see Figure 38).

Figure 38 – Follow up of cardiovascular therapy patients postoperatively



	1A	1P	2P	3P	4P	5P
sleeve	100%	72%	64%	61%	62%	62%
band	100%	80%	74%	71%	71%	69%
bypass	100%	69%	57%	55%	56%	57%

1A: 1 year pre-operative; xP: x year post-operative.

Key points – post-operative medication use

- **Remark that a direct comparison between surgery types regarding their effectiveness in reducing post-operative medication use is not possible, as all outcomes are based on existing non equivalent patient groups before surgery. Furthermore, an important characteristic, the amount of yearly weight loss of the patients is unknown.**
- **However, a five year follow up of patient cohorts associated with sleeve, banding and bypass operations suggests that those procuring a certain type of medication (diabetes medication, lipid lowering agents, cardiovascular medication or antidepressants) before their operation, decrease their medication use in the first two years after surgery. After the second year, some stabilization sets in and there was no evidence of a noticeable renewed increase in medication use up to five years postoperatively.**
- **Based on a non-randomized comparison with a matched cohort, there are indications that based on evolutions of post-operative medication use there is a somewhat better chance to see physiological changes (e.g. diabetes/insulin use) than to see psychological changes (e.g. antidepressants).**

7.5 Bariatric Surgery: post-operative CPAP convention

7.5.1 Sleep apnea post op (RQ_6)

For the last research question concerning Obstructive sleep apnea syndrome (OSAS), adherence to a continued positive airways pressure apparatus (CPAP) convention was used as proxy indicator. However, in contrast to medication use where patients regularly renew their prescription, renewal of CPAP convention tends to take place on a yearly basis. As a consequence, the yearly renewal rate interferes with the standard 1 year measurement period. By definition, if patients started on a CPAP convention ,e.g. 6 months before their operation, their CPAP convention will continue for several months after their operation (i.e. in the first post-operative year). It is only after the convention ends, that the patient has to decide whether or not to continue the CPAP treatment. As such, the *second post-operative year* (a.k.a. "*2P*" -when the patient's choice to continue with CPAP or not has become apparent) is chosen as the target year with respect to measurement outcome.

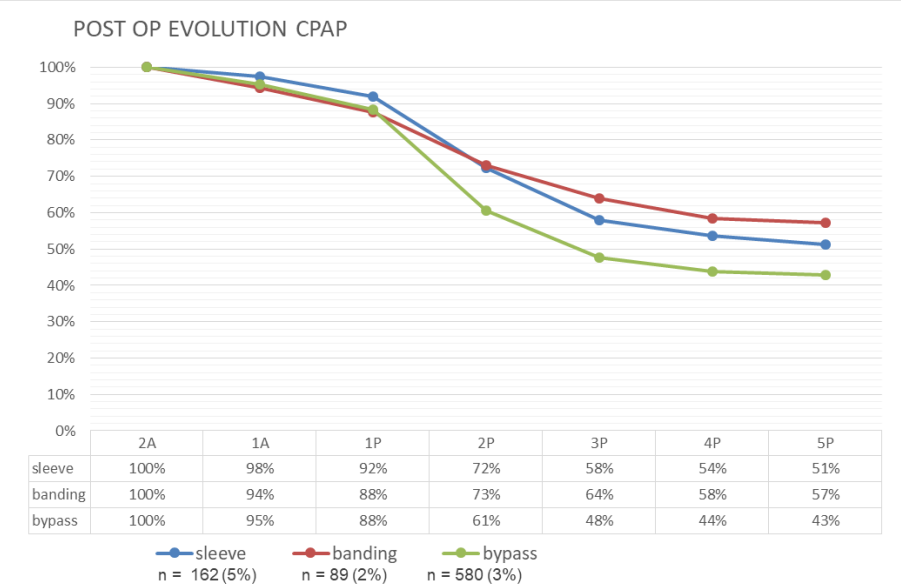
Disadvantages of the CPAP apparatus (noise of the machine, restricted sleep positions, etc.) can sometimes lead patients to discontinue their CPAP machine use, irrespective of whether their underlying condition is resolved. To counterbalance this issue during follow- up, a matched control condition assesses the general population CPAP churn rate. This allows for a baseline against which to establish the pattern as observed in bariatric patients.

All patients adhering to a CPAP convention 2 years prior to surgery were selected for further follow up. The selection at 2 years prior to the operation acts as a safeguard against the surge of recently diagnosed patients in the year before operation (see part 7.5.2). These patients have a higher chance than usual to quit CPAP, as quitting due to an impossibility to get used to the noise and sleep restrictions induced by the CPAP machine tends to immediately follow the initialization phase (i.e. takes place in the starting year). As such the discontinuation wave of an unusual large group of beginners would convolute (even possibly bias) the perceived effects of the bariatric surgery.

Initial prevalence of CPAP use at 2 years pre-operatively varied from about 2 % (banding cohort), over about 3 % (bypass cohort) to about 5 % (sleeve cohort), generating a sample of respectively 89, 580 and 162 patients for follow up for the banding, the bypass and the sleeve cohort.

Figure 39 shows that in all three cohorts there was a pronounced drop in the number of patients adhering to a CPAP convention 2 and 3 years post-operatively, after which patient numbers describe a slow further descent for the next two years of follow up. After five years, about 1 out of 2 original CPAP patients discontinued their CPAP convention.

Figure 39 – Follow- up of CPAP convention after postoperatively



	2A	1A	1P	2P	3P	4P	5P
sleeve	100%	98%	92%	72%	58%	54%	51%
banding	100%	94%	88%	73%	64%	58%	57%
bypass	100%	95%	88%	61%	48%	44%	43%

In order to counteract the risk of overestimating the effect of bariatric surgery, a matched control condition was calculated to set up a baseline by assessing the *general population CPAP continuation rate* (seeTable 30).

In addition, as the probability of an OSAS problem – and possibly also the chances of recovery – is different for different *patient subgroups.* With an older, male population being more at risk, subgroups with a different age/gender profile were studied separately. For *age* two categories were created: those under 40, and those 40 years and above at the time of surgery. *Gender* was also considered, as was Entitlement to Preferential Reimbursement (*EPR –status of the patient* in English; VT- *recht op Verhoogde tegemoetkoming in Dutch, BIM- Bénéficiaire d'intervention majoré in French*, ', i.e. usually indicating either an income replacement allowance or a generally low income).

Generating the required numbers for a detailed subgroup analysis necessitates a wider patient selection: For the bariatric patient groups all patients adhering to a CPAP convention 2 years prior to their first bariatric operation (with first bariatric operations between 2010 and 2014) were selected. For these patients their adherence to a CPAP convention in the second post-operative year was measured. This did generate a total start sample size of 1664 patients. As further differentiation for separate operation types (sleeve, banding, bypass) did generate prohibitively low patient numbers for several combinations, necessarily the sample was kept without further subdivision. Although not ideal, earlier analysis has shown a rather similar course for the different operation types (see Figure 39), making the choice tenable.

Subsequently, for each selected bariatric CPAP patient, three control patients were randomly drawn from a pool of general CPAP patients (not in a bariatric trajectory), each matched on gender, age and EPR-status to the bariatric CPAP patient. For the control patients BMI was unknown. For the controls as well as for the bariatric patients, calculations were performed to assess their CPAP continuation pattern over an equally long timeframe.

Table 30 – Immediate (2P) post-operative follow up: bariatric CPAP patients vs. matched control CPAP patients

	Condition	Gender	Age Group	EPR-status	CPAP Start sample size	CPAP 2P sample size	CPAP 2P %	p-value
	OPERATION	Male	Younger	no EPR	132 (100%)	75	57%	0.55
	CONTROL	Male	Younger	no EPR	396 (100%)	250	63%	
	OPERATION	Male	Younger	EPR	18 (100%)	12	67%	0.55
	CONTROL	Male	Younger	EPR	54 (100%)	32	59%	
	OPERATION	Male	Older	no EPR	832 (100%)	527	63%	0.00
	CONTROL	Male	Older	no EPR	2496 (100%)	2148	86%	
	OPERATION	Male	Older	EPR	180 (100%)	118	66%	0.00
	CONTROL	Male	Older	EPR	540 (100%)	481	89%	
	OPERATION	Female	Younger	no EPR	33 (100%)	17	52%	0.55
	CONTROL	Female	Younger	no EPR	99 (100%)	46	46%	
	OPERATION	Female	Younger	EPR	15 (100%)	9	60%	0.53
	CONTROL	Female	Younger	EPR	45 (100%)	31	69%	
	OPERATION	Female	Older	no EPR	320 (100%)	211	66%	0.00
	CONTROL	Female	Older	no EPR	960 (100%)	805	84%	
	OPERATION	Female	Older	EPR	134 (100%)	84	63%	0.00
	CONTROL	Female	Older	EPR	402 (100%)	321	80%	
TOTAL	**OPERATION**				**1664 (100%)**	**1053**	**64%**	**0.00**
TOTAL	**CONTROL**				**4992 (100%)**	**4114**	**82%**	

Note: Age cut off for groups is set at 40 years at time of operation.

The matched general population CPAP continuation rates set a baseline against which to establish the pattern as observed in bariatric patients.

Conclusions based on the results presented in Table 30:

- *Overall*: There is some difference in favour of bariatric surgery. Yet by taking into account matched CPAP controls (*CPAP continuation rate of 82 % in general population*), the original overall effect seems reduced by half (*CPAP continuation rate of 64% for bariatric patients*). It is possible the gap between both can further decrease as the above control model has not controlled for all potentially confounding variables – a typical issue in observational studies.
- *Subgroups*: Younger patients (under 40 years old), both male and female, do equally well in the matched control group vs. the bariatric surgery group. The realised difference between the bariatric subgroups and the matched control subgroups is mainly found within an older patient group (over 40 years).

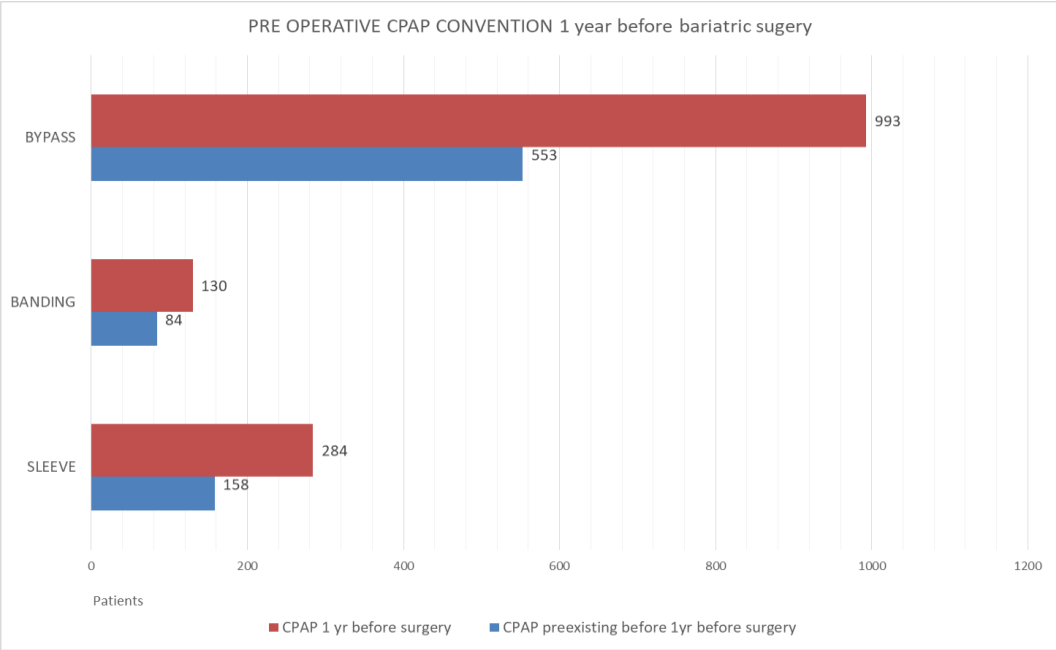
7.5.2 Pre op screening effect sleep apnea

SIDE STORY

In the year before bariatric surgery (“1A”) there is a noticeable increase in amount of patients being newly assigned to a CPAP convention. Almost half of the patients in the bypass and the sleeve cohorts started on a CPAP convention the year before their first bariatric procedure, possibly due to an increased testing protocol in preparing for the operation (or possibly due to a referral for bariatric surgery after an OSAS diagnosis).

For example, as shown in Figure 40 in the bypass cohort 993 of the patients had a CPAP convention in the year before their operation. Of these 993 patients, only 553 patients had a CPAP convention the preceding year (2 years before operation). This implies that 440 patients started a new CPAP convention 1 year before their bariatric procedure. This relative increase in the pre-operative year is somehow less pronounced in the gastric banding cohort than in the sleeve and bypass cohorts.

Figure 40 – Prevalence pre-operative CPAP convention by bariatric surgery type



Key points

- **<u>Pre-operative effect</u> : There seems to be a clear increase in the number of patients newly starting a CPAP convention the year prior to bariatric surgery, probably induced by increased screening efforts in the prospective patient group.**
- **<u>Post-operative</u> :**
  - ***Overall*, the immediate post operative continuation rate of CPAP use in the bariatric patient group is lower than in a matched (on gender, age and EPR -status) general CPAP population.**
  - ***Subgroup specification* : However, the above pattern is only observed for patients over 40 years old. For CPAP patients under 40, CPAP continuation rate is quite similar in bariatric and general population CPAP patients.**
  - **Note: that the matched control group has likely not controlled for all effects. A shortcoming is that it was not possible to match on BMI. However, the matched control at least provides a general idea of the normal population attrition rate against which to assess the post bariatric surgery attrition rate.**

7.6 Bariatric Surgery: Undo, Redo & Adverse events

The actual bariatric surgery may not be the end point of the patient surgery trajectory. The original bariatric surgery may lead to adverse effects, or may require an adjustment, undo or redo work. This may be different according to different types of bariatric surgery. Some examples:

- In case of **gastric banding**: The gastric band may need to be adjusted to progressively reduce the stomach volume, or it may be necessary to fix the position of the band after it has shifted. Alternatively the patient may demand its removal – because of complaints or because the pursued weight reduction has not been attained – possibly implying a demand for one of the other bariatric surgery options.
- In case of **gastric bypass** leakage is possible at the two connection ends of the repositioned intestinal tract. Obstructions or infections may occur.
- In case of **sleeve** intervention leakage is possible due to the stomach incisions. Obstructions and infections may occur.

Reminder: The anatomically reversible options are gastric banding and gastric bypass.

The intended scope of this chapter is to analyse undo and redo procedures as well as adverse effects leading to surgical procedures after bariatric surgery for the **patient group with a 'first' bariatric intervention between 2009 and 2011 (making a 5-year follow up possible)**.

1. In all further analyses patients with a *clear indication* (i.e. a clear nomenclature code) of a *previous bariatric surgery* (of type sleeve, gastric banding or bypass) were excluded. For corresponding operationalisation in nomenclature codes cf. Table 63 in Appendix 6.
2. However, for some patients there is a somewhat unclear indication of a possible previous surgery. Here there is no clear previous nomenclature code referring to bariatric surgery in the dataset, but there is a previous nomenclature code associated with an undo, laparoscopy or adverse effect of bariatric surgery – before the first actual bariatric surgery code. This patient group with a *possible prehistory of bariatric surgery* is indicated in the tables as 'Prehistory'.
3. The previous group is separated from a group of patients with *no prehistory of bariatric surgery* (likely to be first time operations). This group is indicated in the tables as 'Proxy first'. This group will be the focus of further analysis and discussion.

Note: it is impossible to declare a patient group as being 100% conclusively 'free of a history of bariatric surgery' as. 1. Before autumn 2007 bariatric surgery was not specifically coded, 2. Databases only go back to 2006 so anything before that period is unknown, and 3. Patients may also have been surgically treated without reimbursement in the past. So the group with no known history may also contain a few patients with an unidentified prehistory. All selections have been performed as carefully as possible, but due to limitations associated with the databases perfect certainty is not possible.

As such, based on the above patient selection, short (30 days), medium (1 year) and long term (5 years) hospital readmissions were calculated for bariatric patients with sleeve, banding and bypass surgeries. Instead of taking a very general approach of counting all **hospital readmissions** (incl. e.g. knee operations or eye surgery), the below *rehospitalisation estimates target only specific issues thought to be associated with bariatric surgery*.

Note: This is the reason why the estimates below will not compare directly to international studies who count all hospital readmissions. Specific rehospitalisation rates will always be (much) lower than total rehospitalisation rates.

In order to do this, a list of Belgian nomenclature codes reflecting possible events after bariatric surgery was compiled by obesity specialist J. Himpens. The list entails nomenclature codes referring to *undo* or *redo procedures*, *laparascopy, and* several associated *adverse events*. Details on the selected nomenclature codes and associated statistics are described in the following parts: 7.6.1, 7.6.2, 7.6.3, and 7.6.4. The list for adverse events does not identify all possible adverse events post-surgery, only those with a specific link to bariatric interventions, and with a clearly identified coding within the RIZIV – INAMI nomenclature.

Note: This is a conservative estimate of specific rehospitalisation rates, as some (more vague) codes regarding adverse events not only/clearly applying to bariatric surgery were not counted.

Table 31 and Table 32 below represent *specific rehospitalisation rates* after bariatric surgery when the nomenclature codes related to redo, undo, laparascopy and adverse events related to bariatric surgery are considered together. This leads to a very conservative estimate of hospital readmissions after bariatric surgery, yet is more precise as an estimate of possible impact of bariatric surgery than counting all possible hospital readmissions, including unrelated procedures.

Earlier international cohort research[146] has estimated the total 30 day rehospitalisation rate at about 4% in sleeve patients and about 6% for RY bypass patients. Another cohort study[302] offers a literature based wider interval for bypass rehospitalisation rates, with total hospitalisation readmission after 30 days for bypass patients falling between 6% and 11.3%. As expected, the results below regarding specific rehospitalisation rates are somewhat lower than those corresponding to total rehospitalisation rates. However, the specific rehospitalisation rates reach the same conclusion as to ranking order: they also indicate a lower 30-day rehospitalisation for the **sleeve patients** (1.5%) than for the **bypass patients** (2.1%). The **gastric banding patients** have the lowest 30-day rehospitalisation (1.0%). This is in line with the results of an analysis Abraham et al.[144] who found 30-day readmission rates to be the lowest after banding, slightly higher after sleeves, and highest after bypass operations.

In contrast, in the medium and the longer term, the pattern reverses. Both the 1– and 5-year rehospitalisation rates were the highest for the banding cohort, being 3.6% and about 30%, respectively (see Table 31).

Table 31 – Rehospitalisation rates related to post-operative issues among bariatric patients, by original surgery type (short, medium & long term)

			REHOSP n			REHOSP %		
		total n	1M	1Y	5Y	1M	1Y	5Y
Proxy first	**sleeve**	**3384**	51	84	463	*1.5%*	*2.5%*	*13.7%*
	banding	**3966**	41	144	1 199	*1.0%*	*3.6%*	*30.2%*
	bypass	**17 235**	360	555	2 515	*2.1%*	*3.2%*	*14.6%*
Prehistory (=redo, undo, lapo, ae)	**sleeve**	**198**	7	11	54	*3.5%*	*5.6%*	*27.3%*
	banding	**95**	**	8	37	**	*8.4%*	*38.9%*
	bypass	**1181**	48	62	250	*4.1%*	*5.2%*	*21.2%*

*Note: cell counts under 5 (and corresponding percentage information) are censored by ***

For the larger patient group with a first bariatric surgery and no prehistory (i.e. the 'Proxy first' group), the larger numbers allow for a more detailed subgroup analysis presented in Table 32. Results show the following:

- The percentage of patients with issues within ***one month after surgery*** is observed within a range between 0.8% and 2.4% of patients.
- The percentage of patients with issues within ***one year post operatively*** is observed to be between 1.7% and 4.8% of patients.
- This percentage of patients with issues ***within 5 years post-operatively*** is observed to be between 10.8% and 34% of patients affected.

Table 32 – Rehospitalisation rates related to of post-operative issues among bariatric patients, by original surgery type, age class and gender

	TYPE	Gender	Age Group	Total	1 month post		1 year post		5 years post	
				N	N	%	N	%	**N**	%
Proxy first	**sleeve**	Male	Younger	493	8	(1.6%)	11	(2.2%)	**53**	**(10.8%)**
	sleeve	Male	Older	756	10	(1.3%)	29	(3.8%)	**95**	**(12.6%)**
	sleeve	Female	Younger	1138	14	(1.2%)	19	(1.7%)	**160**	**(14.1%)**
	sleeve	Female	Older	997	19	(1.9%)	25	(2.5%)	**155**	**(15.5%)**
	band	Male	Younger	448	6	(1.3%)	12	(2.7%)	**101**	**(22.5%)**
	band	Male	Older	444	5	(1.1%)	10	(2.3%)	**100**	**(22.5%)**
	band	Female	Younger	1905	16	(0.8%)	66	(3.5%)	**648**	**(34.0%)**
	band	Female	Older	1169	14	(1.2%)	56	(4.8%)	**350**	**(29.9%)**
	bypass	Male	Younger	1736	35	(2.0%)	60	(3.5%)	**244**	**(14.1%)**
	bypass	Male	Older	3146	70	(2.2%)	122	(3.9%)	**401**	**(12.7%)**
	bypass	Female	Younger	5930	100	(1.7%)	171	(2.9%)	**915**	**(15.4%)**
	bypass	Female	Older	6423	155	(2.4%)	202	(3.1%)	**955**	**(14.9%)**

For the quality of patients' lives after surgery, the long-term perspective is of utmost importance. This is best reflected by the long–term rehospitalisation rates at 5 years after the operation. It seems that these are relatively substantial, and tied to an *interaction with gender and type of surgery* (see test results in Table 65 in Appendix 6). When modelling all effects, there remained no evidence for an effect of age class.

Patient characteristics:

- ***Gender***: In the long term (5 years post op) *women* seem to have a somewhat higher chance of rehospitalisation associated with bariatric surgery than men. This is in line with recent findings from Bruze et al.,[302] who found a higher risk of rehospitalisation for female bypass patients in the long run (1-6 years) when studying total rehospitalisation rates in Sweden, and with findings from Abraham et al.[144] for short–term readmission rates. The effect of gender plays a mitigating role in the difference in rehospitalisation rates between banding and bypass surgery (see further details in Table 65 in Appendix 6).

Type of surgery:

- The chance of rehospitalisation due to bariatric related issues is strongly tied to the **type of bariatric surgery chosen,** with *gastric banding* surgeries leading to the highest chance of rehospitalisation, and *sleeve* surgeries to the lowest chance of rehospitalisation. This is due to different underlying reasons (i.e. undo, redo, laparascopy or adverse effects), as indicated in further detail in the following paragraphs (part 7.6.1-7.6.4). Also note that the patient groups of different types of operations were distinctly non-equivalent from the start, and these underlying patient differences can also play a role in de proclivity of choosing or requiring a new operation.

Key points

- **Between 10 and 34% of all bariatric patients have issues (undo, redo, adverse events or laparascopy) associated with their bariatric surgery requiring a rehospitalisation within 5 years post-op.**

7.6.1 Redo

Earlier bariatric procedures can be followed by new bariatric surgeries, either of the same or of a different type than the first one. This may imply revision of the first surgery or it may imply undoing the first intervention and opting for one of the other bariatric surgery techniques. Table 33 gives an overview of which bariatric surgery types were followed by which interventions of the same or a different type, and their corresponding amounts within 5 years after the first bariatric surgery took place.

Table 33– Patients with bariatric redo-interventions 5 years post-op by original surgery type

	TYPE	TOT	Redo SLEEVE		Redo BAND		Redo BYPASS		≥1 REDO	
Proxy first	**1st sleeve**	**3384**	23	(0.7%)	6	(0.2%)	184	(5.4%)	**209**	**(6.2%)**
	1st band	**3966**	134	(3.4%)	26	(0.7%)	458	(11.5%)	**613**	**(15.5%)**
	1st bypass	**17 235**	25	(0.1%)	49	(0.3%)	51	(0.3%)	**122**	**(0.7%)**
Prehistory		**1474**	14	(0.9%)	13	(4.9%)	47	(3.2%)	**73**	**(5.0%)**

*Note: the specific columns register whether a specific type of redo has occurred after the first bariatric surgery. The last column '≥1 redo' counts whether one or more redo operation has occurred for a patient. As it is quite possible to have more than one redo operation after the original surgery, the sum of all specific redo operations will be equal to, or higher than the '≥1 redo' count.**Some conclusions:***

- After 5 years patients with gastric banding have more redo interventions than the other patient groups (see statistical test in Table 64 in Appendix 6).
  Note: If patients follow up an original gastric band operation with a second band "redo" operation; this could indicate a repositioning of the original band. However, this occurs relatively infrequently. It is more common for a band operation to be followed by a sleeve or especially bypass operation.
- Although the observed rate of redo interventions for gastric bypass patients is much lower than for sleeve and banding patients, gastric bypasses are not always conclusive either: There are also patients opting for a sleeve or gastric band after a bypass. However, in comparison with the other groups, this is rather exceptional.
  Note: When a primary bypass does not yield the pursued weight loss, a possibility is to add a gastric band to the existing bypass in order to additionally reduce stomach capacity.[137]
- Note that the chance of a redo will be an interplay between both original surgery characteristics, patient charachteristics, and characteristics of follow up surgery – which makes it difficult to make clear judgements concerning the efficacy of different bariatric surgery types.

7.6.2 *Undo*

A patient can have an undo operation either as the end-point or as an intermediary when choosing another bariatric surgery later on (e.g. a gastric band may need to be removed to be replaced by another treatment / or may be removed because of band intolerance or band erosion or port and tubing problems without another bariatric replacement).

The nomenclature below is used to identify undo operations:

a. 241533, 241544 Resection of the stomach or reducing gastroplasty without discontinuation, *short: stomach resection*

b. 220231, 220242 Removal of internal strange body from tissues, *short: removal strange tissue*

c. 243611, 243622 Surgery after perforation of abdominal organ other than appendix, *short: Surgery after perforation*

d. 241555, 241566 Degastro-gastrectomy

e. 241570, 241581 Reconversion of the gastroduodenal transit after previous gastrectomy: *short: Reconversion*

Note: Within the undo surgeries there are some interventions that may be classified as a proxy for an undo of a gastric band surgery (i.e.. a, b and c).

An important remark is that the distinction between an undo and an adverse event is not always clear. For example a stomach resection may be performed to further reduce the stomach volume or when there are ulcers which may be formed as a complication of the initial bariatric surgery.

Table 34 – Patients with bariatric undo interventions 5 years post op by type of original surgery

	type	TOTAL	Stomach resection		Removal strange tissue		Surgery after perforation		Degastro-gastrectomy		Reconversion		≥1 Undo	
			N	%	N	%	N	%	N	%	N	%	N	%
Proxy first	**sleeve**	**3384**	5	(0.1%)	90	(2.7%)	7	(0.2%)	10	(0.3%)	**	(**)	**113**	**(3.3)**
	banding	**3966**	34	(0.9%)	393	(9.9%)	36	(0.9%)	6	(0.2%)	**	(**)	**516**	**(11.4)**
	bypass	**17 235**	24	(0.1%)	374	(2.2%)	182	(1.1%)	161	(0.9%)	40	(0.2%)	**865**	**(4.3)**
Prehistory		**1474**	63	(0.3%)	857	(3.5%)	16	(1.1%)	177	(0.7%)	45	(0.2%)	**124**	**(8.4)**

*Note: cell counts under 5 (and corresponding percentage information) are censored by ***
Note: the specific columns register whether a specific type of undo has occurred after the first bariatric surgery. The last column '≥1 undo' counts whether one or more undo operation has occurred for a patient after the original bariatric surgery. As it is possible to have more than one undo operation after the original surgery, the sum of all specific undo operations will be equal to, or higher than the '≥1 undo' count.

Some conclusions:

- Among the different undo options *removal of strange tissue* is by far the most frequently used. *Reconversion* is the least frequently used.
- **Banding** patients seem to have the most 'removal of strange tissue' (9.9%) in the 5 years after bariatric surgery. However, 'removal of strange tissue' also features in **sleeve** patients (2.7%) and **bypass** patients (2.2%) after five years.
- Patients with prehistory have a relatively high chance of having an undo.
  (*note:* Possibly because the actual time frame for these patients is much longer than for the other patient group. Also they have some indication of earlier intestinal problems, cf. 7.6, which may influence the chance of an undo later.)
- For **bypass**, after 5 years there is a much larger number of patients with an undo nomenclature (n=865, 4.3%), than patients with a redo nomenclature (n=122, 0.7%).
- For **sleeve**, the opposite is true: after 5 years there are less patients with undo nomenclature (n=113, 3.3%), than patients with redo nomenclature (n=209, 6.2%).
- For **banding**, the figures for *undo* (n=516), and *redo with a sleeve or a bypass* later (n=592) tie relatively close together.
  note: One would expect the undo banding figures to be at least equal, even somewhat larger to the figures of banding followed by a sleeve redo / bypass redo (because it seems logical that in redo surgery the band will be removed, and in some cases the undo may be the endpoint as well). Possibly an undo of banding is not necessarily coded if performed in the same operation as a new bariatric operation.

7.6.3 Laparoscopy

Laparoscopy is a technique to investigate the abdominal cavity and the intestines. Frequently, laparoscopy is used in combination with surgical treatment. In the current analysis, laparoscopy is counted only when not used in combination with surgical treatment. Laparoscopy may be used as a diagnostic tool to determine whether further surgical intervention is necessary. Alternatively, laparoscopy can also be used in case of an anastomotic leak in combination with a drain to get rid of excess fluids in the abdominal cavity.[303]

The observations presented in Table 35 show the following:

- Laparoscopy not in combination with a surgical treatment is not used very frequently after a bariatric intervention.
- Post-operative laparoscopy is most often performed after banding.

Table 35 – Patients with laparoscopy 5 years post op by original bariatric surgery type

	TYPE	TOTAL	LAPAROSCOPY	
Proxy first	**sleeve**	**3384**	14	(0.4%)
	band	**3966**	114	(2.9%)
	bypass	**17 235**	154	(0.9%)
Prehistory		**1474**	18	(1.2%)
≥1 REDO		**1017**	40	(3.9%)

7.6.4 Adverse events

Like any surgical treatment, bariatric surgery might lead to complications. As specified in the literature review (chapter 5) there are numerous adverse events, occurring both in the short and the long term. While some adverse events are general, others are more procedure specific.

In Belgium adverse events specific to bariatric surgery can be identified with the codes below, which have been specified by obesity specialist J. Himpens. This list does not identify all possible adverse events. Only those with a direct link to bariatric interventions and with a specific coding within the RIZIV – INAMI nomenclature were selected:

a. 243316, 243320 Treatment of small intestinal obstruction by adhesiolysis as by Noble, Childs or Baker, including gastrostomy, *short: surgery small intestinal obstruction*

b. 243331, 243342 Surgery due to intestinal obstruction (excl. Strangulated Hernia), *short: surgery after obstruction*

c. 241931, 241642 Treatment of an incisional hernia (including redo after treatment of a primary incisional hernia and parastomal hernias), *short: Surgery incisional hernia*

d. 241032, 241043 Diaphragm hernia or hiatus hernia from abdominal side, *short: diaphragm or hiatus hernia*

e. 244716, 244720 Vagotomy with or without stomach drain, associated with complete anti-reflux treatment, *short: vagotomy*

f. 241452, 241463 Total gastrectomy with oesofago-jejunal anastomosis or subtotal gastrectomy with recovery of intestinal transit by interposition of an intestinal segment, *short: (sub) total gastrectomy*

The results in Table 36 show that:

- More than 1 in 10 patients with a **band** or **bypass** have an adverse event within 5 years post-op.
- Patients with a prehistory have a higher chance of further post-op adverse events compared to patients without prehistory
  (*note:* Possibly because the actual time frame for these patients is much longer than for the other patient group)
- Patients with at least one redo are about 3 times as likely to suffer from adverse events as default bariatric patients.
  (*note:* Possibly because these patients were having a harder time already – requiring the redo – and because the redo itself adds another potential risk)

Table 36 – Total patients with adverse events within 5 years post bariatric surgery by original surgery type

	TYPE	TOTAL	ADVERSE EVENTS		NO ADVERSE EVENTS	
Proxy first	**sleeve**	**3384**	185	(5.5%)	3 199	(94.5%)
	band	**3966**	500	(12.6%)	3 466	(87.4%)
	bypass	**17 235**	1765	(10.2%)	15 470	(89.8%)
Prehistory		**1474**	500	(13.3%)	789	(86.7%)
≥1 REDO		**1017**	233	(22.9%)	784	(77.1%)

Table 37 gives more details on a specific adverse event, i.e. post-operative intestinal obstruction. Two different kinds of obstructions are distinguished: *intestinal obstructions* and *small intestinal obstructions*.

- The highest change of obstructions was observed for the gastric banding patients, followed by the bypass patients.

  A much lower chance of obstructions is observed for sleeve patients. This finding concurs with the results of a study of Sippey et al.[146] who found post-operative obstructions to be more common in RY patients than in sleeve patients.

- Redo patients had little evidence of additional obstructions.

- Prehistory patients have a higher chance of obstructions.

  (*note:* Possibly because the actual time frame for these patients is much longer than for the other patient group)

Table 37 – Obstructions within 5 years post op by original bariatric surgery type

	TYPE	TOTAL	SURGERY AFTER OBSTRUCTION		SURGERY SMALL INTESTINAL OBSTRUCTION	
Proxy first	**sleeve**	**3384**	**35**	(1.0%)	**	(**)
	banding	**3966**	397	(10.0%)	**	(**)
	bypass	**17 235**	1 124	(6.5%)	30	(0.2%)
Prehistory		**1474**	109	(7.4%)	**	(**)
≥1 REDO		**1017**	**	(**)	**	(**)

*Note: cell counts under 5 (and corresponding percentage information) are censored by ***

Table 38 provides information about post-op hernia. Two different kinds of hernia are distinguished: diaphragm or hiatus hernias and incisional hernias

- *Diaphragm or hiatus hernias* were most frequently observed for gastric banding patients, followed by sleeve patients. There were almost no bypass patients with a diaphragm or hiatus hernia.

- *Incisional hernias* were most frequently observed for bypass patients, followed by sleeve and gastric banding patients.

- Prehistory patients have a higher chance of post-operative hernia operations
  (*note:* Possibly because the actual time frame for these patients is much longer than for the other patient group)

Table 38 – Hernia operations within 5 years post op by original bariatric surgery type

	TYPE	TOT	DIAPHRAGM OR HIATUS HERNIA		SURGERY INCISIONAL HERNIA	
Truly first	**sleeve**	**3384**	25	(0.7%)	95	(2.8%)
	banding	**3966**	37	(0.9%)	71	(1.8%)
	bypass	**17 235**	24	(0.1%)	607	(3.5%)
Prehistory		**1474**	**	(**)	79	(5.4%)
≥1 REDO		**1017**	11	(1.1%)	**	(**)

*Note: cell counts under 5 (and corresponding percentage information) are censored by ***

Table 39 **provides information about post op gastrectomy.** Five years after the original bariatric surgery, this code is used in around 1 % of cases. It is used for serious complications as it entails a complex intervention in which the intestinal transit needs to be restored.

Table 39 – Patients with (sub) total gastrectomy 5 years post op

	TYPE	TOT	(SUB) GASTRECTOMY	TOTAL
Proxy first	**sleeve**	**3384**	41	(1.2%)
	banding	**3966**	16	(0.4%)
	bypass	**17 235**	107	(0.6%)
Prehistory		**1474**	15	(1.0%)
≥1 REDO		**1017**	**	(**)

*Note: cell counts under 5 (and corresponding percentage information) are censored by ***

Prevalence of other adverse events post op

'Vagatomy, with or without stomach drain associated with complete anti-reflux treatment' interventions were not encountered in the studied bariatric cohort with the given nomenclature. Usually they are performed to manage stomach ulcers or duodenum ulcers. However, stomach ulcers are nowadays also treated with pharmacologic therapy.

Key points – redo/undo/laparoscopy/adverse events

- **Redo: The primary intervention with most redo after 5 years post op is gastric banding, followed by sleeve, and bypass.**
  In contrast, the preferred redo surgery is bypass, followed by sleeve, and banding
- **Undo: There is probably an underestimation of the number of undo interventions, possibly because other codes are used and/or they are not explicitly coded when occuring at the same time as a bariatric redo of a different type.**
- **Adverse events: Generally the observed adverse event rate is lowest for sleeve operations, followed by gastric bypass, and gastric banding. The most frequently occuring problems are: intestinal obstruction, followed by incisional hernia.**
- **Laparoscopy: Laparoscopy not in combination with a surgical treatment is not used very frequently after a bariatric intervention.**

Key points – bariatric surgery types

The analyses did illustrate that both the intensity of rehospitalisation, as well as the underlying reasons are characteristic for the type of bariatric surgery

- **Gastric band: Leads to more undo procedures for "removal strange tissue", and more redo surgery afterwards (mainly bypass redo), more investigative laparascopy, and as far as adverse events coincide with somewhat more obstructions**
- **Sleeve: Sleeve patients generally have a lower chance of adverse events (excl. a relative higher chance for total gastrectomy) than bypass and banding patients**

Note that the chance of a new operation related to bariatric issues (undo, redo, adverse events or laparascopy) will be an interplay between the original surgery characteristics, patient characteristics, and -in the case of a redo- possible benefits of a new bariatric surgery, or -in the case of an undo- ease of an undo. This makes it difficult to form hard conclusions concerning the efficacy of the different bariatric surgery options based on real-world data.

7.7 Bariatric Surgery: Mortality

Table 40 provides information about the mortality risk after bariatric surgery. For the three types of bariatric surgery, this risk is relatively low. This finding is in line with another international recent cohort study from Denmark[94] that found a very limited perioperative (30-day) mortality after bypass, and virtually no difference in mortality after 4 years post operation between the bariatric patients and a matched control cohort.

Table 40 – Mortality after bariatric surgery per surgery type

	type	sleeve	sleeve	band	band	bypass	bypass
	cohort	**2009-2011**	**2012-2014**	**2009-2011**	**2012-2014**	**2009-2011**	**2012-2014**
	total operations	3587	7989	4067	1905	18436	24262
Number							
	0 to 1 months after surgery	***	9	***	***	23	21
	2 to 5 months after surgery	***	8	***	***	14	20
	6 to 11 months after surgery	6	8	***	***	12	33
	12 to 23 months after surgery	5	16	***	***	41	56
	24 to 35 months after surgery	7		9		53	
	36 to 47 months after surgery	9		***		41	
	48 to 59 months after surgery	***		11		42	
Per thousand							
	0 to 1 months after surgery	***	1	***	***	1	1
	2 to 5 months after surgery	***	1	***	***	1	1
	6 to 11 months after surgery	2	1	***	***	1	1
	12 to 23 months after surgery	1	2	***	***	2	2
	24 to 35 months after surgery	2		2		3	
	36 to 47 months after surgery	3		***		2	
	48 to 59 months after surgery	***		3		2	
	Cumulative per mille :						
	- 1 year mortality	3	3	2	3	3	3
	- 2-year mortality	9	10	5	9	10	10
	- 5-year mortality	12		9		15	

Note: Normal general population mortality overall over gender (male/ female) at 40 yrs : ca. 1 per mille per year
*Note: cellcounts under 5 (and corresponding per mille information) are censored by ****
Note: for patients first operated in the period 2012-2014 a follow-up of 5 years was not yet possible.

Key points – mortality

- **There is a low 30-day mortality risk (about 1 promille) for all types of bariatric surgery (sleeve, banding, bypass).**
- **longer follow up suggests that mortality levels at 2-5 years are slightly higher than those for the normal general population. However, it is difficult to disentangle the effects of being overweight and the bariatric surgery itself.**

7.8 Bariatric Surgery: participation by EPR status

Another observation is the increasing relative presence of people with 'EPR' (Entitled to Preferential Reimbursement – indicating a lower income or special status) among the patients undergoing bariatric surgery. This pattern is observed for all types of bariatric surgery (see Table 41). For gastric banding the relative presence of 'EPR'-status patients among those undergoing surgery starts a small fall back after the peak in 2014.

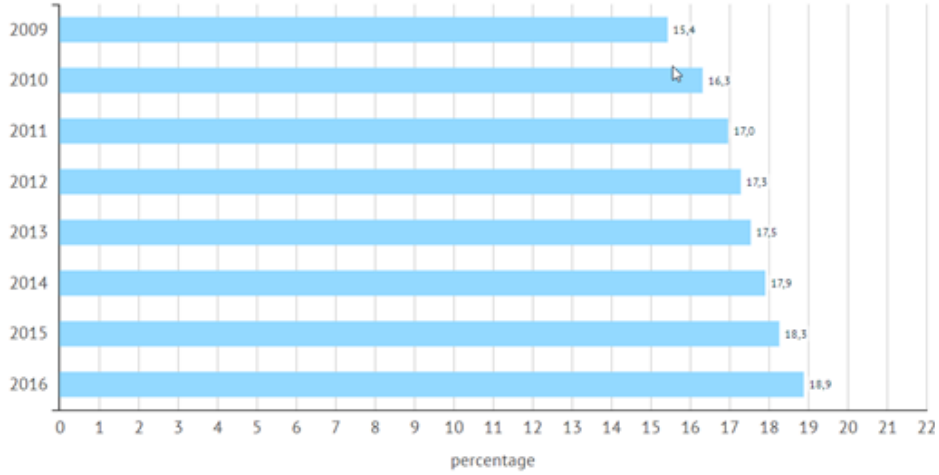
Table 41 – EPR participation by operation year and bariatric surgery type

Type	Year	#Surgeries	no EPR	EPR
sleeve	**2009**	**821**	79%	21%
sleeve	**2010**	**1183**	77%	23%
sleeve	**2011**	**1583**	76%	24%
sleeve	**2012**	**2046**	76%	24%
sleeve	**2013**	**2616**	75%	25%
sleeve	**2014**	**3327**	74%	26%
sleeve	**2015**	**3751**	73%	27%
sleeve	**2016**	**4648**	73%	27%
band	**2009**	**1649**	84%	16%
band	**2010**	**1346**	82%	18%
band	**2011**	**1072**	78%	22%
band	**2012**	**873**	77%	23%
band	**2013**	**563**	77%	23%
band	**2014**	**469**	74%	26%
band	**2015**	**366**	76%	24%
band	**2016**	**332**	77%	23%
bypass	**2009**	**5036**	83%	17%
bypass	**2010**	**5901**	82%	18%
bypass	**2011**	**7499**	81%	19%
bypass	**2012**	**8012**	80%	20%
bypass	**2013**	**8092**	80%	20%
bypass	**2014**	**8158**	79%	21%
bypass	**2015**	**8027**	79%	21%
bypass	**2016**	**8402**	79%	21%

sleeve	**2009-2011**	**3587**	77%	23%
sleeve	**2012-2014**	**7989**	75%	25%
band	**2009-2011**	**4067**	82%	18%
band	**2012-2014**	**1905**	76%	24%
bypass	**2009-2011**	**18436**	82%	18%
bypass	**2012-2014**	**24262**	80%	20%

Part of the pattern of the relative increasing demand for bariatric surgery by people with an 'EPR'– status could be influenced by the increasing percentage of Belgians with an EPR status, as illustrated in Figure 41.

Figure 41 – Evolution (2009 - 2016) of EPR prevalence in Belgium



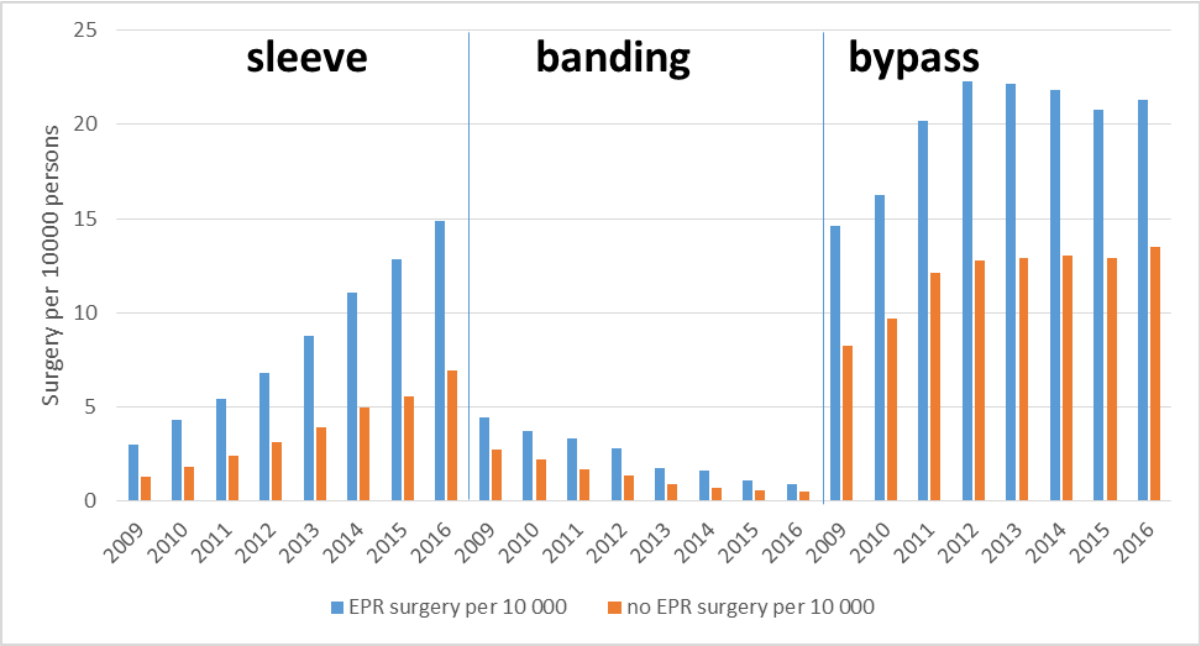
Source: IMA Atlas

In order to avoid this issue when ascertaining the prevalence of bariatric surgery, a first proxy is defined as the number of bariatric surgeries with EPR reimbursement per 10 000 EPR entitled individuals. Analogous, another proxy is defined as the number of bariatric surgeries without EPR reimbursement per 10 000 individuals without Entitlement to Preferential Reimbursement.

There is a small error margin as a (discarded) fraction of individuals have EPR status unknown (less than 1%). The denominator duly refers to the active adult population between 20 and 60 years as this is the population age when bariatric surgery tends to take place.

As illustrated in Figure 42, the observed trends for different types of bariatric surgery are quite similar for both EPR and non EPR calculations. However, there is a systematic noticeable higher occurrence of bariatric surgery in the EPR group, compared to the non-EPR group – irrelevant of operation year or surgery type.

Figure 42 – EPR and non EPR populations: prevalence of bariatric surgery by surgery type



Key points

- **There is an increasing participation of patients with an 'EPR' status– these are patients with a lower income or special status.**
- **This is especially true with respect to sleeve operations: 27% of the patients with a sleeve operation in 2016 did hold an EPR-status.**
- **Overall, the same popularity patterns for different types of bariatric surgery (increasing popularity for sleeves, decreasing popularity for banding, and high yet fluctuating popularity for bypass operations) hold in both the EPR and non-EPR patient populations.**

8 COST-EFFECTIVENESS OF BARIATRIC SURGERY: LITERATURE REVIEW

8.1 Literature search

8.1.1 Search strategy

A systematic search for economic literature about the cost-effectiveness of bariatric surgery for the treatment of obesity was performed by consulting various databases. First of all, **reviews** on this topic were searched by consulting the CRD (Centre for Reviews and Dissemination) HTA database and websites of HTA institutes mentioned on the INAHTA (International Network of Agencies for Health Technology Assessment) website. Websites of ex- or non-member HTA institutes such as NICE (National Institute for Health and Care Excellence) were also consulted. We also consulted the non-public POP database (Planned and Ongoing Projects – May 2018) accessible to EUnetHTA partners (European Network for Health Technology Assessment).

The search strategy started in April 2018 by looking for HTA reports on websites of HTA institutes and consulting CRD's HTA database (see Appendix 1). In August 2018, a limited search[g] for more up-to-date reviews of economic evaluations was performed in Pubmed.

Finally, an extra search was performed in October 2018 to find **supplementary primary economic evaluations**. Medline (OVID) and EMBASE databases were searched to retrieve extra full economic evaluations of bariatric surgery for the treatment of obesity. Since the most recent identified systematic review performed its search up to September 2015,[304] our search was limited to the period 2015-2018. The NHS EED (CRD's Economic Evaluation Database) was not consulted since bibliographic records were published on NHS EED until 31st March 2015. Since then, this database is not updated anymore (https://www.crd.york.ac.uk/CRDWeb/). No language restrictions were imposed. An overview of this search strategy and results is provided in Appendix 1.

8.1.2 Selection criteria

All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, comparator, and design (Table 42). For the population and intervention, we refer to the medical in- and exclusion criteria (see part 4.1.1). The comparator should include no surgery as an alternative. This can be interpreted in a broad sense and includes descriptions such as 'lifestyle modifications', 'conservative treatment', 'conventional medical management', etc. The design is restricted to full economic evaluations, i.e. studies comparing at least two alternative treatments in terms of costs and outcomes. Both cost-effectiveness and cost-utility analyses were eligible. Before/after studies, not directly comparing surgery with a no-surgery group, were excluded.

The selection of relevant articles was performed in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of a full-text assessment. Reference lists of the selected studies were checked for additional relevant citations.

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g This limited search only included the Mesh terms for economic evaluations ("Cost-Benefit Analysis"[Mesh]) and bariatric surgery ("Bariatric Surgery"[Mesh]) and provided 187 references. The most recent identified review was the article by Campbell and colleagues (2016).[304]

Table 42 – Economic evaluation selection criteria

	Inclusion criteria	Exclusion criteria
Population	patients with overweight or obesity	
Intervention	Any of the following bariatric surgery techniques: LAGB, RYGB, sleeve gastrectomy.	Scopinaro, endoscopic, and other techniques An evaluation of the (cost-)effectiveness of the waiting period before bariatric surgery is also out of the scope of this report.
Comparator	No surgery	Scopinaro, duodenal switch, endoscopic techniques[a], comparisons of variations of the same basic technique[b], open versus laparoscopic surgery, pharmacotherapy
Design	Full economic evaluations: cost-effectiveness and cost-utility analysis[c]	Other designs such as cost calculations or 'before/after' evaluations

LAGB: laparoscopic adjustable gastric banding; RYGB: Roux-en-Y gastric bypass.
a: A preliminary evaluation learned that these techniques are not yet mature, with no RCTs being published so far. As a result, economic evaluations on this topic are also excluded.
b: Except for the "mini gastric bypass", a.k.a. "one-anastomosis gastric bypass", which was explicitly asked by our external reviewers for consideration in the present report.
c: due to the large amount of relevant publications, only cost-effectiveness (CEA) and cost-utility analyses (CUA) are selected. Cost-consequences analysis (CCA) are excluded.

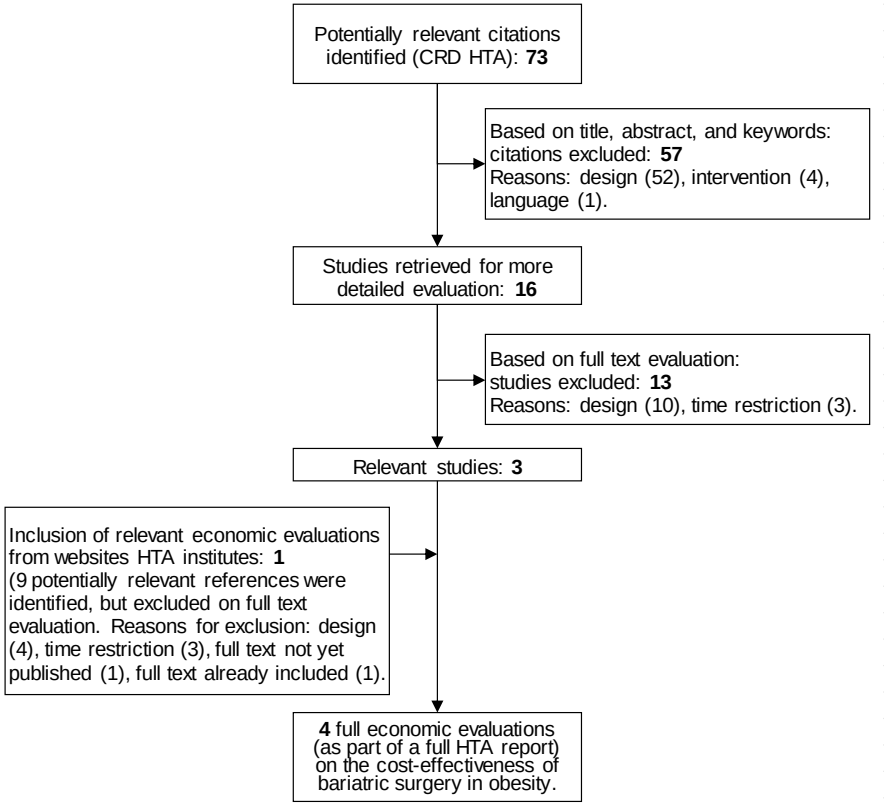
8.1.3 Presentation of results

The economic evaluations are identified from three different sources: 1) the de novo economic evaluations that were part of a full HTA report and were identified when searching for a systematic review of economic evaluations of bariatric surgery; 2) the economic evaluations that were identified in the selected systematic reviews; and 3) the evaluations that were identified when performing an update of the literature search for primary economic evaluations published in the period 2015-2018, i.e. after the inclusion period of the identified systematic reviews. The tables with general information describing the economic evaluations will present the results for these three groups (see part 8.3.1). Similarly, this will also be done in part 1.1.1 were an overview of results and authors' conclusions will be presented. Thereafter, the results and conclusions will be discussed for 1) the indications that currently fall within the reimbursement criteria (part 8.3.3) and 2) indications that fall outside of these reimbursement criteria being adolescents and lower BMI categories (part 8.3.4).

8.2 Results of the economic search strategy

Figure 43 provides the flow chart of the selection process to retrieve relevant reports from CRD's HTA database and websites of HTA institutes. Of the 73 references identified in CRD's HTA database, only three[305-307] included a primary economic evaluation. Of the extra potentially relevant reports found on the websites of HTA institutes, one extra report[308] included a primary economic evaluation.

Figure 43 – Selection of relevant reports from CRD's HTA database and websites of HTA institutes



CRD HTA: Centre for Reviews and Dissemination Health Technology Assessment database.

Several of the other reports also searched for relevant references which we could use to identify primary economic evaluations. The study by Picot et al.[307] published in 2009 performed an elaborated systematic literature search for economic evaluations up to 2008. Therefore, we only looked for more recently published systematic reviews. Finally, our quick search in PubMed also identified a systematic review of economic evaluations of bariatric surgery published in 2016.[304] The POP database identified no other institutes making a report on the topic of bariatric surgery. The list of included systematic reviews is provided in Table 43.

Table 43 – List of relevant references identified in CRD's HTA database and websites of HTA institutes

References
Reports including a primary economic evaluation
Gulliford MC, Charlton J, Booth HP, Fildes A, Khan O, Reddy M, et al. Costs and outcomes of increasing access to bariatric surgery for obesity: cohort study and cost-effectiveness analysis using electronic health records. Health Serv Deliv Res 2016;4(17).[305]
Ollendorf DA, Cameron CG, Loos AM, Synnott PG, Pearson SD. Bariatric Surgery: Final Evidence Report. ICER (Institute for Clinical and Economic Review); April, 2015.[306]
Klarenbach S, Padwal R, Wiebe N, Hazel M, Birch D, Manns B, Karmali S, Sharma A, Tonelli M. Bariatric Surgery for Severe Obesity: Systematic Review and Economic Evaluation. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010 (Technology report no. 129).[308]
Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technol Assess. 2009;13(41):1-190, 215-357, iii-iv.[307]
Reports including a review of primary economic evaluations
Canadian Agency for Drugs and Technologies in Health (CADTH). Bariatric Surgery for the Long-Term Treatment of Obesity: A Review of the Clinical Effectiveness and Cost-Effectiveness. July 2016.[309]
Canadian Agency for Drugs and Technologies in Health (CADTH). Bariatric Surgical Procedures for Obese and Morbidly Obese Patients: A Review of Comparative Clinical and Cost-Effectiveness, and Guidelines. April, 2014.[310]
National Clinical Guideline Centre (NCGC). Obesity: Identification, assessment and management of overweight and obesity in children, young people and adults – Methods, evidence and recommendations. Commissioned by the National Institute for Health and Care Excellence (NICE). November 2014.[311]
Healthcare Improvement Scotland (HIS). What is the relative clinical effectiveness, cost effectiveness and safety of different bariatric surgery techniques (gastric bypass, gastric banding and sleeve gastrectomy)? Number 6 June 2012.[312]
Institute of Health Economics (IHE). Bariatric treatments for adult obesity. Edmonton AB: Institute of Health Economics. 2012.[313]
NHS Quality Improvement Scotland (NHS QIS). Bariatric surgery in adults. Evidence Note 28. June 2010.[314]
Systematic review identified in PubMed
Campbell JA, Venn A, Neil A, Hensher M, Sharman M, Palmer AJ. Diverse approaches to the health economic evaluation of bariatric surgery: a comprehensive systematic review. Obes Rev. 2016;17(9):850-94.[304]

The review of economic evaluations of Campbell et al.(2016) is considered to be the most recent and most complete systematic review. The authors identified 77 studies. However, their selection criteria also allowed 'before and after' evaluations. Our selection criteria only allowed full economic evaluations comparing bariatric surgery with an alternative and looking at both costs and effects. From the 77 studies, only the 25 modelling studies that generated cost-effectiveness or cost-utility metrics are included in our overview (see Table 44). From these 25 studies, two studies[315, 316] were excluded because vertical banded gastroplasty was the intervention under consideration. Another study[317] was excluded because gastric bypass surgery at age 40 (BMI>40) was compared with a diet and exercise program at age 18 (BMI >33). Comparing an intervention at age 40 with another

intervention at age 18 is not within our scope. In the report of Gulliford et al.,[305] another primary economic evaluation was identified.[318] As such, based on these review reports, another 23 relevant economic evaluations could be identified.

As shown in Table 44, several other studies were identified in other systematic reviews but were not included in the overview of Campbell et al. However, these studies could be excluded for the following reasons:

- Keating et al., 2015:[319] this is a cost analysis and not a full economic evaluation.
- Wang et al., 2013:[320] this is an overview of six underlying studies.[318, 321-325] Five of these studies are included in the overview of Campbell et al. One of these studies (Mäklin et al., 2011[318]) was identified in the review of Campbell et al. but not marked as a full economic evaluation. In our opinion, this study is a full economic evaluation and will also be included in our overview.
- IHE, 2012:[313] the underlying studies of Anselmino and Klarenbach (see further) are included.
- Picot, 2012:[326] this is an update of the economic evaluations performed in the report by these authors published in 2009 with similar results.
- Padwal, 2011:[327] this study includes an overview of 13 underlying studies,[307, 317, 321, 328-337] of which 11 are already included in the overview of Campbell. Of the two remaining studies, the study of Paxton et al.[337] is a cost-minimization study comparing open and laparoscopic RYGB. The other study of Clegg et al.[335] published in 2002 was updated by Picot and colleagues in 2009.[307]
- Klarenbach, 2010:[308] This is the CADTH report published in 2010. The review included 11 studies.[307, 315-317, 332-338] The three studies not included in the review of Campbell were the two previously mentioned studies of Paxton et al.[337] and Clegg et al.[335] and the cost-analysis of Martin et al.[338] The primary economic evaluation performed by Klarenbach et al. is included in our overview.
- Picot, 2009:[307] the underlying studies identified in this review are already included in the review of Campbell et al (see Table 44). The primary economic evaluation published in this HTA report is also inlcuded in our overview.
- Boudreau, 2007:[339] the studies identified in this review are no full economic evaluations[340, 341] or are already included[315] in the review of Campbell et al.
- Stephenson, 2007:[342] the study identified five primary evaluations. The study of Finkelstein et al.[343] is a cost analysis excluding the utility improvement to the patient. The studies of Ackroyd et al.[334] and van Mastrigt et al.[315] were already included. The studies of Siddiqui et al.[344] and Paxton et al.[337] compared open with laparoscopic RYGB.
- Paxton, 2005:[337] this study is a cost-minimization study and will not be discussed.
- Clegg, 2002:[335] an update of this report was published by Picot et al.(2009)[307]

Table 44 – Overview of included (primary) economic evaluations in the identified reviews

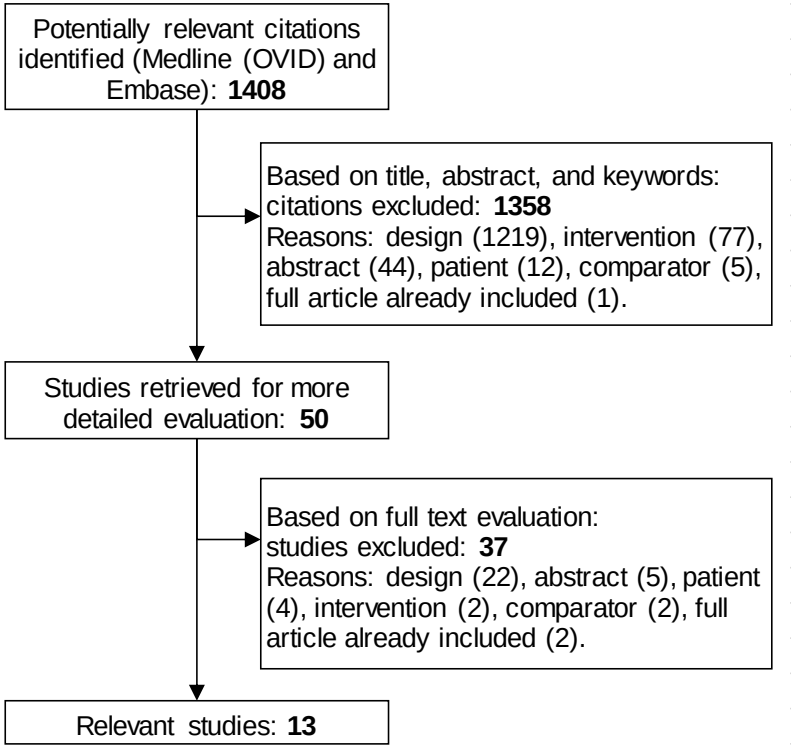
	Campbell, 2016[304]	Gulliford, 2016[305]	Ollendorf, 2015[306]	CADTH, 2016[309]	CADTH, 2014[310]	NCGC, 2014[311]	HIS, 2012[312]	IHE, 2012 [313]	CADTH, 2010 [308]	NHS QIS, 2010[314]	Picot, 2009[307]
De novo primary EE		x	x						x		x
Bairdain, 2015[345]	x										
Borisenko, 2015[346]	x	x		x							
Keating, 2015[319]				x							
Castilla, 2014[347]	x			x							
Wang, 2014[325]	x	x	x		x						
Faria, 2013[323]	x				x						
Lee, 2013[348]	x	x									
Pollock, 2013[349]	x	x				x					
Song, 2013[324]	x										
Wang, 2013[320]		x									
IHE, 2012[313]					x						
Michaud, 2012[350]	x										
Picot, 2012[326]		x				x					
Chang, 2011[322]	x										
Padwal, 2011[327]		x	x								
Ananthapavan, 2010[351]	x										
Campbell, 2010[321]	x										
Hoerger, 2010[328]	x					x	x				
Klarenbach, 2010[308]							x	x			
McEwen, 2010[329]	x										
Anselmino, 2009[330]	x							x			

Ikramuddin, 2009[331]	x							
Keating, 2009[332]	x			x		x		
Keating, 2009[352]	x							
Picot, 2009[307]				x	x	x	x	
Cremieux, 2008[353]	x							
Salem, 2008[333]	x					x		x
Boudreau, 2007[339]							x	
Stephenson, 2007[342]							x	
Ackroyd, 2006[334]	x					x		x
van Mastrigt, 2006[315]	x					x		x
Jensen, 2005[317]	x					x		x
Paxton, 2005[337]						x	x	
Clegg, 2002[335]						x	x	
Craig, 2002[336]	x					x		x
van Gemert, 1999[316]	x					x		
Martin, 1995[338]						x		
Extra references identified in reference list from included studies								
Mäklin, 2011[318]		x*						

** This study was identified indirectly in the report of Gulliford et al.,[305] This report included a review of Wang et al.[320] One of the six studies in this review was the evaluation of Mäklin et al.[318]*

Figure 44 provides the flow chart of the selection process to retrieve extra primary economic evaluations published during the period 2015-2018 and indexed in Medline (OVID) or Embase. Another 13 extra relevant references were identified (Table 45). As such, 40 primary economic evaluations are included in this overview.

Figure 44 – Selection of extra primary economic evaluations from Medline (OVID) and Embase (period 2015-2018)



Remark: Propensity score-matched analyses were not explicitly mentioned in the inclusion or exclusion criteria. Given the already large amount of identified primary economic evaluations, it was decided not to include the analyses of Krishna et al.[354] comparing mortality and healthcare resource utilization (hospital length of stay and cost) in a propensity-score matched analyses.

Table 45 – List of relevant references identified in OVID and Embase (period 2015-2018)

References
Alsumali A, Eguale T, Bairdain S, Samnaliev M. Cost-Effectiveness Analysis of Bariatric Surgery for Morbid Obesity. Obes Surg. 2018 Aug;28(8):2203-14.[355]
Borisenko O, Lukyanov V, Debergh I, Dillemans B. Cost-effectiveness analysis of bariatric surgery for morbid obesity in Belgium. J Med Econ. 2018 Apr;21(4):365-73.[356]
Panca M, Viner RM, White B, Pandya T, Melo H, Adamo M, et al. Cost-effectiveness of bariatric surgery in adolescents with severe obesity in the UK. Clin Obes. 2018 Apr;8(2):105-13.[357]
Sanchez-Santos R, Padin EM, Adam D, Borisenko O, Fernandez SE, Dacosta EC, et al. Bariatric surgery versus conservative management for morbidly obese patients in Spain: a cost-effectiveness analysis. Expert Rev Pharmacoecon Outcomes Res. 2018 Jun;18(3):305-14.[358]
Borisenko O, Lukyanov V, Johnsen SP, Funch-Jensen P. Cost analysis of bariatric surgery in Denmark made with a decision-analytic model. Dan Med J. 2017 Aug;64(8).[359]
Borisenko O, Mann O, Dupree A. Cost-utility analysis of bariatric surgery compared with conventional medical management in Germany: a decision analytic modeling. BMC Surg. 2017 Aug 3;17(1):87.[360]
Cohen RV, Luque A, Junqueira S, Ribeiro RA, Le Roux CW. What is the impact on the healthcare system if access to bariatric surgery is delayed? Surg Obes Relat Dis. 2017 Sep;13(9):1619-27.[361]
James R, Salton RI, Byrnes JM, Scuffham PA. Cost-utility analysis for bariatric surgery compared with usual care for the treatment of obesity in Australia. Surg Obes Relat Dis. 2017 Dec;13(12):2012-20.[362]
Klebanoff MJ, Chhatwal J, Nudel JD, Corey KE, Kaplan LM, Hur C. Cost-effectiveness of Bariatric Surgery in Adolescents With Obesity. JAMA Surg. 2017 Feb 1;152(2):136-41.[363]

Lucchese M, Borisenko O, Mantovani LG, Cortesi PA, Cesana G, Adam D, et al. Cost-Utility Analysis of Bariatric Surgery in Italy: Results of Decision-Analytic Modelling. Obes Facts. 2017;10(3):261-72.[364]
Wentworth JM, Dalziel KM, O'Brien PE, Burton P, Shaba F, Clarke PM, et al. Cost-effectiveness of gastric band surgery for overweight but not obese adults with type 2 diabetes in the U.S. J Diabetes Complications. 2017 Jul;31(7):1139-44.[365]
Sinha AC, Singh PM, Bhat S. Are we operating too late? Mortality Analysis and Stochastic Simulation of Costs Associated with Bariatric Surgery: Reconsidering the BMI Threshold. Obes Surg. 2016 Jan;26(1):219-28.[366]
Tang Q, Sun Z, Zhang N, Xu G, Song P, Xu L, et al. Cost-Effectiveness of Bariatric Surgery for Type 2 Diabetes Mellitus: A Randomized Controlled Trial in China. Medicine (Baltimore). 2016 May;95(20):e3522.[120]

Remark: The primary economic evaluations published by Gulliford et al. in 2017[367] was based on their full report published in 2016.[305] Only the full report is included in our overview.

8.3 Overview of identified economic evaluations

8.3.1 General description

Table 46 gives an overview of a selection of general characteristics of the identified economic evaluations: country (+ currency and year of costing), time horizon (and discount rate for costs and effects), perspective of the analysis, type of the analysis, population, intervention and comparator.

Most studies were performed in the US (15), Australia (6) and the UK (4). Two studies were performed for Spain. One study was identified for the following countries: Belgium, Brazil, Canada, China, Denmark, Finland, Germany, Italy, Korea, Portugal and Sweden. Two studies present results for three countries (France, Germany and the UK and Austria, Italy and Spain). Most studies apply a lifetime time horizon and perform the study from a health care payer's perspective. Only four studies mention to perform the study from a societal perspective. However, in e.g. the study of Faria et al.,[323] it is not clear whether indirect costs associated with bariatric surgery or obesity were included. Also in the study of Wentworth et al.[365] it is not clear which wider societal costs were included. Almost all studies are cost-utility analysis. Only two studies are cost-effectiveness analysis.[350, 352] One 'return-on-investment' study[353] calculated the time required for third-party payers to recover the initial investment associated with bariatric surgery. Another study is a threshold analysis[366] in which the authors calculate the BMI were 1) the increased risk of obesity over normal weight equals the risk associated with bariatric surgery, and 2) the future discounted obesity-associated morbidity costs become greater than present day real costs of bariatric surgery.

There are large differences in the included population with respect to BMI (≥30, ≥35, ≥40 kg/m2 or a range (e.g. 30-35 kg/m2) with or without comorbidities, etc.). In two studies the BMI range started at 20[359] and 23 kg/m2.[364] There were also large differences in age (e.g. minimum age of 18, starting age of 30, average of about 40 or 50, etc.). There were only four studies for adolescents.[345, 351, 357, 363] The population mainly consisted of women (see Table 46). Some studies focus on one of the relevant bariatric surgery procedures, while others discuss bariatric surgery as a whole, including both LAGB, RYGB and SG. The share of these three bariatric surgeries can be very different, e.g. SG represents only 1.6% in the studies of Borisenko et al.[346] while this is 30% in the study of Mäklin et al.[318] The description of the 'no surgery' comparator was often limited (e.g. 'optimal medical management', 'conventional medical management' or 'conservative management' without providing further details).

Finally, it is important to notice that the strength of an economic evaluation depends on the reliability of the underlying evidence. Whether this evidence comes from RCTs, matched controlled studies, observational data, etc. has an impact on the confidence that researchers and stakeholders can have in the results of the economic evaluations and the conclusions reached. The overview in chapter 4 on the efficacy/effectiveness of MBS has shown that the strongest evidence is found for the indications that are currently reimbursed in Belgium (BMI ≥40 or BMI ≥35 with specific comorbidities). The evidence is less strong for adolescents and lower BMI levels. Therefore, for these two indications, we will specifically add the underlying main source for the treatment effect and impact on QoL. We refer the reader to part 8.3.4 for further details.

Table 46 – General characteristics of identified cost-effectiveness and cost-utility analyses

	Country (currency)	Time horizon (discount rate)	Perspective	Type of analysis	Population	Intervention & comparator
Economic evaluations identified in the full HTA reports						
Gulliford, 2016[305]	UK (£, 2014)	Lifetime (C&E: 3.5%)	HCP	CUA	BMI: ≥40 (Morbid obesity) or 35-39.9 (Severe obesity) Age: 46 years (range 20-74)	Surgery (LAGB, RYGB or SG) vs. no surgery
Ollendorf, 2015[306]	US ($, 2015)	10 years (C&E: 3%)	HCP	CUA	BMI: BMI≥30 & subgroups with BMI range (30-34.9, 35-39.9, and ≥40) Adults	RYGB, LAGB, SG, or BPD/DS (i.e., with duodenal switch) vs. no surgery
Klarenbach, 2010[308]	Canada (CAD, 2009)	1, 10, 20 & lifetime (C&E: 5%)	HCP	CUA	Mean BMI: 47 kg/m2 Average age: 48 years Women: 80% Diabetes mellitus: 15%	RYGB, LAGB, SG or BPD vs. no surgery
Picot, 2009[307]	UK (£, 2007/8)	2, 5 & 20 years (C&E: 3.5%)	HCP	CUA	Group 1: BMI ≥40 Group 2: BMI ≥30 and <40 & T2D Group 3: BMI ≥30 and <35	LAGB or RYGB (group 1) or LAGB (group 2 & 3) vs. no surgery
Economic evaluations included in the review of Campbell et al.[304]						
Bairdain, 2015[345]	US ($, 2013)	7 years (C&E: 3%)	HCP	CUA	BMI, median (SD): 48.7 (6.6) Mean age: 17.3 (range 14 – 20) Women: 90%	RYGB vs. no surgery
Borisenko, 2015[346]	Sweden (€, 2012)	Lifetime (C&E: 3%)	HCP	CUA	BMI: 42.8 (range 30–60) Mean age: 41 (range 25–65) Diabetes: 18.4% Women: 76%	GB (98%), SG (1.6%) & (L)AGB (0.4%) vs. no surgery
Castilla, 2014[347]	Spain (€, 2012)	Lifetime (C&E: 3%)	HCP	CUA	BMI: 50.7 (range 36.6-76.3) Age: 18–55 years Diabetes: 20.3% Women: 87.3%	GB vs. no surgery
Wang, 2014[325]	US ($, 2010)	Lifetime (C&E: 3%)	HCP	CUA	Base case: BMI = 44, 53 years, female	lap. RYGB, open RYGB, LAGB vs. no surgery

	Country (currency)	Time horizon (discount rate)	Perspective	Type of analysis	Population	Intervention & comparator
Faria, 2013[323]	Portugal (€, NA)	Lifetime (C&E: 3%)	Societal	CUA	Base case: mean BMI = 49.6, 40 years	(L)AGB, GB vs. no surgery
Lee, 2013[348]	Australia (AUD, 2003)	Lifetime (C&E: 3%)	HCP	CUA	- Individuals with BMI ≥40 - Individuals with BMI ≥35	LAGB vs. no surgery
Pollock, 2013[349]	UK (£, 2010)	40 years (C&E: 3.5%)	HCP	CUA	BMI: 37.1 (range 30-40) Mean age (SD): 46.9 (8.7) Patients with type 2 diabetes (mean duration of diabetes: 1 year) Women: 53.5%	LAGB vs. no surgery
Song, 2013[324]	Korea ($, 2011)	Lifetime (C&E: 5%)	HCP	CUA	BMI: range 30-40 Starting age: 30 years	Surgery (LAGB, RYGB, SG) vs. no surgery
Michaud, 2012[350]	US ($, 2010)	46 years (C&E: 3%)	Societal	CEA	- Current eligibility: BMI ≥40 or BMI 35-40 with qualifying co-morbidities - Extended eligibility: BMI ≥35 or BMI 30-35 with qualifying co-morbidities (heart disease, hypertension, diabetes and stroke)"	RYGB vs. no surgery
Chang, 2011[322]	US ($, 2010)	Lifetime (C&E: 3%)	NA (HCP)	CUA	BMI ≥35 (mean BMI: 39.96) Mean age: 39.7	Bariatric surgery vs. no surgery
Ananthapavan, 2010[351]	Australia (AUD, 2001)	Lifetime (C&E: 3%)	Societal	CUA	BMI ≥35 28 adolescents: - mean age: 18 years (range 15-19) - 2 boys and 26 girls	LAGB vs. no surgery
Campbell, 2010[321]	US ($, 2006)	Lifetime (C&E: 3%)	HCP	CUA	BMI ≥40 or BMI ≥35 with comorbid conditions. Age: 18 to 74 years	RYGB, LAGB vs. no surgery
Hoerger, 2010[328]	US ($, 2005)	Lifetime (C&E: 3%)	NA (HCP)	CUA	BMI ≥35 kg/m2 and diabetes (newly diagnosed or established diabetes)	(L)AGB, GB vs. no surgery

	Country (currency)	Time horizon (discount rate)	Perspective	Type of analysis	Population	Intervention & comparator
McEwen, 2010[329]	US ($, NA)	2 years and lifetime (C&E: 3%)	NA (HCP)	CUA	BMI ≥35 with two life-threatening comorbidities or BMI≥40 Patients were generally middle-aged, female, and white. Diabetes: 37%	RYGB vs. no surgery
Anselmino, 2009[330]	Austria, Italy, and Spain (€, 2009)	5 years (C&E: 3.5%)	HCP	CUA	BMI≥35 and T2DM	(L)AGB, GB vs. no surgery
Ikramuddin, 2009[331]	US ($, 2007)	35 years (C&E: 3%)	HCP	CUA	Mean BMI: 48.4 (12.8% BMI <40) Mean age: 50.1 years Women: 77.9% Patients with T2DM	RYGB vs. no surgery
Keating, 2009[352]	Australia (AUD, 2006)	2 years (no discounting)	HCP	CEA	BMI ≥30 and <40 Diagnosed type 2 diabetes	LAGB vs. no surgery
Keating, 2009[332]	Australia (AUD, 2006)	Lifetime (C&E: 3%)	HCP	CUA	mean BMI 37 (range 30-40) Diagnosed type 2 diabetes	LAGB vs. no surgery
Cremieux, 2008[353]	US ($, 2005)	6 years (C&E: 3.07%)	HCP	RoI	Morbidly obese patients aged 18 years or older	Bariatric surgery vs. no surgery
Salem, 2008[333]	US ($, 2004)	Lifetime (C&E: 3%)	HCP	CUA	Base case: BMI: 40 Age: 35	LAGB, RYGB vs. no surgery
Ackroyd, 2006[334]	France, Germany, UK (€, £, 2005)	5 years (C&E: 3.5%)	HCP	CUA	BMI ≥35 and T2DM	(L)AGB, GB vs. no surgery
Craig, 2002[336]	US ($, 2001)	Lifetime (C&E: 3%)	HCP	CUA	BMI: 40-50 Age: 35 to 55 years	GB vs. no surgery
Mäklin, 2011[318]	Finland (€, 2010)	10 years (C&E: 3%)	HCP	CUA	BMI: average 47 (range 38-59) Age: 43 (range 33-63) Women: 65%	Bariatric surgery (LAGB (2%), GB (68%), SG (30%)) vs. no surgery

	Country (currency)	Time horizon (discount rate)	Perspective	Type of analysis	Population	Intervention & comparator
Economic evaluations identified in the search strategy between 2015 and 2018						
Alsumali, 2018[355]	US ($, 2016)	Lifetime (C&E: 3%)	HCP	CUA	BMI: ≥35 kg/m2 (range 35-69) Age: 18 to 74 years Women: 78%	LAGB, RYGB, SG vs. no surgery
Borisenko, 2018[356]	Belgium (€, 2012)	10 years and lifetime (C: 3%, E: 1.5%)	HCP	CUA	BMI: 41.44 kg/m2 (range 23–58) Age: 39.2 years (range 21–56) Women: 79.31% Diabetes mellitus: 9.17%	Bariatric surgery (LAGB, RYGB, SG) vs. no surgery
Panca, 2018[357]	UK (£, 2013-2014)	Lifetime (C&E: 3.5%)	HCP	CUA	Mean age: - RYGB (n=9): 17.8 years - SG (n=9): 18.7 years Mean BMI: - RYGB: 48.3 kg/m2 (SD 6.2) - SG: 60.0 kg/m2 (SD 9.3) Women: - RYGB: 56% - SG: 44%	RYGB or SG vs. no surgery
Sanchez-Santos[358]	Spain (€, 2017)	10 years and lifetime (C&E: 3%)	HCP	CUA	BMI: 47.56 kg/m2 (range 30–60) Age: 41.1 years (range 25–65) Women: 80.5% Diabetes mellitus: 18.6%	Bariatric surgery (LAGB, RYGB, SG) vs. no surgery
Borisenko, 2017[359]	Denmark (DKK, 2012)	10 years and lifetime (C&E: 3%)	HCP	CUA	BMI: 42 kg/m2 (range 20–68) Age: 40 years (range 22–57) Women: 77.4% Diabetes mellitus: 23.2%	Bariatric surgery (LAGB, RYGB, SG) vs. no surgery
Borisenko, 2017[360]	Germany (€, 2012)	10 years and lifetime (C&E: 3%)	HCP	CUA	BMI: 48.8 kg/m2 (range 30–60) Age: 40.4 years (range 25–65) Women: 73.7% Diabetes mellitus: 20.6%	Bariatric surgery (LAGB (33%), RYGB (51%), SG (17%)) vs. no surgery
Cohen, 2017[361]	Brazil ($, NA)	20 years (C&E: 5%)	HCP	CUA	BMI: 48.6 kg/m2 (range 47.3–50) Age: 41 years (range 40.4–42.4)	Surgery vs. no surgery

	Country (currency)	Time horizon (discount rate)	Perspective	Type of analysis	Population	Intervention & comparator
					Women: 79.0% (range 76.4–81.3) T2D: 22.3% (range 18.5–26.6)	
James, 2017[362]	Australia (AUD, 2015)	Lifetime ~50 years (C&E: 5%)	HCP	CUA	BMI: ≥35 kg/m2 Age: 30 years	LAGB, RYGB, SG vs. no surg.
Klebanoff, 2017[363]	US ($, 2015)	3 years (NA)	NA (HCP)	CUA	BMI: 53 (range 34-88) Mean age: 17 years (SD 1.6) Women: 75%	Bariatric surgery (RYGB or SG) vs. no surg.
Lucchese, 2017[364]	Italy (€, 2015)	10 years and lifetime (C&E: 3%)	HCP	CUA	BMI: 46.2 kg/m2 (range 23–58) Age: 40.6 years (range 21–56) Women: 75.36% Diabetes mellitus: 20%	Bariatric surgery (LAGB, RYGB, SG) vs. no surg.
Wentworth, 2017[365]	Australia (US$, 2015 - AUD1 = US$0.78)	10 years (C&E: 3%)	Societal	CUA	BMI: 25 to 30kg/m2 Age: 18-65 years Patients with diabetes	LAGB vs. no surg.
Sinha, 2016[366]	US ($, 2007)	Lifetime (50 years) (C&E: 3%)	NA (HCP)	Threshold analysis	BMI categories: <25, 25.0 to 29.9, 30.0 to 34.9, and ≥35 kg/m2. Age: 40-50 years	LAGB or RYGB vs. no surg.
Tang, 2016[120]	China ($, NA)	2 years (C&E: 5%)	NA (HCP)	CUA	BMI: ≥28 kg/m2 - SG group: 38.4 kg/m2 (SD 8.6) - RYGB group: 37.8 kg/m2 (SD 5.6) Age: 16 to 65 years - SG group: 36.6 years (SD 8.0) - RYGB group: 40.4 years (SD 12.3) Women: - SG group: 88% - RYGB group: 80% T2DM patients	RYGB or SG vs. no surg.

AUD: Australian dollar; BMI: body mass index; BPD/DS: Biliopancreatic Diversion/Duodenal Switch; C: costs; CAD: Canadian dollar; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; DKK: Danish Krone; E: effects; GB: gastric bypass; HCP: health care payer; LAGB: laparoscopic adjustable gastric banding; NA: not available; RoI: return on investment; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; T2DM: type 2 diabetes mellitus.

8.3.2 *Overview of results and authors' conclusions*

In Table 47, we provide an overview of the results presented in the idientified economic evaluations. In this part, we focus on the main results of the base-case analysis. More details, e.g. from extensive sensitivity analyses, are available in the original articles. Most studies express their results in extra costs per quality-adjusted life year (QALY) gained. Faria et al.[323] express results as the net monetary benefit (NMB) at a willingness-to-pay (WTP) of €20 000 per QALY. Two studies[348, 351] express results in disability-adjusted life years (DALYs) avoided. Klarenbach et al.[308] express their results at one year as the incremental cost per decrement in BMI. Their results on a longer time horizon are also expressed as extra costs per QALY gained.

In the text following this table, we provide an overview of the results and conclusions by quoting the authors of the original studies. Thereafter we will discuss the outcomes of studies reflecting the cost-effectiveness of bariatric surgery when used in indications falling withing the current reimbursement criteria (part 8.3.3). In part 8.3.4 we discuss the studies that look at indications that fall outside these reimbursement criteria (adolescents and lower BMI).

Table 47 – Results of the identified cost-effectiveness and cost-utility analyses

	Population, intervention & comparator	Mean cost/QALY (unless otherwise stated)
Economic evaluations identified in the full HTA reports		
Gulliford, 2016[305]	BMI: ≥40 (Morbid obesity) or 35-39.9 (Severe obesity); Age: 46 years (range 20-74). Surgery (LAGB, RYGB or SG) vs. no surgery.	General: £7129 Morbid obesity and diabetes: £6176 Severe obesity: £7675
Ollendorf, 2015[306]	BMI ≥30 & subgroups with BMI range (30-34.9, 35-39.9, and ≥40); Adults. RYGB, LAGB, SG, or BPD vs. no surgery.	BMI: ≥30 / 30-34.9 / 35-39.9 / ≥40 RYGB: $37 423 / $53 021 / $42 534 / $30 995 SG: $29 087 / $43 122 / $33 789 / $23 784 LAGB: $35 680 / $51 826 / $41 073 / $29 552 BPD: $46 508 / $63 011 / $51 743 / $38 790
Klarenbach, 2010[308]	Mean BMI: 47 kg/m2; Average age: 48 years; Women: 80%; Diabetes mellitus: 15%. RYGB, LAGB, SG or BPD vs. no surgery.	At 1 year: incremental cost per decrement in BMI. At 10 years, 20 years & lifetime: CAD/QALY. 1 year / 10 years / 20 years / lifetime RYGB: CAD2 990 / CAD21 595 / CAD13 674 / CAD9398 LAGB: CAD5 764 / CAD37 910 / CAD21 240 / CAD12 212 SG: CAD2 184 BPD: CAD3 064
Picot, 2009[307]	Group 1: BMI ≥40 (LAGB or RYGB) Group 2: BMI ≥30 and <40 & T2D (LAGB) Group 3: BMI ≥30 and <35 (LAGB)	Group 1: - LAGB: £1897 - £3863 - RYGB: £3160 - £4127 Group 2: - 2 years: £18 930 - 5 years: £4580 - 20 years: £1367

	Population, intervention & comparator	Mean cost/QALY (unless otherwise stated)
		Group 3: - 2 years: £60 754 - 5 years: £16 381 - 20 years: £12 763
Economic evaluations included in the review of Campbell et al.[304]		
Bairdain, 2015[345]	BMI, median (SD): 48.7 (6.6); Mean age: 17.3 (range 14 – 20); Women: 90%. RYGB vs. no surgery.	1 year: $409 110 2 years: $187 397 3 years: $115 304 4 years: $80 065 5 years: $59 474 6 years: $46 157 7 years: $36 570
Borisenko, 2015[346]	BMI: 42.8 (range 30–60); Mean age: 41 (range 25–65); Diabetes: 18.4%; Women: 76%. GB (98%), SG (1.6%) & (L)AGB (0.4%) vs. no surgery.	Dominant
Castilla, 2014[347]	BMI: 50.7 (range 36.6-76.3); Age: 18–55 years; Diabetes: 20.3%; Women: 87.3%. GB vs. no surgery.	5 years: Dominated 10 years: €4044.98 15 years: €90.19 20 years: Dominant Lifetime: Dominant
Wang, 2014[325]	Base case: BMI = 44, 53 years, female. lap. RYGB, open RYGB, LAGB vs. no surgery.	lap. RYGB: $6600 open RYGB: $17 300 LAGB: $6200
Faria, 2013[323]	Mean BMI = 49.6, 40 years. (L)AGB, GB vs. no surgery.	NMB (at a WTP of €20 000): Medical management: €247 098 LAGB: €260 656 GB: €297 967 (dominant)
Lee, 2013[348]	BMI >40 or >35. LAGB vs. no surgery.	BMI >40: dominant BMI >35: $2154/DALY
Pollock, 2013[349]	BMI: 37.1 (range 30-40); Mean age (SD): 46.9 (8.7); Patients with type 2 diabetes (mean duration of diabetes: 1 year); Women: 53.5%. LAGB vs. no surgery.	£5163 per LYG £3602 per QALY gained
Song, 2013[324]	BMI: range 30-40; Starting age: 30 years. Surgery (LAGB, RYGB, SG) vs. no surgery.	$1771

	Population, intervention & comparator	Mean cost/QALY (unless otherwise stated)
Michaud, 2012[350]	- Current eligibility: BMI >40 or BMI 35-40 with qualifying co-morbidities; - Extended eligibility: BMI >35 or BMI 30-35 with qualifying co-morbidities (heart disease, hypertension, diabetes and stroke). RYGB vs. no surgery.	Current eligibility: $8171/LYG Extended eligibility: $10 579/LYG
Chang, 2011[322]	BMI >35 (mean BMI: 39.96); Mean age: 39.7. Bariatric surgery vs. no surgery.	Patients with obesity-related disease*: dominant (both in LYG & QALYs) Patients without obesity-related disease: dominant in LYG, $1904/QALY
Ananthapavan, 2010[351]	BMI >35; 28 adolescents: - mean age: 18 years (range 15-19) - 2 boys and 26 girls. LAGB vs. no surgery.	AUD4400/DALY
Campbell, 2010[321]	BMI >40 or BMI >35 with comorbid conditions; Age: 18 to 74 years. RYGB, LAGB vs. no surgery.	LAGB vs no surg.: $5400 RYGB vs no surg.: $5600
Hoerger, 2010[328]	BMI >35 kg/m2 and diabetes (newly diagnosed or established diabetes). (L)AGB, GB vs. no surgery.	Patients with newly diagnosed diabetes: - GB: $7000 - (L)AGB: $11 000 Patients with established diabetes: - GB: $12 000 - (L)AGB: $13 000
McEwen, 2010[329]	BMI ≥35 with two life-threatening comorbidities or BMI≥40; generally middle-aged, female, and white; Diabetes: 37%. RYGB vs. no surgery.	2-year time horizon: $48 662 Lifetime time horizon: $1425
Anselmino, 2009[330]	BMI≥35 and T2DM. (L)AGB, GB vs. no surgery.	(L)AGB: - Austria: -€2861 (dominant) - Italy: -€1077 (dominant) - Spain: €1456 GB - Austria: -€1447 (dominant) - Italy: -€1246 (dominant) - Spain: €2664
Ikramuddin, 2009[331]	Mean BMI: 48.4 (12.8% BMI <40); Mean age: 50.1 years; Women: 77.9%; Patients with T2DM. RYGB vs. no surgery.	$21 973
Keating, 2009[352]	BMI >30 and <40; Diagnosed type 2 diabetes. LAGB vs. no surgery.	AUD16 600 per case of diabetes remitted.
Keating, 2009[332]	Mean BMI 37 (range 30-40); Diagnosed type 2 diabetes. LAGB vs. no surgery.	Dominant (both per LYG & QALY gained)

	Population, intervention & comparator	Mean cost/QALY (unless otherwise stated)				
Cremieux, 2008[353]	Morbidly obese patients aged 18 years or older. Bariatric surgery vs. no surgery.	Total surgery costs are fully recovered after 53 months.				
Salem, 2008[333]	Base case: BMI: 40; Age: 35. LAGB, RYGB vs. no surgery.	Men: LAGB: $11 604/QALY; RYGB: $18 543/QALY Women: LAGB: $8878/QALY; RYGB: $14 680/QALY				
Ackroyd, 2006[334]	BMI ≥35 and T2DM. (L)AGB, GB vs. no surgery.	GB	Germany	France	UK	
		1 year	€4825	dominant	£14 328	
		2 years	dominant	dominant	£6214	
		3 years	dominant	dominant	£3579	
		4 years	dominant	dominant	£2293	
		5 years	dominant	dominant	£1517	
		(L)AGB				
		1 year	€16 988	€4448	£24 511	
		2 years	€2989	dominant	£9185	
		3 years	dominant	dominant	£4758	
		4 years	dominant	dominant	£2886	
		5 years	dominant	dominant	£1929	
Craig, 2002[336]	BMI: 40-50; Age: 35 to 55 years. GB vs. no surgery.		Cost per life-year		Cost per QALY	
		Age 35	Men	Women	Men	Women
		BMI: 40	$844 700	/	$28 600	$14 700
		BMI: 50	$70 300	$9 130 000	$10 700	$5700
		Age 55				
		BMI: 40	$100 200	$248 500	$35 600	$16 100
		BMI: 50	$30 700	$38 900	$13 300	$5400
Mäklin, 2011[318]	BMI: average 47 (range 38-59); Age: 43 (range 33-63); Women: 65%. Bariatric surgery (LAGB (2%), GB (68%), SG (30%)) vs. no surgery.	Dominant				
Economic evaluations identified in the search strategy between 2015 and 2018						
Alsumali, 2018[355]	BMI: ≥35 kg/m2 (range 35-69); Age: 18 to 74 years; Women: 78%. LAGB, RYGB, SG vs. no surgery.	RYGB vs. no surg.: $5446 SG vs. no surg.: $7655 *(on average: dominated)* LAGB vs. no surg.: $8214 *(on average: extendedly dominated)*				
Borisenko, 2018[356]	BMI: 41.44 kg/m2 (range 23–58); Age: 39.2 years (range 21–56); Women: 79.31%; Diabetes mellitus: 9.17%. Bariatric surgery (LAGB, RYGB, SG) vs. no surgery.	10 years: €2809 Lifetime: dominant				

	Population, intervention & comparator	Mean cost/QALY (unless otherwise stated)
Panca, 2018[357]	Mean age: RYGB (n=9): 17.8 years; SG (n=9): 18.7 years Mean BMI: RYGB: 48.3kg/m2 (SD 6.2); SG: 60.0kg/m2 (SD 9.3) Women: RYGB: 56%; SG: 44%. RYGB or SG vs. no surgery	RYGB vs. no surgery: - Males: £2018 (95% CI £1942 - £2042) - Females: £2005 (95% CI £1974 - £2031) SG vs. no surgery: - Males: £1978 (95% CI £1954 - £2002) - Females: £1941 (95% CI £1915 - £1969)
Sanchez-Santos[358]	BMI: 47.56 kg/m2 (range 30–60); Age: 41.1 years (range 25–65); Women: 80.5%; Diabetes mellitus: 18.6%. Bariatric surgery (LAGB, RYGB, SG) vs. no surgery.	10 years: €5966 Lifetime: dominant
Borisenko, 2017[359]	BMI: 42 kg/m2 (range 20–68); Age: 40 years (range 22–57); Women: 77.4%; Diabetes mellitus: 23.2%. Bariatric surgery (LAGB, RYGB, SG) vs. no surgery.	10 years: DKK17 818 Lifetime: dominant
Borisenko, 2017[360]	BMI: 48.8 kg/m2 (range 30–60); Age: 40.4 years (range 25–65); Women: 73.7%; Diabetes mellitus: 20.6%. Bariatric surgery (LAGB (33%), RYGB (51%), SG (17%)) vs. no surgery.	10 years: €2457 Lifetime: dominant
Cohen, 2017[361]	BMI: 48.6 kg/m2 (range 47.3–50); Age: 41 years (range 40.4–42.4); Women: 79.0% (range 76.4–81.3); T2D: 22.3% (range 18.5–26.6). Surgery vs. no surgery.	Surgery: $735.85 (delayed surgery: dominated)
James, 2017[362]	BMI: >35 kg/m2; Age: 30 years. LAGB, RYGB, SG vs. no surgery.	LAGB: AUD24,454 RYGB: AUD22,645 SG: AUD27,523
Klebanoff, 2017[363]	BMI: 53 (range 34-88); Mean age: 17 years (SD 1.6); Women: 75%. Bariatric surgery (RYGB or SG) vs. no surgery.	36 months: $154 684 48 months: $114 078 60 months: $91 032
Lucchese, 2017[364]	BMI: 46.2 kg/m2 (range 23–58); Age: 40.6 years (range 21–56); Women: 75%; Diabetes mellitus: 20%. Bariatric surgery (LAGB, RYGB, SG) vs. no surgery.	10 years: €2412 Lifetime: dominant
Wentworth, 2017[365]	BMI: 25 to 30kg/m2; Age: 18-65 years; Patients with diabetes. LAGB vs. no surgery.	2 years: $94 387 5 years: $52 453 10 years: $29 007 (base case) 15 years: $21 629

	Population, intervention & comparator	Mean cost/QALY (unless otherwise stated)
Sinha, 2016[366]	BMI categories: <25, 25.0 to 29.9, 30.0 to 34.9, and ≥35 kg/m2; Age: 40-50 years. LAGB or RYGB vs. no surgery.	Obesity vs Bariatric Surgery Mortality Risk: threshold were increased risk of obesity over normal weight equals risk associated with bariatric surgery: - Caucasian men: 25 kg/m2 (LAGB), 27 kg/m2 (open gastric banding or laparoscopic gastric bypass), 37.5 kg/m2 (open gastric bypass) - African-American men: any BMI (LAGB), 25 kg/m2 (open gastric banding or laparoscopic gastric bypass), 42 kg/m2 (open gastric bypass) - Caucasian women: 25.5 kg/m2 (LAGB), 28.5 kg/m2 (open gastric banding or laparoscopic gastric bypass), 45 kg/m2 (open gastric bypass) - African-American women: 27.5 kg/m2 (LAGB), 33.5 kg/m2 (open gastric banding or laparoscopic gastric bypass), >50 kg/m2 (open gastric bypass) Obesity-Related Morbidity vs Bariatric Surgery Costs: the BMI threshold at which future discounted obesity-associated morbidity costs become greater than present day real costs of bariatric surgery: - Men: 30 kg/m2 (laparoscopic gastric bypass), 34.5 kg/m2 (LAGB) - Women: 32 kg/m2 (laparoscopic gastric bypass), 37 kg/m2 (LAGB).
Tang, 2016[120]	BMI: ≥28 kg/m2 SG: 38.4 kg/m2 (SD 8.6); RYGB: 37.8 kg/m2 (SD 5.6) Age: 16 to 65 years SG: 36.6 years (SD 8.0); RYGB: 40.4 years (SD 12.3) Women: SG: 88%; RYGB: 80% T2DM patients. RYGB or SG vs. no surgery.	SG: $1028.97 (versus no surgery) RYGB: $1197.44 (versus no surgery)

**: in this study, obesity comorbidities included coronary heart disease, hypertension, type 2 diabetes, stroke, dyslipidemia, endometrial, breast, and colon cancers.*
The exchange rate was as follows on 21 January 2019 for the following currencies: 1$ = €0.88; 1£ = €1.13, 1 Australian dollar (AUD) = €0.63; 1 Canadian dollar (CAD) = €0.66; and 1 Danish Krone (DKK) = €0.13 (source: www.xe.com/currencyconverter).
BPD: Biliopancreatic Diversion; LAGB: laparoscopic adjustable gastric banding; LYG: life year gained; NMB: net monetary benefit; QALY: quality-adjusted life year; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; T2DM: type 2 diabetes mellitus

Economic evaluations identified in the full HTA reports

- Gulliford et al., 2016:[305]

  Results: "**In persons with morbid obesity** aged 20–74 years, bariatric surgery was associated with increased longevity and reduced time living with diabetes. Incremental costs associated with bariatric surgery were £15,258 (95% CI £15,184 to £15,330), including costs of bariatric surgical procedures of £9164 per participant. Incremental QALYs were 2.142 (95% CI 2.031 to 2.256) per participant. The estimated cost per QALY gained was £7129 (95% CI £6775 to £7506). … Estimates were similar across gender, age and deprivation subgroups. Bariatric surgery was slightly more cost-effective in patients with morbid obesity and diabetes at £6176 (95% CI £5894 to £6457) per QALY, and slightly less cost-effective in severe obesity, at £7675 (95% CI £7339 to £8037)."

  Conclusions: "*Bariatric surgery is associated with increased immediate and long-term health-care costs but these are exceeded by expected health benefits to obese individuals with reduced onset of new diabetes, remission of existing diabetes and lower mortality. Diverse obese* ***individuals have clear capacity to benefit from bariatric surgery at acceptable cost****.*"

- Ollendorf et al., 2015:[306]

  Results: "*In the 10 year time horizon analysis, bariatric surgery resulted in additional quality-adjusted life-years (QALYs) and increased costs compared with standard care … . The use of RYGB was associated with a gain of approximately 0.5 QALYs and incremental costs of nearly $20,000 ($54,110 vs. $34,923 for the standard care strategy). This led to an incremental cost per QALY of $37,423 for RYGB. VSG and LAGB are less costly, but less effective than RYGB, while BPD/DS is more expensive and more effective. However, in comparison to standard care, cost-effectiveness estimates are similar for all surgery types (ranging from $29,000 - $47,000 per QALY gained). Cost-effectiveness ratios were not calculated for VSG and LAGB in reference to RYGB (because they were less effective). The cost per QALY gained for BPD/DS was $77,574 in comparison to RYGB across all levels of BMI.*"

  Conclusions: "*We compared the cost-effectiveness of four bariatric surgery procedures to standard nonsurgical management* ***for all obese individuals (BMI≥30) as well as for subgroups defined by BMI range*** *(i.e., 30-34.9, 35-39.9, and ≥40). Across all levels of BMI and procedure type, we found that surgical procedures to treat obesity improve health related quality of life, reduce BMI and other comorbidities, and are associated with higher healthcare costs compared to standard nonsurgical management. Cost-effectiveness estimates for bariatric surgery ranged from $23,784 to $63,011, suggesting that* ***bariatric surgery for the treatment of obesity may be considered cost-effective*** *in comparison to well-accepted benchmarks (i.e., $50,000-$100,000 per QALY gained).*"

- Klarenbach et al., 2010:[308]

  Results: "*The primary economic evaluation in Canadian dollars comparing bariatric surgery to standard care results in ICURs of $21,600 per quality-adjusted life-year (QALY) to $37,910 per QALY at 10 years (for RYGB and LAGB respectively) and $9,400 per QALY to $12,000 per QALY using a lifetime horizon. The results were generally robust in one-way sensitivity analysis, and the probability that RYGB would be cost-effective using a threshold of $20,000 per QALY was 91%. In scenario analysis a more attractive ICUR was observed as the proportion of patients with comorbid disease (diabetes, sleep apnea, hypertension, and dyslipidemia) increased, and bariatric surgery was dominant when only patients with type 2 diabetes were considered. All bariatric surgical procedures were associated with ICURs between $6,500 per QALY and $12,000 per QALY compared with standard care over a lifetime horizon. Because of inherent uncertainty and a lack of data for some procedures, the relative cost-effectiveness between procedures could not be established.*"

  Conclusions: "*The economic evaluation comparing* ***bariatric surgery*** *to lifestyle modification (standard care) suggests that the treatment of patients with* ***BMI of 35 kg/m2 or more with obesity-related comorbidity, or a BMI of 40 kg/m2 or more****,* ***may be attractive compared with accepted thresholds of cost-effectiveness****. These*

results seemed to be mainly driven by gains in quality of life, and remained robust during sensitivity and scenario analysis. Estimated cost-utility ratios tended to decrease with greater levels of comorbidity in the population studied, and bariatric surgery was dominant (more effective and less costly) among obese people with concomitant diabetes mellitus. While all types of bariatric surgery that were considered were associated with cost-utility ratios that may be attractive when compared with standard care, there were fewer data (and thus greater uncertainty) on the relative merits and costs of the procedures — especially because the preferences of the patient and surgeon may influence the choice of surgery."

- Picot et al., 2009:[307]

  Results: "*Surgical management was more costly than non-surgical management in each of the three patient populations analysed, but gave improved outcomes. For morbid obesity, incremental cost-effectiveness ratios (ICERs) (base case) ranged between £2000 and £4000 per QALY gained. They remained within the range regarded as cost-effective from an NHS decision-making perspective when assumptions for deterministic sensitivity analysis were changed. For BMI ≥30 and <40, ICERs were £18,930 at two years and £1397 at 20 years, and for BMI ≥30 and <35, ICERs were £60,754 at two years and £12,763 at 20 years. Deterministic and probabilistic sensitivity analyses produced ICERs which were generally within the range considered cost-effective, particularly at the long twenty year time horizons, although for the BMI 30-35 group some ICERs were above the acceptable range.*"

  Conclusions: "*Bariatric surgery appears to be a **clinically effective and cost-effective intervention for moderately to severely obese people** compared with non-surgical interventions. Uncertainties remain and further research is required to provide detailed data on patient QoL; impact of surgeon experience on outcome; late complications leading to reoperation; duration of comorbidity remission; resource use. Good-quality RCTs will provide evidence on bariatric surgery for young people and for adults with class I or class II obesity. New research must report on the resolution and/or development of comorbidities such as Type 2 diabetes and hypertension so that the potential benefits of early intervention can be assessed.*"

Economic evaluations included in the review of Campbell et al., 2016:[304]

- Bairdain et al., 2015:[345]

  Results: "*At one year follow-up, mean weight loss was 37.5 (std. = 13.5) kg and the corresponding BMI was 35.4 (reduction of 13.2, p<0.01). Mean total intervention costs/person were $25 854 (std. = 2,044). A unit change in BMI was associated with future medical care savings of $157/year (p<0.01) and with an increase in HRQL of 0.004 (p<0.01) and life expectancy. At a threshold of a 100 000/QALY, bariatric surgery was not cost-effective in the first three years, but became cost-effective after that ($80 065/QALY in year four and $36 570/QALY in year seven).*"

  Conclusions: "*Our results suggest that **bariatric surgery among adolescents may be cost-effective** when evaluated over a long period of time. Future studies on a large scale are needed to show a continued improvement in QALYs and to evaluate earlier cost-effectiveness of the procedure.*" (median BMI: 48.7 kg/m2)[h]

- Borisenko et al., 2015[346]

  Results: "*Bariatric surgery was cost saving in comparison with conservative management. It also led to a substantial reduction in lifetime risk of events: from a 16 % reduction in the risk of transient ischaemic attacks to a 62 % reduction in the incidence of type 2 diabetes. Over a lifetime, surgery led to savings of €8408 and generated*

[h] We add this information if the results or conclusions of the authors do not provide information on the included population in their analysis.

an additional 0.8 years of life and 4.1 quality-adjusted life years (QALYs) per patient, which translates into gains of 32 390 quality-adjusted person-years and savings of €66 million for the cohort, operated in 2012. Analysis of the consequences of a 3-year delay in surgery provision showed that the overall lifetime cost of treatment may be increased in patients with diabetes or a body mass index >40 kg/m2. Delays in surgery may also lead to a loss of clinical benefits: up to 0.6 life years and 1.2 QALYs per patient over a lifetime."

Conclusions: "*Bariatric surgery, over a lifetime horizon, may lead to* ***significant cost savings*** *to health care systems* ***in addition to the known clinical benefits***." (average BMI: 42.8 kg/m2)

- Castilla et al., 2014[347]

  Results: "*Patients with gastric bypass result in a lifetime increase of 5.63 quality-adjusted life years (QALYs) (18.18 vs. 12.55 QALYs). In addition, because of the reduced spending associated with the treatment of various obesity-related comorbidities, final savings stand at 13,994 €. The total cost of the intervention branch is close to half the cost of the non-intervention branch (17,431 vs. 31,425 €).*"

  Conclusions: "***Gastric bypass*** *is an intervention that* ***dominates*** *over the option of not intervening when a lifetime horizon is considered.*" (average BMI: 50.7 kg/m2)

- Wang et al., 2014[325]

  Results: "*Bariatric surgery produced additional life expectancy (80 to 81 years) compared to no surgery (78 years). The incremental cost-effectiveness ratios (ICERs) of the surgical procedures were $6600 per QALY gained for LRYGB, $6200 for LAGB, and $17,300 for ORYGB (3% discount rate for cost and QALYs). ICERs varied according to choice of BMI forecasting method and clinically plausible variation in parameter estimates. In most scenarios, the ICER did not exceed a threshold of $50,000 per QALY gained.*"

  Conclusions: "***Gastric bypass and banding procedures are likely to be cost-effective*** *for obese patients compared to nonsurgical treatment at conventional cost-effectiveness thresholds.*" (average BMI: 44 kg/m2)

- Faria et al., 2013:[323]

  Results: "***Gastric bypass is a dominant strategy****, rendering a significant decrease in lifetime costs and increase in quality-adjusted life years (QALYs). Comparing with the best medical management, in the global population of patients with a BMI of >35 kg/m2, gastric bypass renders 1.9 extra QALYs and saves on average €13 244 per patient. Younger patients, patients with a BMI between 40 and 50 kg/m2, and patients without obesity-related diseases are the ones with a bigger benefit in terms of cost effectiveness.*"

  Conclusions: "*Gastric bypass surgery increases quality-adjusted survival and saves resources to health systems. As such, it can be an important process to control the ever-increasing health expenditure.*" (average BMI: 49.6 kg/m2)

- Lee et al., 2013:[348]

  Results: "*The ICER for the scenario providing LAGB surgery to all individuals with a* ***BMI >40*** *was dominant [95% CI: dominant - $588] meaning that the intervention led to both improved health and cost savings. The ICER when providing surgery to those with a* ***BMI >35*** *was $2154/DALY averted [95% CI: dominant - $6 033]. Results were highly sensitive to changes in the likelihood of long-term complications.*"

  Conclusions: "*LAGB* ***surgery is highly cost-effective*** *when compared to the $50 000/DALY threshold for cost-effectiveness used in Australia. LAGB surgery also ranks highly in terms of cost-effectiveness when compared to other population-level interventions for weight loss in Australia. The results of this study are in line with other economic evaluations on LAGB surgery. This study recommends that the Australian federal government provide a full subsidy for LAGB surgery to morbidly obese Australians with a BMI >40.*"

- Pollock et al., 2013:[349]

  Results: "*LAGB was associated with benefits in HbA1c, systolic blood pressure, body mass index and serum lipid concentrations, which led to significant increases in discounted life expectancy (an increase of 0.64 years) and quality-adjusted life expectancy (an increase of 0.92 quality-adjusted life years, QALYs) and reduced incidence of diabetes complications relative to SMM [standard medical management]. Treatment costs in the LAGB arm increased by 4552 Great British Pounds (GBP), but this was partially offset by cost savings resulting from a reduction in the incidence of all modelled diabetes complications. The incremental cost-effectiveness ratio of GBP 3602 per QALY in the base case fell well below commonly quoted willingness-to-pay thresholds in the UK setting.*"

  Conclusions: "*On the basis of data from a recent randomized controlled trial, **LAGB is likely to be considered cost-effective** from the healthcare payer perspective when compared with SMM of obesity in **patients with type 2 diabetes** in the UK setting.*" (average BMI: 37.1 kg/m2)

- Song et al., 2013:[324]

  Results: "*The cost-utility analysis study indicated that bariatric surgery had US$1522 incremental costs and 0.86 incremental QALYs as compared to nonsurgical interventions. Through the base case analysis, ICER was US$1771/QALY. The sensitivity analyses were performed using a variety of assumptions, and the robustness of the study results was also demonstrated.*"

  Conclusions: "*The study indicated that **bariatric surgery was a cost-effective alternative** to nonsurgical interventions over a lifetime, providing substantial lifetime benefits for **severely obese** Korean people.*" (BMI range 30-40 kg/m2)

- Michaud et al., 2012:[350]

  Results: "*We find that the total social value of bariatric surgery is large for treated patients, with incremental social cost-effectiveness ratios typically under $10 000 per life-year saved. On the other hand, pharmaceutical interventions against obesity yield much less social value with incremental social cost-effectiveness ratios around $50 000.*"

  Conclusions: "*On balance, **bariatric surgery generates substantial private value** for those treated, in the form of health and other economic consequences.*"(for both 'current eligibility' and 'extended eligibility')

- Chang et al., 2011:[322]

  Results: "*Our results suggest that bariatric surgery in general is cost-effective for obese people with BMI greater than 35 kg/m2, as ICERs are less than US$4000 per QALY gained. It is even cost-saving for those severely obese patients whose BMI is greater than 50 kg/m2 and who have at least one or more obesity-related comorbidities before surgery.*"

  Conclusions: "*We find that **surgery treatment is in general cost-effective for people whose BMI is greater than 35 kg/m2 with or without obesity-related comorbidities**, and it is **even cost-saving for super obese (BMI ≥50 kg/m2) with obesity-related comorbidities**. Our results also suggest that **surgery can be cost-effective for the mildly obese (BMI ≥30 kg/m2)**. The bottom line is that bariatric surgery should be universally available to all classes of obese people.*"

- Ananthapavan et al., 2010:[351]

  Results: "*The intervention reached 4120 severely obese, privately insured adolescents. It cost AUD130M (95% UI 52–265) and resulted in an incremental savings of 55 400 body mass index units (95% UI 12 600 –140 000) at 3 years after surgery, which translated into 12 300 disability-adjusted life years (95% UI 5000–24 670) saved during their lifetime. The cost-offsets totaled AUD75M (95% UI 30.5–150), resulting*

in a net cost per disability-adjusted life year saved of AUD4400 (95% UI 2900–6120)."

Conclusions: "*Although **the intervention was cost-effective** using the current modeling assumptions, it is unlikely to be acceptable to all stakeholders, including some severely obese adolescents. Nevertheless, gastric banding has an important role in the management of **morbid obesity in adolescents**.*"

- Campbell et al., 2010:[321]

  Results: "*Our base-case analyses, which used estimates of treatment effectiveness from a prospective randomized trial of LAGB versus LRYGB,[129] showed both LAGB and LRYGB to be cost-effective compared with no treatment. The ICERs for LAGB versus no treatment ($5400 per QALY gained) and for LRYGB versus no treatment ($5600 per QALY gained) are approximately equivalent.*"

  Conclusions: "*Results of our analyses lead us to conclude that **both LAGB and LRYGB provide significant weight loss and are cost-effective** at conventionally accepted thresholds for medical interventions compared with no treatment.*" (BMI >40 kg/m2 or BMI >35 kg/m2 with comorbid conditions)

- Hoerger et al., 2010:[328]

  Results: "*In all analyses, bariatric surgery increased QALYs and increased costs. Bypass surgery had cost-effectiveness ratios of $7000/QALY and $12 000/QALY for severely obese patients with newly diagnosed and established diabetes, respectively. Banding surgery had cost-effectiveness ratios of $11 000/QALY and $13 000/QALY for the respective groups. In sensitivity analyses, the cost-effectiveness ratios were most affected by assumptions about the direct gain in QoL from BMI loss following surgery.*"

  Conclusions: "*Our analysis indicates that **gastric bypass and gastric banding are cost-effective** methods of reducing mortality and diabetes complications in **severely obese adults with diabetes**.*"

- McEwen et al., 2010:[329]

  Results: "*In analyses that took a lifetime time horizon, projected future costs based on age and obesity and discounted costs and health utilities at 3% per year, the cost–utility ratio for bariatric surgery versus no surgery was approximately $1400 per quality-adjusted life-year gained.*"

  Conclusions: "*Although not cost-saving, **bariatric surgery represents a very good value for money**. Its long-term cost effectiveness appears to depend on the natural history and cost of late postsurgical complications and the natural history and cost of untreated morbid obesity.*" (BMI ≥35 kg/m2 with two life-threatening comorbidities or BMI ≥40 kg/m2)

- Anselmino et al., 2009:[330]

  Results: "*In Austria and Italy, both AGB and GBP are cost-saving and are thus dominant in terms of incremental cost-effectiveness ratio compared to CT. In Spain, AGB and GBP yield a moderate cost increase but are cost-effective, assuming a willingness-to-pay threshold of 30 000 euro per quality adjusted lifeyear. Under worst-case analysis, AGB and GBP remain cost-saving or around breakeven in Austria and Italy and remain cost-effective in Spain.*"

  Conclusions: "*In **patients with T2DM and BMI≥35 kg/m2** at 5-year follow-up vs. CT, AGB and GBP are not only clinically effective and safe but represent satisfactory **value for money from a payer perspective in Austria, Italy, and Spain**.*"

- Ikramuddin et al., 2009:[331]

  Results: "*The ICERs for the base-case and most sensitivity analyses fell below $50 000 per life-year gained, a level that may be considered cost-effective in the United States.[368, 369] Only shorter time horizons (5 and 10 years) and exclusion of the impact of increased BMI on the patient's quality of life yielded ICERs above that level.*"

Conclusions: "*This study has demonstrated that under our base-case assumptions, **bariatric surgery provides good value for the money** compared with standard medical management of T2DM, with an ICER of $21 973 per QALY gained. When assumptions were varied in sensitivity analyses (reduced effects on A1C, exclusion of lipid effects, lower and higher discount rates, and lower costs of treatment as observed at the medical center where bariatric surgery was performed), the ICERs remained under $50 000 per QALY in most cases. Only when the time horizon was greatly reduced and the quality-of-life impact of increased BMI was excluded did the ICERs exceed that standard guideline.*" (patients with T2DM and average BMI of 48.4 kg/m2)

- Keating et al., 2009:[352]

  Results: "*Mean 2-year intervention costs per patient were 13 400 AUD for surgical therapy and 3400 AUD for conventional therapy, with laparoscopic adjustable gastric band (LAGB) surgery accounting for 85% of the difference. Outpatient medical consultation costs were three times higher for surgical patients, whereas medication costs were 1.5 times higher for conventional patients. The cost differences were primarily in the first 6 months of the trial. Relative to conventional therapy, the incremental cost-effectiveness ratio for surgical therapy was 16 600 AUD per case of diabetes remitted (currency exchange: 1 AUD = 0.74 USD).*"

  Conclusions: "***Surgical therapy appears to be a cost-effective option** for managing **type 2 diabetes in class I and II obese patients**.*"

- Keating et al., 2009:[332]

  Results: "*The mean number of years in diabetes remission over a lifetime was 11.4 for surgical therapy patients and 2.1 for conventional therapy patients. Over the remainder of their lifetime, surgical and conventional therapy patients lived 15.7 and 14.5 discounted QALYs, respectively. The mean discounted lifetime costs were 98 900 AUD per surgical therapy patient and 101 400 AUD per conventional therapy patient. Relative to conventional therapy, surgically induced weight loss was associated with a mean health care saving of 2400 AUD and 1.2 additional QALYs per patient.*"

  Conclusions: "***Surgically induced weight loss is a dominant intervention** (it both saves health care costs and generates health benefits) for managing **recently diagnosed type 2 diabetes in class I/II obese patients** in Australia.*"

- Cremieux et al., 2008:[353]

  Results:"*The mean bariatric surgery investment ranged from approximately $17 000 to $26 000. After controlling for observable patient characteristics, we estimated all costs to have been recouped within 2 years for laparoscopic surgery patients and within 4 years for open surgery patients.*"

  Concusions: "***Downstream savings associated with bariatric surgery are estimated to offset the initial costs in 2 to 4 years**. Randomized or quasiexperimental studies would be useful to confirm this conclusion, as unobserved characteristics may influence the decision to undergo surgery and cannot be controlled for in this analysis.*" (morbid obesity)

- Salem et al., 2008:[333]

  Results: "*For both men and women LRYGB and LAGB were cost-effective at less than $25 000/QALY even when evaluating the full range of baseline BMI and estimates of adverse outcomes, weight loss and costs. For base-case scenarios in men (age 35, BMI 40) the ICER was $11 604 per QALY for LAGB, compared to $18 543 per QALY for LRYGB. For base-case scenarios in women (age 35, BMI 40) the ICER was $8878 per QALY for LAGB, compared to $14 680 per QALY for LRYGB.*"

  Conclusions: "*Modeled cost-effectiveness analysis showed that both operative interventions **for morbid obesity, LAGB and RYGB, were cost-effective** at less than $25 000, and LAGB was more cost-effective than RYGB for all the base-case scenarios.*"

- Ackroyd et al., 2006:[334]

  Results: "*Compared to CT, GBP yielded +80.8 kg/m2.years, +2.6 T2DM-free-years and +1.34 QALYs. AGB yielded +57.8 kg/m2.years, +2.5 T2DM-free-years and +1.03 QALYs. In Germany and France, both GBP and AGB yielded a cost decrease, and were thus dominant in terms of ICER compared to CT. In the UK, GBP and AGB yielded a cost increase, but were cost-effective.*"

  Conclusions: "*In **patients with T2DM and BMI ≥35 kg/m2**, AGB and GBP are effective at 5-year follow-up in **cost-saving in Germany and France**, and are **cost-effective in the UK** with a moderate BI vs CT.*"

- Craig et al., 2002:[336]

  Results: "*The base case cost-effectiveness ratios ranged from $5000 to $16 100 per QALY for women and from $10 000 to $35 600 per QALY for men, depending on age and initial body mass index. In a few subgroups of older, less obese men, variation in parameters such as loss of excess weight, obesity-related quality of life, complication rates, and perioperative mortality affected the cost-effectiveness ratios. Parameter variation did not result in meaningful changes in the remaining patients.*"

  Conclusions: "***Gastric bypass is a cost-effective alternative** to no treatment, providing substantial lifetime benefits in patients who are severely obese.*" (BMI range: 40-50 kg/m2)

- Mäklin et al., 2011:[318]

  Results: "*In the base-case analysis, bariatric surgery was both more effective and less costly than the ordinary treatment. The mean costs were €33 870 and €50 495, and the mean number of quality-adjusted life-years 7.63 and 7.05, for bariatric surgery and ordinary treatment respectively. Uncertainty around the parameter values was tested comprehensively in sensitivity analyses, and the results were robust.*"

  Conclusions: "***Surgery for morbid obesity increases health-related quality of life, and reduces the need for further treatments and total healthcare costs**. According to this analysis, non-operative care would be more costly for the Finnish healthcare system on average after 5 years following surgery.*"

Economic evaluations identified in the search strategy between 2015 and 2018

- Alsumali et al., 2018:[355]

  Results: "*LRYGB was cost-effective with higher QALYs (17.07) and cost ($138,632) than LSG (16.56 QALYs; $138,925), LAGB (16.10 QALYs; $135,923), and no surgery (15.17 QALYs; $128,284). Sensitivity analysis showed initial cost of surgery and weight regain assumption were very sensitive to the variation in overall model parameters. Across patient groups, LRYGB remained the optimal bariatric technique, except that with morbid obesity 1 (BMI 35–39.9 kg/m2) patients, LSG was the optimal choice.*"

  Conclusions: "***LRYGB is the optimal bariatric technique**, being the most cost-effective compared to LSG, LAGB, and no surgery options **for most subgroups**. However, **LSG was the most cost-effective choice when initial BMI ranged between 35 and 39.9 kg/m2**.*"

- Borisenko et al., 2018:[356]

  Results: "*In the base-case analysis over a 10-year time horizon, the increment in quality-adjusted lifeyears (QALYs) gained from bariatric surgery vs CMM was 1.4 per patient, whereas the incremental cost was €3,788, leading to an incremental cost-effectiveness ratio (ICER) of €2,809 per QALY. Over a lifetime, bariatric surgery produced savings of €9,332, an additional 1.1 life years and 5.0 QALYs. Bariatric surgery was cost-effective at 10 years post-surgery and dominant over conventional management over a lifetime horizon.*"

  Conclusions: "*It was demonstrated that a **current mix of bariatric surgery methods was cost-effective at 10 years post-surgery and cost-saving over the lifetime** of the Belgian patient cohort considered in this analysis.*" (average BMI: 41.44 kg/m2)

- Panca et al., 2018:[357]

  Results: "For RYGB vs. no surgery, the incremental cost/QALY was £2018 (95% CI £1942 - £2042) for males and £2005 (95% CI £1974 - £2031) for females. For SG vs. no surgery, the incremental cost/QALY was £1978 (95% CI £1954 - £2002) for males and £1941 (95% CI £1915 - £1969) for females."

  Conclusions: "**Bariatric surgery in adolescents** with severe obesity **is cost-effective**; it is more costly than no surgery however it markedly improved quality of life." (average BMI: 48.3 kg/m2 (RYGB group) and 60 kg/m2 (SG group))

- Sanchez-Santos et al., 2018:[358]

  Results: "*Over the 10-year horizon, BS led to a cost increment of €9,386 and 1.6 additional QALY (€5,966/QALY). Leading to 0.6 LYG and 4.4 QALY gains and €300/patient average cost savings over lifetime, BS could potentially significantly reduce diabetes and cardiovascular disease risk over the considered horizons. Despite short-term cost reductions, surgery delay may lead to significant clinical benefits loss.*"

  Conclusions: "*Compared to CM, **BS is a more effective and less costly alternative for treating morbid obesity** in Spain.*"

- Borisenko et al., 2017:[359]

  Results: "In the ten-year base-case analysis, bariatric surgery led to a cost increment of 19,332 DKK and generated an additional 1.1 quality-adjusted life years (QALYs). In the course of a lifetime, surgery leads to savings of 36,403 DKK, an additional 0.7 life years and 2.9 QALYs. Bariatric surgery was cost-effective at ten years with an incremental cost-effectiveness ratio of 17,818 DKK per QALY and was dominant over conservative management in the course of a lifetime. Up to three years of delay in the provision of surgery resulted in a reduction of life years, a lower QALY gain and a minor decrease in healthcare costs."

  Conclusions: "In Denmark, **bariatric surgery is cost-effective at ten years and may produce a significant reduction in healthcare costs over the course of a lifetime** in persons with severe obesity." (average BMI: 42 kg/m2)

- Borisenko et al., 2017:[360]

  Results: "*Over 10 years, bariatric surgery led to the incremental cost of €2909, generated additional 0.03 years of life and 1.2 quality-adjusted life years (QALYs). Bariatric surgery was cost-effective at 10 years with an incremental cost-effectiveness ratio of €2457 per QALY. Over a lifetime, surgery led to savings of €8522 and generated an increment of 0.7 years of life or 3.2 QALYs. The analysis also depicted an association between surgery and a reduction of obesity-related adverse events (diabetes, cardiovascular disorders). Delaying surgery for up to 3 years, resulted in a reduction of life years and QALYs gained, in addition to a moderate reduction in associated healthcare costs.*"

  Conclusions: "***Bariatric surgery is cost-effective at 10 years post-surgery and may result in a substantial reduction in the financial burden on the healthcare system over the lifetime** of the treated individuals. It is also observed that delays in the provision of surgery may lead to a significant loss of clinical benefits.*" (average BMI: 48.8 kg/m2)

- Cohen et al., 2017:[361]

  Results: "*Prompt surgery was the least costly and most effective strategy compared with any delay. Costs increased and effectiveness diminished progressively with the length of delays. Waiting 7 years for surgery was the most expensive and least effective strategy. Prompt surgery maintained dominance in 99.9%, 90.7%, 96.1%, and 94.2% of simulations in probabilistic sensitivity analyses versus 1-, 2-, 4-, and 7-year delays, respectively. Immediate surgery was very cost effective compared with no surgery in the case base. In the scenario with all patients having type 2 diabetes, immediate surgery was dominant to any strategy, including the no surgery group.*"

  Conclusions: "*Delaying bariatric operations is more expensive and less effective compared with prompt **surgery** and **very cost effective compared with no surgery**. Public health systems should pursue*

strategies to accelerate access to surgery to decrease obesity related complications and mortality of patients, but also to improve cost effectiveness." (average BMI: 48.6 kg/m2)

- James et al., 2017:[362]

  Results: "*All bariatric surgeries were effective. The incremental cost-effectiveness ratios were similar at $24,454 for AGB, $22,645 for RYGB, and $27,523 for SG, compared with UC. At a willingness to pay threshold of $70,000 per quality-adjusted life year, the probabilities of being cost-effective were 64%, 75%, and 71% for AGB, RYGB, and SG, respectively. Subgroup analysis showed that bariatric procedures are less cost-effective for older cohorts. For those with diabetes, all the procedures were dominant in comparison with UC.*"

  Conclusions: "*This model shows that **all bariatric procedures are** a **cost-effective** treatment for the management of obese patients. When given to a **subgroup with diabetes, bariatric interventions become cost-saving**.*" (BMI >35 kg/m2)

- Klebanoff et al., 2017:[363]

  Results: "*After 3 years, surgery led to a gain of 0.199 QALYs compared with no surgery at an incremental cost of $30 747, yielding an unfavorable ICER of $154 684 per QALY. When the clinical study results were extrapolated to 4 years, the ICER decreased to $114 078 per QALY and became cost-effective by 5 years with an ICER of $91 032 per QALY. Outcomes were robust in most 1-way and probabilistic sensitivity analyses.*"

  Conclusions: "*Bariatric surgery incurs substantial initial cost and morbidity. We found that **surgery could be a cost-effective treatment for adolescents** with severe obesity **if assessed over a time horizon of 5 years**. Our study underscores the need for long-term clinical trials in adolescents with at least 5 years of follow-up data that capture financial and quality-of-life end points.*" (average BMI: 53 kg/m2)

- Lucchese et al., 2017:[364]

  Results: "*In the base-case analysis, over 10 years, bariatric surgery led to cost increment of EUR 2,661 and generated additional 1.1 quality-adjusted life years (QALYs). Over a lifetime, surgery led to savings of EUR 8,649, additional 0.5 life years and 3.2 QALYs. Bariatric surgery was cost-effective at 10 years with an incremental cost-effectiveness ratio of EUR 2,412/QALY and dominant over conservative management over a lifetime.*"

  Conclusions: "*In a comprehensive decision analytic model, a current mix of surgical methods for **bariatric surgery was cost-effective at 10 years and cost-saving over the lifetime** of the Italian patient cohort considered in this analysis.*" (average BMI: 46.2 kg/m2)

- Wentworth et al., 2017:[365]

  Results: "*The incremental cost-effectiveness ratio for* [LA]*GB surgery at two years exceeded $90,000 per quality-adjusted life year gained but decreased to $52,000, $29,000 and $22,000 when the health benefits of surgery were assumed to endure for 5, 10 and 15 years respectively. The cost-effectiveness of* [LA]*GB surgery was sensitive to utility gained from weight loss and, to a lesser degree, the costs of* [LA]*GB surgery. However, the cost-effectiveness of* [LA]*GB surgery was affected minimally by improvements in HbA1c, systolic blood pressure and cholesterol.*"

  Conclusions: "[LA]*GB **surgery for overweight but not obese people with T2D appears to be cost-effective in the U.S. setting if weight loss endures for more than five years**. Health utility gained from weight loss is a critical input to cost-effectiveness estimates and therefore should be routinely measured in populations undergoing bariatric surgery.*"

- Sinha et al., 2016:[366]

  Results: "Bariatric surgery produces significant lifetime cost savings associated with diabetes, gallstones, hypertension, high cholesterol, colon cancer, heart disease, and stroke in men at BMI 30 kg/m2 for laparoscopic gastric bypass. For women, laparoscopic gastric bypass saves cost at BMI 32 kg/m2 and laparoscopic gastric banding at BMI 37 kg/m2. In white men, relative to single-year mortality risks by BMI, surgical intervention becomes risk-beneficial at BMI 25 kg/m2 for laparoscopic gastric banding, BMI 27 kg/m2 for laparoscopic gastric bypass procedure and open gastric banding, and BMI 37 kg/m2 for open gastric bypass. Risk benefit for African-American men by procedure occurs at BMI <25 kg/m2, BMI 27 kg/m2, and BMI 42 kg/m2, respectively. In white women, surgical intervention is beneficial at BMI 25.5 kg/m2 (laparoscopic gastric banding), BMI 28.5 kg/m2 (laparoscopic gastric bypass procedure), and BMI 45 kg/m2 (open gastric banding). Risk benefit for black women by procedure occurs at BMI 27.5 kg/m2, BMI 33.5 kg/m2, and BMI 50+kg/m2, respectively."

  Conclusions: "Risk and cost benefit suggest surgical guidelines should be reconsidered. **Threshold for bariatric surgery should be redefined to BMI 35 kg/m2 or BMI 30 kg/m2 with comorbidities.**"

- Tang et al., 2016:[120]

  Results: "*From our analysis results, LSG and LRYGB are both have taken a great effect on the reduction of fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and bodyweight in patients with T2DM. The costeffectiveness ratios of medical treatment, LSG, and LRYGB respectively are 1589.02, 1028.97, and 1197.44 dollars per QALY.*"

  Conclusions: "*Our analysis indicates that **LSG appear to provide a cost-effective method of T2DM treatment for the patients**.*" (average BMI: 38.4 kg/m2 (SG group) and 37.8 kg/m2 (RYGB group))

8.3.3 *Economic evaluations related to current reimbursement of bariatric surgery*

In Belgium, at present, primary (first-time) bariatric surgery can be reimbursed for patients having failed dietary intervention (dietary attempt during at least 1 year without durable effect) and:

- who are ≥18 years of age and have a BMI ≥40 kg/m² (class III or morbid obesity), or
- have a BMI ≥35 (class II or severe obesity) associated with one or more of the following comorbidities being (type 2) diabetes mellitus which needs pharmacological treatment, therapy resistant hypertension necessitating at least anti-hypertensive drugs, or having a diagnosis of obstructive sleep apnoe syndrome (OSAS),

All identified economic evaluations conclude that bariatric surgery is cost-effective for the treatment of morbid obesity or severe obesity with obesity-related comorbidities.

The intervention is accompanied by an initial extra cost for the bariatric surgery. But the decline in diabetes (reduced onset of new diabetes as well as remission of existing diabetes), a modelled improvement in mortality, and primarily a QoL improvement, ensure that the initial expenditure can be seen as an efficient use of resources. These results were found unanimously in all identified economic evaluations, both those published as part of a full HTA report, as well as the primary economic evaluations published as a journal article.

In the above tables only the base-case results are mentioned. These indicate that the best results are obtained for higher BMI, in the presence of obesity-related comorbidities and when applying a longer time horizon. We note that several studies even indicate that bariatric surgery is a dominant intervention (better and cheaper) compared to standard care.[334, 346-348, 353, 364] This is most pronounced in case of a population with diabetes.[308, 361, 362]

These results were also generally robust in the sensitivity analyses performed in many of the identified studies. Due to the large amount of data, results of all individual sensitivity analyses are not shown. But results remained positive for both male/female and older/younger patients. All studies indicated that the intervention could be considered cost-effective in these reimbursed indications if a sufficiently long time horizon is applied. In addition to the time horizon, the results were most sensitive to changes in the QoL assumptions.

The amount of QALYs gained varied widely between studies going on average from about one or less QALYs gained (0.5,[306] 0.58,[318] 0.86,[324] 0.92,[349] 0.93 (for LAGB),[355] and 1.03[334]), to about two QALYs gained (1.9,[323], 1.9 (for RYGB),[355] and 2.14[305]), up to more than three QALYs gained (3.2,[360, 364] 4.1,[346] 4.4,[358] 5.0,[356] more than 5.5,[357] and 5.63[347]). We remark that in the latter group five out of the seven references are linked to the research of Borisenko.

Lee et al.[348] and McEwen et al.[329] also point at the sensitivity of results to changes in the likelihood of long-term complications.

8.3.4 *Economic evaluations related to adolescents or lowering the BMI threshold*

At present there is no reimbursement for bariatric surgery in patients below the age of 18, neither for patients with a BMI below 35 kg/m2 or patients with a BMI <40 kg/m2 without obesity-related comorbidities.

Several economic evaluations have tried to calculate the cost-effectiveness of bariatric surgery in these patients. We summarize the main conclusions below.

8.3.4.1 *Adolescents*

Four economic evaluations calculating the cost-effectiveness of bariatric surgery in adolescents were identified. The following table provides an overview of the main sources of supporting evidence used in these economic evaluations for both the general treatment effect and impact on QoL. In these four economic evaluations, none of the studies was based on RCT-based evidence. Three studies used relatively small cohorts of adolescents (11, 18 or 28 patients) receiving MBS. One study relied on data from a prospective observational study including data from 228 adolescents. For QoL, none of the studies relied on RCT data and an indirect link to utility or DALY gains was modelled (see Table 48). The four economic evaluations are briefly discussed hereafter.

Table 48 – Economic evaluations in adolescents – main source of evidence for treatment effect & QoL

Study	Treatment effect	Quality of life
Ananthapavan et al.[351]	Case series of 28 adolescents receiving LAGB. On average 18 years (range 15-19) and BMI ≥35.	BMI to DALY model[370]
Bairdain et al.,[345]	11 adolescents receiving RYGB. Median age of 17 years. Median BMI of 48.7 (SD 6.6).	Estimation that a unit of BMI was associated with a difference in HRQL of 0.0042. The Medical Expenditures Panel Survey (MEPS) was used to estimate the association between BMI and HRQoL derived from questions from the EQ-5D survey.
Klebanoff et al.[363]	Prospective observational study with data from 228 adolescents (Teen-LABS study). Patients received either RYGB (70.6%) or SG (29.4%). Mean age of 17 years and mean BMI of 53 (range 34-88).	0.0056 QALYs per BMI unit, referring to a study with an adult population of Hoerger et al.[328] and Dennett et al.[371] QoL decrements for the initial surgery, minor and major complications referring to a study of Campbell et al.[321]
Panca et al., 2018[357]	18 adolescents receiving RYGB (n=9) or SG (n=9). Mean age: RYGB: 17.8 years; SG: 18.7 years. Mean BMI: RYGB: 48.3 (SD 6.2); SG: 60.0 (SD 9.3).	A utility gain for 1 unit BMI reduction of 0.017, referring to a study of Hakim et al.[372] Disutilities related to age, diabetes, CHD, stroke and colon cancer.

BMI: body mass index; CHD: coronary heart disease; DALY: disability-adjusted life year; HRQoL: health-related quality of life; LAGB: laparoscopic adjustable gastric banding; RYGB: Roux-en-Y gastric bypass; SD: standard deviation; SG: sleeve gastrectomy.

Ananthapavan et al.[351]

The study of Ananthapavan et al.[351] used evidence of the effectiveness and costs from a case series of 28 adolescents (2 boys and 26 girls) who had undergone gastric banding in Melbourne from 1996 to May 2005 and extrapolated the data to the eligible Australian adolescent population. The 28 adolescents were on average 18 years (range 15-19) and had a BMI ≥35 kg/m2. The average baseline BMI was not mentioned in the study. The mean change in BMI at 3 years was 13.93 kg/m2. It was assumed that change in BMI at 3 years was maintained at 4 years and into the future. The authors argue this was a conservative assumption since greater losses were experienced by the small number of adolescents in their database who had more than 3 years of follow-up (unpublished data).[351] The ICER was calculated as the cost per disability-adjusted life year (DALY) saved, which were determined by the change in BMI at 3 years after surgery. These DALYs were modelled for the rest of life or 100 years. Based on a model translating BMI to DALYs,[370] the authors mention that on average 2.98 and 2.54 DALYs are saved per child for boys and girls, respectively. DALYs take into account both the mortality and the morbidity burden.[351] Unfortunately, in contrast with QALYs, DALYs do not take into account the impact of possible adverse events or complications caused by the intervention. The authors conclude that under their assumptions, bariatric surgery is a cost-effective intervention. However, due to the lack of robust underlying evidence, these calculations are rather hypothetical and should be interpreted with caution.

Bairdain et al.,[345]

In the study of Bairdain et al.,[345] data from 11 patients were analysed (January 2010 to December 2013). Also in this study, the majority of adolescents were women (90%). The median age at surgery was 17.3 years (range 14-20). Median preoperative BMI was 48.7 kg/m2. One year after the patients received RYGB, their BMI reduced to 35.4 (reduction of 13.2, p<0.01). The authors assumed post-surgical weight regain of 5% per year in the first five years, which remained at 25% after year five. In the 'no surgery' cohort, the authors assumed that BMI remained unchanged over time. A model was set up to calculate differences in costs and QALYs between patients who underwent bariatric surgery and those without bariatric surgery. These changes in costs and QALYs were calculated by making a link between BMI and HRQoL, life expectancy and costs. The US Medical Expenditures Panel Survey (MEPS) was used to estimate the association between reductions in BMI and future savings (from reduced medical care use) and increased HRQoL. The annual savings per unit of BMI were estimated at -$157 (SD=47) and a unit change in BMI was associated with a change in HRQoL of 0.0042 (SD=0.0011). Data from the Centers for Disease Control and Prevention were used to make a link between BMI and life expectancy.[345] In the short term, ICERs were very high (i.e. >$115 000/QALY within the first three years). However, extending the time horizon to more than 6 years decreased the ICERs to less than $50 000/QALY. The authors concluded that their results suggest that bariatric surgery among adolescents may be cost-effective when evaluated over a long period of time. However, they also stress that future studies on a large scale are needed to show a continued improvement in QALYs.[345]

Klebanoff et al.[363]

Also Klebanoff et al.[363] assessed the cost-effectiveness of bariatric surgery for adolescents with obesity. They used data from the Teen-Longitudinal Assessment of Bariatric Surgery study (Teen-LABS).[84] This study included a larger cohort of adolescents that underwent bariatric surgery and were prospectively observed. Of the 228 patients included, the mean (SD) age was 17 (1.6) years, the mean BMI was 53 (range 34-88), and 75% were female. This is thus rather a population of super obese adolescents. In the Teen-LABS study, patients received either RYGB (70.6%) or SG (29.4%).[84] The study found that total body weight decreased by 27% at 3 years after surgery.[84]

It was assumed that in the non-surgical group BMI remained constant. The authors consider this as conservative since modelling a weight gain in the comparator group would improve the cost-effectiveness of bariatric surgery.[363] The weight-loss in the surgery group was based on data from the Teen-LABS study during the first three years. Thereafter, data from the Swedish Obese Subjects study were used.[373]

That bariatric surgery is not a riskless intervention is reflected by including a 30-day mortality of 0.15% and 0.10% for RYGB and SG, respectively. Since the Teen-LABS study was too small to extract reliable estimates, this was based on data from the American College of Surgeons National Surgical Quality Improvement Program database.[145] Patients also faced risks of early major complications (ie, life-threatening complications or complications requiring reoperation in 9.3% with RYGB and 4.5% with SG) and minor complications (e.g., readmission for dehydration – in 16.8% with RYGB and 11.9% with SG). This information was also based on data from the Teen-LABS study.[157] Risks of late complications were based on data from a meta-analysis[374] and assumed to be constant for the first 4 years and halved thereafter.[363]

While the authors refer to a systematic review indicating that surgery also helped patients avoid obesity-related comorbidities (type 2 diabetes, renal damage, hypertension, and dyslipidemia),[375] the model did not include health care costs for treating obesity-related comorbidities. While this might have underestimated the positive effect of bariatric surgery, the authors justify this by referring to the Swedish Obese Subjects study, which found that surgically treated patients incurred more costs than nonsurgical patients in the first 6 years after the operation.[376]

Similar to the previous study, the QoL improvement was also modelled applying a QALY improvement per BMI unit decrease. In this study it was higher at 0.0056 QALYs per BMI unit. Furthermore, QoL decrements were applied for the initial surgery, minor and major complications.

The results of this study also show relatively high ICERs in the short term (>$114 000/QALY within the first four years). Their finding was sensitive to the uncertainty surrounding the initial cost of bariatric surgery and the probability of late complications. We remark that the cost for the initial surgery in this US study (on average $25 070 and $23 708 for RYGB and SG, respectively) was relatively high in comparison with the costs in European countries (see discussion).

According to the authors, the intervention could be a cost-effective treatment for adolescents if assessed over a longer-term time horizon (>5 years). Nevertheless, they also stress the need for long-term clinical trials in adolescents with at least 5 years of follow-up data that capture both financial and QoL end points.[363]

Panca et al., 2018[357]

Finally, the most recently published study from Panca et al.[357] included information from 18 adolescents who underwent bariatric surgery at University College London Hospitals between January 2008 and December 2013. Half of them received RYGB and the other half SG. Half of the patients were female. The mean age was 17.8 years and 18.7 years in the RYGB and SG group, respectively. BMI was ≥40 kg/m2 with an average of 48.3 kg/m2 (SD 6.2) and 60.0 kg/m2 (SD 9.3) in the RYGB and SG group, respectively.[357]

The model focused on the increased risk of developing diabetes, CHD, stroke and colon cancer. The impact on these variables and the costs for treating comorbidities was taken from a variety of published sources. The possibility of having multiple co-morbidities at the same time was not incorporated in the model. This assumption underestimated the burden associated with obesity-related co-morbidities.[357]

To model the impact on QoL, the authors refer to a study published in 2002 reporting a gain in utility of 0.0170 over a 1-year period per BMI unit decrease,[372] which is much higher than in the previously discussed studies. The initial decline in BMI due to surgery was taken from the cohort of 18 adolescents. After one year, BMI reduced with 12.28 kg/m2 (SD 2.98) in the RYGB group. The reduction was 16.16 kg/m2 (SD 9.96) for adolescents who underwent SG. An annual 'obesity drift' was included to reflect the changes in BMI over time (with an increase up to the age of 45 years). The authors assumed that BMI remained constant in the no surgery group. Furthermore, utility decrements were applied when co-morbidities occurred. This was based on a UK catalogue of EQ-5D values.[377] Based on their lifetime model, compared with no surgery, adolescents receiving RYGB or SG gained more than 5.5 QALYs.

In comparison with the previous study, the cost for the initial procedure is much lower in this UK study (on average £7100 and £7312 for RYGB and SG, respectively.). Compared with no surgery, the lifetime incremental cost per person for both RYGB and SG was about £11 000. However, no costs for possible long-term complications or revisions were included. On the other hand, the authors argue their estimate is rather conservative since it only captures direct costs while costs related to productivity losses caused by obesity and its comorbidities were not included in the analysis (see discussion).[357]

In their lifetime model, ICERs were around £2000/QALY gained for both surgery options and for both male and female adolescents (see Table 47). The authors conclude that bariatric surgery in adolescents with severe obesity is cost-effective; it is more costly than no surgery however it markedly improved quality of life.[357]

In conclusion, the four identified studies calculating the cost-effectiveness of bariatric surgery for adolescents indicate the procedure might be cost-effective. We remark that the underlying samples of patients only include (a very small sample of) adolescents with a very high initial BMI (with an average or mean >48 kg/m2). All underlying studies are non-randomized studies and authors make large assumptions about the long-term impact. Calculations are thus rather hypothetical and show the potential of the procedure. Authors also stress the need for long-term clinical trials including a measurement for the impact on QoL.

8.3.4.2 *BMI <35 kg/m2 with obesity-related comorbidities or BMI <40 kg/m2 without such comorbidities*

Several economic evaluations have also carried out an analysis for an indication that falls outside the current reimbursement conditions. In some studies[324, 332, 349, 352] patients with a BMI between 30 and 40 kg/m2 were included and there was thus a partial agreement with current reimbursement criteria for diabetic patients with a BMI >35 kg/m2. For example, the study of Pollock et al.[349] included diabetic patients with an average BMI of 37.1 kg/m2. Such studies with only a population that fall partly within the reimbursement criteria are not discussed in further detail. Those studies calculating the cost-effectiveness of bariatric surgery for one or several groups for which at least one patient population completely falls outside the current reimbursement criteria are discussed hereafter.

Table 49 provides an overview of the main sources of supporting evidence for the general treatment effect and impact on QoL. The applied methods impact the reliability researchers may have on the results and conclusions. Only two studies[307, 365] rely on RCT evidence to model the treatment effect. For the impact on QoL, only the study of Wentworth et al.[365] includes utility data derived from a generic instrument (SF-36) applied in an RCT. In the other studies, no adjumstens for QoL are included or an indirect link is modelled (see Table 49).

Table 49 – Economic evaluations in T2DM patients with BMI 30-35 - main source of evidence for treatment effect & QoL

Study	Treatment effect	Quality of life
Picot, 2009[307]	Effectiveness data have been derived from an RCT of LAGB and an intensive medical programme for patients (n=80) with a BMI of greater than 30 and less than 35.[67]	A utility gain for 1 unit BMI reduction of 0.017, referring to a study of Hakim et al.[372]
Michaud et al., 2012[350]	The study relies on the Future Elderly Model (FEM), a microsimulation model of aging and health. This model is used to forecast lifetime health and economic trajectories for individuals possessing different baseline health characteristics and treated with different health interventions.	No adjustment for QoL.
Ollendorf et al., 2015[306]	The risk of mortality is based on age and BMI. For standard care, mortality rates in US Life Tables were multiplied by BMI-specific mortality relative risks derived from the published literature (referring to Campbell et al.[321] and Flegal et al.[378]). The authors assumed that bariatric surgery was associated with a reduction in the risk of mortality (RR 0.71; 95% CI 0.54, 0.92) after more than 2 years for all bariatric surgeries versus standard care based on long-term data from the prospective, non-randomized controlled Swedish Obese Subjects study.[373]	Estimates of BMI-specific utilities were derived from a regression analysis of EQ-5D data referring to Rothberg et al. [379] (ΔEQ-5D= 0.71995 - 0.68279*EQ-5D$_{Baseline}$ - 0.00285*BMI$_{Baseline}$ - 0.00957*NoComorb + 0.0073*ΔBMI)
Sinha et al., 2016[366]	Data regarding the age-standardized rate of mortality by BMI, sex, and race for never smokers with any history of significant disease was	No adjustment for QoL

	available from the study of Calle et al. published in 1999.[380] Data from this study were used to calculate the rate difference for each category relative to the reference BMI category of 23.5 to 24.9 kg/m^2.	
Wentworth et al., 2017[365]	RCT including 48 patients.[365] Average age of 52.2 years (SD 6.7) and diabetes for a duration of 2.3 years (SD 1.9). Average BMI of 28.9 (SD 1.1).	Utility data derived from the SF-36 instrument applied in the RCT.

BMI: body mass index; LAGB: laparoscopic adjustable gastric banding; QoL: quality of life; RCT: randomized controlled trial; RR: relative risk.

Picot, 2009[307]

Picot et al.[307] made an analysis for three groups. The results show the link between baseline BMI and type 2 diabetes (T2D) comorbidity and the cost-effectiveness of bariatric surgery. In the group with BMI ≥40kg/m2, the ICERs were relatively low (between £1900/QALY and £4100/QALY for LAGB and RYGB). In the group with a BMI between 30 and 40 kg/m2 and T2D, the ICER was somewhat higher: £18 930, £4580 and £1367/QALY gained at 2, 5 and 20 years, respectively (see Table 47). Applying a 20-year time horizon, the probability of surgical management being cost-effective was 100% at a willingness-to-pay thresholds of £20 000/QALY, irrespective of assumptions regarding the pattern of early weight loss.[307] When surgery (LAGB) was limited to adults with a BMI between 30 and 35 kg/m2, the ICERs were higher at £60 754, £16 381 and £12 763/QALY gained at 2, 5 and 20 years, respectively. For this group, modelling results over a 20-year time horizon and applying a willingness-to-pay (WTP) threshold of £20 000/QALY, LAGB had a probability of being cost-effective of 64%. Increasing the WTP threshold to £30 000/QALY, this became 98%.

For the impact on QoL, this study refers to the study of Hakim and colleagues[372] estimating that a one-unit decrease in BMI as associated with a gain of 0.017 utilities over a one-year period. Picot et al. used this estimated since they judge this to be the most methodologically sound estimates derived from subjects across a wide range of obesity levels. On the other hand, they also state that the assumption of the linear relationship between the change in utility and the change in BMI may have produced biased estimates of utility gain over the range of extreme BMI values.

The results in this lower BMI category show thus the potential cost-effectiveness of bariatric surgery in this category. However, in their conclusion, the authors also state that uncertainties remain and further research is required to provide detailed data on patient QoL.

Michaud et al., 2012[350]

The economic evaluation of Michaud et al.[350] also includes calculations for extended eligibility (BMI ≥35 kg/m2 or BMI 30-35 kg/m2 with qualifying co-morbidities being heart disease, hypertension, diabetes and stroke). The cost-effectiveness of RYGB was calculated from a societal point of view. In contrast with the previous calculations, no adjustment for QoL improvements was made and outcomes were expressed in costs per life-year gained. On the other hand, the calculations tried to include non-medical economic consequences (pensions, disability insurance, taxes, and earnings). The authors state that this would account for 20% of the total social cost of these treatments. Unfortunately, little is known about the effect on e.g. wages and productivity. None of the identified studies in the medical part of this report have measured the impact on e.g. productivity. The authors included this component by using a policy module that transforms health and economic outcomes into public expenditures and revenues. For example, a 'medical expenditure calculator' predicts the expected Medicare, Medicaid and private medical expenditures, based on a given set of health, economic and demographic states and characteristics.[350] Regressions are run of total expenditures related to health outcomes, demographics and others. In brief, the inclusion of these elements is thus not based on information retrieved

from a well-designed study with inclusion of patients undergoing bariatric surgery. Therefore, results should be interpreted with caution.

In the end, the authors calculated that under current eligibility criteria, the cost-effectiveness of bariatric surgery versus no surgery was $8171/LYG. Under extended eligibility criteria this became $10,579/LYG. The authors concluded that bariatric surgery generates substantial private value for those treated, in the form of health and other economic consequences.

Ollendorf et al., 2015[306]

The US study of Ollendorf et al.[306] calculated results for both BMI≥30 & subgroups with a specific BMI range (30-34.9, 35-39.9, and ≥40) and for several bariatric surgery techniques. Applying a 10-year time horizon, the average ICERs where between $23 000 and $39 000/QALY gained for morbid obese patients. In the group of class II obese patients, average ICERs increased with more than $10 000/QALY. For class I obese patients, the average ICERs were between $43 000 and $63 000/QALY gained (see Table 47).

Also in this study, QoL estimates are not based on empirical data from RCTs. In contrast, BMI-specific utilities were derived from a regression analysis of EQ-5D data performed by Rothberg et al.[379] The factors associated with QoL were baseline EQ-5D score, baseline BMI, baseline number of comorbidities, and change in BMI. The formula of this relationship was as follows: $\Delta EQ\text{-}5D=0.71995-0.68279*EQ\text{-}5D_{Baseline}-0.00285*BMI_{Baseline}-0.00957*NoComorb+0.0073*\Delta BMI$.

The calculations suggest that all types of bariatric surgery are associated with higher healthcare costs in comparison to non-surgical management but improve QoL. They conclude that at WTP-thresholds of $50 000-$100 000/QALY bariatric surgery for the treatment of obesity may be considered cost-effective.[306]

Sinha et al., 2016[366]

The study of Sinha et al. will not be described in much detail since it does not calculate ICERs. It is a threshold analysis in which the authors try to calculate the BMI threshold at which the increased risk of obesity over normal weight equals risk associated with bariatric surgery as well as the BMI threshold at which future discounted obesity-associated morbidity costs become greater than present day real costs of bariatric surgery. Impact on QoL, is not taken into account in this analysis. Also strong assumptions are made. For example, the authors assume that benefits, whether mortality related or cost related, from bariatric surgery may be realized at lower BMI levels than has been previously assumed, also at levels of 25 kg/m2.

The authors come up with a BMI threshold for LAGB of 25kg/m2 for Caucasian men to equal the mortality risk and 30kg/m2 to equal costs. In combination, LAGB would thus become a dominant strategy above a BMI of 30 kg/m2. For other bariatric interventions, the threshold values are higher (see Table 47). The authors conclude that their outcomes for costs and mortality risks suggest that the surgical guidelines should be reconsidered. They suggest that the threshold for bariatric surgery should be redefined to BMI ≥35 kg/m2 or BMI ≥30 kg/m2 with comorbidities.[366]

Wentworth et al., 2017[365]

Wentworth et al.[365] calculated the cost-effectiveness of gastric band surgery in combination with multidisciplinary care in overweight but not obese people (BMI 25-30 kg/m2) who receive standard diabetes care. Data relied on outcomes from an RCT including 48 patients with an average age of 52.2 years (SD 6.7) and diabetes for a duration of 2.3 years (SD 1.9). The BMI was on average 28.9 kg/m2 (SD 1.1).[365]

In contrast with all previously described studies, this study revealed utility scores from QoL measures applied to the participants in the underlying RCT. ScHARR utility score conversion software from the University of Sheffield[381] was used to derive 'standard gamble' SF-6D utility scores from the SF-36 questionnaire that was administered at baseline and at 2 years. The derived health utilities at baseline were 0.72 (SD 0.14) and 0.71 (SD 0.12) for the LAGB and control groups respectively (mean difference − 0.00; 95% CI −0.08 to 0.07). After 2 years, the mean health utility increased by 0.08 (95% CI 0.01 to 0.15) to 0.80 (SD 0.13) in the intervention group but remained relatively stable at 0.72 (SD 0.14) in control group.[365] In combination with an

incremental cost of $7551 (95% CI $3292 to $11 810) the QALY gain of 0.08 (95% CI 0.01 to 0.16) results in an ICER of about $94 000/QALY for the within-trial analysis at 2 years.[365] When the benefit was assumed to last longer, the ICERs decreased to about $52 000, $29 000, and $22 000/QALY at 5, 10 and 15 years, respectively. Sensitivity analysis showed that results were most sensitive to the health utility gained from weight loss and, to a lesser extent, the up-front and maintenance costs of the gastric band.[365]

The authors remark that their findings might not apply to overweight people who have had T2D for more than five years. They refer to findings from the Swedish Obese Subjects cohort study that indicate that longer disease duration in obese people with T2D is associated with lower rates of diabetes remission and lesser protection from diabetes complications after bariatric surgery.[382] If this would be the case, ICER estimates would become less favourable. Furthermore, they also point at the choice for LAGB surgery because people with relatively minor excess weight might be less likely to accept the higher risks and irreversible nature of SG or RYGB.[365]

In the end, the authors conclude that gastric banding surgery for overweight but not obese people with T2D appears to be cost-effective in the U.S. setting if weight loss endures for more than five years. Being a critical input for cost-effectiveness estimates, the impact on health utilities should be routinely measured in populations undergoing bariatric surgery.[365]

Other studies

Other studies also performed a subgroup analysis for lower BMI levels as part of their sensitivity analysis. For example, Borisenko et al.[346] included scenario analyses for different BMI levels: 30–34 (moderate), 35–39 (severe), 40–50 (morbid), and >50 kg/m2 (super obese). Bariatric surgery was cost saving in these four cohorts for diabetic patients. For non-diabetic patients, surgery was cost saving in all cohorts except for moderately obese patients where the ICERs were very low (€459 and €51/QALY gained for moderately obese male and female patients, respectively).[346]

Borisenko and colleagues adjusted their first economic evaluation on bariatric surgery to adjust it to different national contexts. In their analysis for Belgium,[356] over a 10-year horizon, bariatric surgery was cost saving in all the eight diabetic cohorts considered (moderately, severely, morbidly, and super obese males and females). In the non-diabetic cohorts, average ICERs for these eight cohorts ranged between €652 and €6802/QALY gained.[356] Surgery was cost saving in all eight diabetic cohorts considered (moderately, severely, morbidly and super obese males and females) in their Spanish,[358] Danish,[359] German,[360] and Italian[364] study. In these studies, over a lifetime horizon, the highest ICERs were calculated for moderately obese males for which the average ICER was €3500/QALY,[358] DKK7253/QALY,[359] €1171/QALY,[360] and €155/QALY.[364]

Faria et al.[323] estimated the cost-effectiveness for gastric bypass surgery to be about €13 000/QALY gained for patients with a BMI of 30-35 kg/m2 and T2DM. They mentioned this finding needs further validation and if confirmed this provides an argument to extend the current guidelines and recommend bariatric surgery to patients with T2DM and a BMI of 30–35 kg/m2.[323]

Chang et al.[322] also calculated favourable ICERs (on average <$4300/QALY gained) for patients with a BMI between 30 and 35 kg/m2. They concluded that bariatric surgery was cost-effective for at least the mildly obese with or without obesity-related comorbidities.[322]

Hoerger et al.,[328] also analyzed the effect of surgery for a diabetic population with a BMI between 30-34 kg/m2. They assumed a similar percentage change in excess weight loss as in their main analysis, which leads to a smaller change in BMI and QoL improvement. The authors mention this approximately doubled the cost-effectiveness ratios due primarily to the lower BMI loss and consequently smaller change in QoL (results not shown).[328]

Finally, a budget impact analysis performed by the Dutch HTA institute (Zorginstituut Nederland – ZINL) estimated the costs of bariatric surgery in diabetic patients with a BMI between 30-35 kg/m2 to be €200 to €600 million. Medication savings were estimated to be €40 to €200 million per year, resulting in a payback time of about five years. Nevertheless, the authors concluded that there are still insufficient (long-term) data to qualify patients with diabetes in combination with a BMI of 30-35 kg/m2 as an autonomous indication for bariatric surgery. Therefore, it was recommended not to include this indication in the insurance package.[383]

Similarly as for the analysis on adolescents, most studies show the potential of bariatric surgery in lower BMI categories. However, the underlying evidence used in the analysis is not very strong. Only one of the above studies used input from an RCT and strong assumptions are made for the QoL impact and long-term implications. How these shortcomings are taken into account in the author's conclusions is very different. For example, based on their positive economic findings, Sinha et al.[366] suggest that the threshold for bariatric surgery should be redefined to BMI 35 kg/m2 or BMI 30 kg/m2 with comorbidities. In contrast, the Dutch analysis of ZINL also provided very positive results but the authors' conslusions are more restrictive and took into account that there is still no reliable evidence base to recommend inclusion in the reimbursement package.[383]

Key points related to current reimbursement criteria:

- **Results from the identified economic evaluations show that bariatric surgery in the current reimbursement criteria can be considered a cost-effective intervention. In people with high BMI levels and/or diabetic patients, the intervention could even be dominant (i.e. better outcomes and less costs) if outcomes are modelled over a long-term horizon.**

General key points:

- **Results are most sensitive to the modelled time horizon, QoL improvement and presence of T2DM. Some studies also point at the sensitivity of results for long-term complications. On the other hand, with exception for very short time horizons, results of performed sensitivity analyses in general do not change the conclusions of the studies.**
- **There is a lack of empirical data measuring the impact on QoL. The economic evaluations indirectly model the impact on QoL and costs through a reduction in BMI. The applied utility gain per BMI unit decrease vary widely.**
- **Including a generic utility instrument (such as EQ-5D), as recommended by the EUnetHTA guidelines, would provide information related to the impact on QoL which can be used in economic evaluations for the calculation of QALYs.**
- **It is not always clear if and how long-term adverse events complications/revisions are included in the models.**
- **The studies only include the impact on direct healthcare related costs. In almost all studies, impact on productivity, which might improve cost-effectiveness results, is not included.**

Adolescents:

- **The economic evaluations for adolescents are largely based on findings from very small non-randomized studies (three studies with 11, 18 and 28 adolescents and one larger prospective cohort study with 228 patients). None of the economic evaluations for adolescents is based on RCT data.**
- **The underlying studies include adolescents with very high initial BMI levels – morbid (≧40kg/m2) or super (≧50kg/m2) obesity – with an average or median BMI >48 kg/m2.**
- **The conclusions of the identified studies are in general positive. However, given the shortcomings of the economic evaluations, the studies are rather hypothetical and show the potential cost-effectiveness of bariatric surgery for adolescents with morbid obesity when a long-term horizon is modelled.**
- **Authors stress the need for further evidence on a larger scale for both QoL and long-term implications.**

BMI <35 kg/m2 with obesity-related comorbidities or BMI <40 kg/m2 without such comorbidities:

- **Only one of the economic evaluations for BMI <35kg/m2 relies on RCT data including 48 patients in which health utilities are also measured with a generic instrument.**

- **In most studies, linear assumptions between a decrease in BMI and an increase in QoL are made. Readers should pay caution for the potential biased effects this might induce, especially in a lower range of BMI values.**
- **The conclusions of the identified studies are in general positive. However, due to the lack of reliable evidence on the most important variables in the model (e.g. QoL), the results of the identified studies should be interpreted with caution. Nevertheless, although good evidence from large RCTs is lacking, the identified economic evaluations show the potential cost-effectivenss (or even cost-savings) for diabetic patients with a BMI <35 kg/m2 and non-diabetic patients with a BMI <40 kg/m2.**
- **Also in this indication, authors stress the need for further validation of these findings. This especially involves the need for further evidence on a larger scale about the impact of bariatric surgery on patient's QoL.**

8.4 Discussion

8.4.1 General findings

In our search for economic evaluations, we immediately noticed that a lot of literature has already been published on this topic. In our approach, we first identified primary economic evaluations from existing HTA reports and a recent systematic review. As such, primary economic evaluations that met our inclusion criteria (e.g. pre-post studies were excluded) have already been identified in 4 HTA reports and 23 journal articles. The most comprehensive review performed its literature search strategy in September 2015. For this report, it was decided to perform an update for the period 2015-2018, which was carried out in October 2018. An additional 13 primary economic evaluations were identified, bringing the total to 40 evaluations that fulfilled our selection criteria.

An overview of the general characteristics, as well as the results and conclusions of these evaluations, is presented in this chapter of the report. The presentation of results was subdivided into two parts: 1) results and conclusions concerning the current reimbursement criteria (part 8.3.3), and 2) results and conclusions relating to an extension of the reimbursement criteria to adolescents and patients with a lower BMI (part 8.3.4).

In the first group of analyses including indications falling within the current Belgian reimbursement criteria, all economic evaluations point to an average ICER that is relatively low or even cost saving (better and cheaper). The best results are achieved for populations with a higher initial BMI (as a result of the higher absolute risk reductions obtained in a population at higher baseline risk), presence of diabetes and in analyses taking into account a longer time horizon.

In the second group, the results are also positive for both adolescents and a reduction in the BMI threshold. For the reduction of the BMI threshold, most studies focus on patients with diabetes and a BMI between 30 and 35 kg/m2. A number of studies also make calculations for non-diabetic patients with a BMI <40 kg/m2. The studies on adolescents include patients with a very high BMI (if stated, the average or median BMI was higher than 48 kg/m2). However, results in these groups need more nuance. We need to

stress that there is great uncertainty about the presented calculations because of the absence of good underlying evidence. Due to the lack of robust underlying evidence, these calculations are rather hypothetical and should be interpreted with caution. Authors of a recently published economic evaluation for adolescents also "*stress the need for long-term clinical trials in adolescents with at least 5 years of follow-up data that capture both financial and QoL end points*".[363] The economic evaluations therefore illustrate the potential cost-effectiveness of bariatric surgery in these extended indications rather than being based on hard evidence.

Based on the results of the 40 identified economic evaluations, we can conclude that bariatric surgery can be viewed as an intervention with a relatively low ICER for the current reimbursement criteria and as an intervention with a potentially relatively low ICER for the treatment of diabetes patients with a BMI between 30 and 35 kg/m2 and adolescents with a very high BMI. For the latter categories, further evidence is needed to validate these results.

Since the results and conclusions of all identified economic evaluations are consistently positive and since no new large RCTs were identified, it was decided not to carry out a de novo economic evaluation. This is in line with the conclusion of NICE's guideline development group which "*felt that the review of this literature was sufficient to assess the cost-effectiveness of bariatric surgery for the management of recent onset type 2 diabetes in people with obesity, and did not think that conducting an additional economic analysis would be of benefit. Therefore this area is considered to be of low priority for original economic analysis.*"[384] They agreed that the cost-effectiveness evidence that existed was sufficient to base recommendations on.[384] We refer to this argumentation because we also judged that performing an additional economic evaluation would not add much to the already large amount of published economic evaluations.

In the following parts we will go deeper into detail in a number of elements such as the uncertainty about (the modeling of) the impact on patient's quality of life.

8.4.2 *Impact on QoL*

Improvements in QoL are thought to be a key benefit of weight loss.[306] In the ideal situation, the modelled treatment effect of MBS on QoL relies on utility values measured with a generic utility instrument in RCTs. Unfortunately, the included QoL values in the economic evaluations are not always based on such evidence. Exceptionally, values are based on information retrieved from an RCT in which QoL was measured using a generic utility instrument. This is the case, for example, in the study by Wentworth et al.[365] where SF-6D utility scores were derived from the SF-36 surveys administered at baseline and at 2 years. In most studies, the QoL impact is included by making a link between the changes in BMI and QoL. Many different correlations are made, of which here are a few examples:

- In the study of Ollendorf et al.,[306] BMI-specific utilities were derived from a regression analysis in which the following formula is applied: ΔEQ-5D=0.71995-0.68279*EQ-5D$_{Baseline}$-0.00285*BMI$_{Baseline}$ - 0.00957*NoComorb+0.0073*ΔBMI. The authors state that patients with more severe obesity (i.e., BMI ≥40) will achieve higher gains in QoL than those with less severe obesity (i.e., BMI ≥30-34.9) given patients with severe obesity are more likely to have lower QoL at baseline, more co-morbidities, and achieve more weight loss.[306] In this study, a disutility was included for undergoing bariatric surgery, subsequent surgery or complications. However, the above regression analysis was based on the estimates of BMI-specific utilities from a regression analysis of EQ-5D data from Rothberg et al.[379] In this study, the authors studied "*188 obese patients with BMI ≥32 kg/m2 with one or more comorbidities or ≥35 kg/m2. All patients had baseline and follow-up assessments of BMI and HRQL using the EuroQol (EQ-5D) and its visual analog scale (VAS) before and after 6 months of medical weight loss that employed very low calorie diets, physical activity, and intensive behavioral counseling.*"[379] This population does not include patients who received bariatric surgery. Transferring results from the impact of weight loss on QoL from a non-bariatric population to a population receiving bariatric surgery induces uncertainty.

- Picot et al.[307] and Klarenbach et al.[308] refer to the study of Hakim et al.[372] to include a utility increase for each unit of BMI decrease of 0.017 for non-diabetic patients and 0.0285 for diabetic patients. The underlying study of Hakim et al.[372] investigated the effect of changes in BMI on health state preferences. Multiple regression analysis on pooled data from a clinical study was used. However, the data used were collected in a randomised double-blind study comparing orlistat with placebo on top of a dietary modification intervention.[385] Also in this underlying study, bariatric surgery is not the intervention under consideration and outcomes might thus not be applicable to our study population.
- Cohen et al.[361] include a utility increase for each unit of BMI decrease of 0.0079 for non-diabetics and 0.0100 for diabetics. The authors mention to include the median estimate of three studies.[321, 372, 386] One study is the previously mentioned study of Hakim et al.[372] The second one of Campbell et al.[321] refers to another study[387] looking at the impact of obesity on HRQoL in the general adult US population. And the third study[386] included patients from the Health Outcomes Data Repository (HODaR) were multiple regression analysis demonstrated that both BMI and diabetes status had a significant effect on utility. Again, also in these studies, the underlying population does not reflect patients receiving bariatric surgery.
- Ackroyd et al.[334] refer to a database of 13 547 individuals provided by the HODaR Cardiff Research Consortium.[388-390] In this HODaR database, societal-perspective utility scores were calculated for each patient using their answer to the EQ-5D-3L questionnaire. A utility increase was determined for each unit of BMI decrease of 0.0128 for non-diabetics and 0.0108 for diabetics. This approach is applied in all studies of Borisenko and colleagues.[346, 356, 358-360, 364] In these studies, the impact of obesity-related comorbidities on QoL were incorporated separately and were informed by data from UK adaptations of the US Medical Expenditure Panel Survey EQ-5D mapping study.[377]
- Klebanoff et al.,[363] performing a study in adolescents, applied a QoL improvement of 0.0056 QALYs per BMI unit decrease. This number could be identified in one of the articles they refer to. However, this article of Hoerger et al.[328] was a cost-effectiveness analysis for adult patients and no supporting source was provided for the assumed mean utility improvement per unit of BMI decline.
- Gulliford et al.[305] include a decrease in utilities per BMI category (-0,085 (BMI 30-34); -0,17 (BMI 35-39); -0,255 (BMI>40)) and for age and obesity-related comorbidities (T2DM, CHD, stroke, cancer and depression). They refer to the study of Sullivan et al.[377] providing a UK-based catalogue of EQ-5D index scores. Also in this study, the utility decrements were not specificly retreived from a population receiving bariatric surgery.

Most formulas make linear assumptions and do not take into account the initial BMI (with the exception of the approaches used by Ollendorf et al.[306] and Gulliford et al.[305]) or how close patients are to their 'ideal' BMI. This criticism is also provided by other authors. For example, Picot et al. state that "*a potentially serious weakness in published utility models is an assumption of linear additivity, with respect to BMI or change in BMI, where the effect of reduction in BMI is assumed to be constant over the range of BMI values.*"[307] "*The assumption of the linear relationship between the change in utility and the change in BMI may have produced biased estimates of utility gain over the range of extreme BMI values.*"[307] "*An additional, implicit, assumption is that the utility change is independent of initial BMI or that it is independent of proximity to an 'ideal' or target BMI.*"[307] Not taking this into account might thus lead to incorrect results, especially when studying the impact of bariatric surgery in lower BMI categories.

In addition, the underlying studies show that the formulas are not retrieved from populations that received bariatric surgery. The included utility changes also vary widely across studies. For example, Cohen et al.[361] include a utility increase for each unit of BMI decrease of 0.0079 for non-diabetic patients while this is about twice as high (0.017) in the studies relying on Hakim et al.[372] For diabetic patients, this is 0.01 and 0.0285 in these studies, respectively.

The (long-term) impact on QoL of the occurrence of AEs is also not always included. As mentioned by Picot et al.,[307] the cost-effectiveness model applies utility values for reduction in BMI associated with surgical or non-surgical management of obesity, but takes no account of any utility impact of side effects or complications of interventions. Several models did include such a link (e.g. Ollendorf, Gulliford, Borisenko, etc.). However, Picot et al. also mention that "*reporting of long-term adverse effects – such as frequent vomiting or flatulence – following surgery is variable and of limited duration in included trials (up to three years post-surgery). However, where reported, the proportion of patients reporting such effects are non-trivial (28.5% frequent vomiting,[131] 13–25% emesis and 13–22% flatulence[391]). The likely duration of the side effects is not clear nor is it apparent how far the impact of these effects may offset any utility gains from reduction in BMI alone.*"[307] "*A major source of uncertainty in the economic model relates to the absence of reliable, long-term data on the effectiveness (in terms of sustained weight loss) and the need for operative revision and conversion to alternative weight-loss methods. … The relatively short duration of the majority of the RCTs available for inclusion in this review may mean that the impact of late complications (such as gastric ulcers, stomal stenosis and erosions, and band slippage) and the need for revisional surgery are underestimated.*"[307] The analysis of the Belgian data also confirms that the percentage of reinterventions should not be underestimated (see part 7.6). Good evidence about the impact on QoL of such events is however lacking.

Finally, we also note that RCT-based evidence about the impact of bariatric surgery on QoL measured with a generic instrument did not show any statistically significant improvements at 1 year (see part 4.2.3) The best longer-term results were presented in the STAMPEDE trial[13, 98] (see part 4.2.3). This is in line with the results of the systematic review of Göthberg et al.[392] which concluded that there was low quality of evidence (GRADE ⊕⊕◯◯) that bariatric surgery compared to conventional treatment in severely obese adolescents may improve health-related quality of life.

The studies may be too small and/or there is too much loss to follow-up to provide more reliable results. Of the 16 identified RCTs there were only 8 in which generic or disease-specific QoL values were identified. For future studies, it is important to include the correct instruments to measure the impact of bariatric surgery on patients' QoL. The EUnetHTA guidelines recommend to make use of a generic utility instrument (such as EQ-5D) in complement with disease-specific QoL instruments.[393]

8.4.3 *Different types of surgery*

There are several bariatric surgical procedures possible. Currently, in Belgium, the most commonly performed procedures are gastric bypass and sleeve gastrectomy (see part 7.2). Based on the results of the included economic evaluations, it is not clear whether one intervention should be preferred above the other for a specific target group. For example, the Canadian HTA report indicates "*the results of this cost-effectiveness analysis are less clear for the selection of the optimal surgical approach. All the procedures that were considered are associated with cost-effectiveness ratios that may be attractive compared with standard care. However, given the lack of data … uncertainty exists about the relative merits and costs.*"[308] Also the IHE review mentions that "*within bariatric surgical interventions, there is limited evidence to identify which type of surgery is the most cost-effective.*"[313] Determining the relative cost-effectiveness of the different bariatric procedures is thus not possible. As shown in the overview, a large part of the identified economic evaluations consider bariatric surgery as a whole, without making a difference between the chosen techniques.

Klebanoff et al. indicate it is likely that weight loss, comorbidity resolution, and complication risk differ according to the type of procedure.[363] Identified evidence might thus not be perfectly applicable when differences exist between the performed procedures in the identified evidence used in the economic models and the actual procedure performed in a specific country. For example, Borisenko et al.[394] notice that their results are for 98% based on gastric bypass surgery, being the dominating procedure in Europe, while the SOS study only included 13% gastric bypass patients.

We also prefer not to compare results of economic evaluations with different techniques. As Hoerger et al.[328] caution, more or less favourable results might be due to different characteristics of the people who opt for one or another surgical approach (e.g. differences in BMI and comorbidities). Health Institute Scotland (HIS) mentions direct trials of clinical effectiveness

are needed before the relative cost effectiveness of the procedures can be established.[312]

In the end, the patient and surgeon may influence the choice of surgery to be offered.[308] There is the prerequisite that patients are well-informed about all treatment alternatives. Nevertheless, "*patients may prefer one type of surgery versus another based on the characteristics of the surgery, the perceived or actual risk of short-term complications, and the anticipated degree of weight loss. Similarly, individual surgeons may prefer different procedures based on experience.*"[308] These individual considerations are of course not included in the identified economic evaluations which refer to the cost-effectiveness of an intervention for a specific indication/population and don't include individual preferences.

8.4.4 Modelling long-term outcomes

The results of the economic models are sensitive to the modelled time horizon with better outcomes for bariatric surgery when a longer time horizon is considered. The initial bariatric surgery involves an initial increase in expenditures and a short-term decrease in Qol due to the procedure and hospitalisation while benefits accrue over time. Modelling is necessary to include long-term advantages. The follow-up period of the underlying evidence is often much shorter than the applied time horizon in the economic evaluations. For example, Gulliford et al.[305] remark that the treatment effect of bariatric surgery is derived from a randomised trial with generally short follow-up and non-randomised studies of longer duration. The use of non-randomised studies was necessary because there have not been sufficient clinical trials that evaluated substantive clinical outcomes over more than a few years of follow-up.[305] Also Ollendorf et al. note that data on the long-term patterns of comorbidity remission and relapse are scarce. In their longer-term model, they use BMI changes as a proxy for measurement of comorbidity and QoL.[306]They also assumed that bariatric surgery was associated with a reduction in the risk of mortality (RR 0.71; 95% CI 0.54, 0.92) after two years when comparing with standard care. This was based on data from the Swedish Obese Subjects study.[92] Given the controversy over this topic, they also conducted alternative analyses assuming no mortality benefit.[306] In their analysis, varying the all-cause mortality risk associated with bariatric surgery from a hazard ratio of 0.50 (versus 0.71 in the base-case) to 1.0 (no mortality benefit) changed the ICER only slightly to $36 651 and $39 756 per QALY, respectively.[306] Another example is the analysis of Picot et al. including a maximum time horizon of 20 years to allow for some extrapolation of trends in weight loss beyond the end of trial follow-up. They argue that this time horizon represents a trade-off between allowing the benefits of continued weight reduction (compared with baseline) to accrue and the limited long-term follow-up data, including the absence of reliable data on long-term reoperation rates and conversions.[307]

In an editorial, Doble expresses his concern that the models identified relied on clinical data from only 3 to 5 years of follow-up, despite the average time horizon of the models being 50 years.[395] This is indeed true for the longest time horizons, but promising results were already modelled when applying a time horizon ranging from 5 to 10 years. Furthermore, not extrapolating to a longer time horizon would underestimate the potential of the initial procedure or ignore the impact of long-term adverse events. Of course, as mentioned by Doble,[395] the need to extrapolate, perform sensitivity analyses and model validation, use appropriate sources of health state utility values, consider patient heterogeneity, etc. are common methodological elements that should be considered in any economic evaluation of a healthcare intervention.[396, 397]

Furthermore, Picot et al. also note the uncertainty over the applicability of applied evidence in the models to the current clinical practice and surgical technology.[307] There is for example the evoluation from open surgery to laparoscopic procedures,[394] and in Belgium, the use of banding has clearly decreased while the use of both RYGB and SG have become more popular. "*Empirical economic data, although being the source of information of the greatest validity, are always available with delay, usually have limited follow-up and often do not correspond to the current treatment practice.*"[394] However, "*decision analytic modelling has an inevitable complementary role to inform clinical and policy decision-making, acknowledging its simplification over reality. Omitting data generated by comprehensive modelling would lead to underestimation of true economic value of modern bariatric surgery.*"[394]

Nevertheless, we should take into account the shortcomings of these models such as a lack of long-term evidence to validate the modelled outcomes. As mentioned by Borisenko et al.,[394] it is acknowledged that there would always be not enough validation attempts, as clinical data evolve over time. However, they also agree that additional specific validation exercises would be of benefit.[394] Special attention could go to the impact on QoL and AEs, including long-term reoperation rates/conversions. Such (long-term) evidence about established procedures and evidence related to newly performed techniques should be gathered to be able to provide correct information to patients, physicians and other involved stakeholders. Using medical records might also help to overcome extrapolation issues without long-term trial follow-up data.[398]

8.4.5 Direct healthcare related costs

8.4.5.1 Costs of surgery

Cost-effectiveness results were also sensitive to the included costs of bariatric surgery. For example, in their base case analysis, Ollendorf et al.[306] assumed that RYGB costs $24 277. Varying this cost by 50 to 200% changed the ICER from $10 009 to $72 968 per QALY, respectively.[306] Large differences in costs for the initial bariatric surgery are noticed between studies. One Belgian study included an APR-DRG-based costs of €4433 and €14 577 for bariatric surgery (LAGB, SG or RYGB) without and with complications, respectively.[356]

Especially the US studies, surgery costs are higher. The lowest cost for bariatric surgery in a US study was an average cost for laparoscopic RYGB surgery of $10 393 (n=73).[329] In the other US studies, the costs for RYGB were somewhat higher: $25 854,[345] $16 691 or $20 675 for laparoscopic and open RYGB,[325] $27 560,[333] $27 767,[355] or $25 070.[363]. For LAGB, the US costs were somewhat lower: on average $14 159,[325] $15 169,[328] $16 200,[333] $18 544,[355] or $20 830.[366] For SG, US costs were on average $24 179[355] and $23 708.[363]

In contrast, all European studies included a cost of less than €10 000 for bariatric surgery without complications: €4915 (bariatric surgery),[346] £7100 (RYGB) and £7312 (SG),[357] €6572 (SG) and €7025 (RYGB),[358] €5621 (LAGB) and €8104 (SG & RYGB),[360] or €5681 (bariatric surgery).[364]

The generalizability of the results of the identified economic evaluations to our Belgian context may be limited due to these differences in context-specific costs. On the other hand, the Belgian costs for bariatric surgery (see part 7.1.3) are in the range of costs found in the other European analyses and lower than the costs applied in the US studies. Including Belgian cost estimates in these studies would thus not worsen ICER outcomes. The results of these studies are thus informative for the Belgian situation.

8.4.5.2 Other costs

A limitation of existing economic evaluations is that it is not always clear whether all relevant cost items have been taken into account, such as preoperative costs and costs for re-do surgery, body-contouring procedures, etc.. Omission of including such costs might have an influence on the cost-effectiveness of bariatric surgery.

There are preoperative costs from testing and referrals to specialists (e.g. psychologist and dietitian). For example, Picot et al. explicitly includes such costs and mentions that "*for every patient undergoing surgery, four patients are screened for eligibility and two undergo workup (by VLCD* [very-low-calorie diet]*) to assess suitability for treatment, based on figures reported in Andersen and colleagues.[399] This corresponded to seven outpatient visits, four dietitian consultations and one session with a psychologist.*"[307] In contrast, the analysis of the IHE does not include services that may have been provided prior to admission and after discharge from hospital (e.g., pre-surgical counselling and post-surgical support following discharge). The authors mention their analysis underestimates the costs of bariatric surgery.[313]

The systematic review of Campbell et al.,[304] identified that costs due to reoperations/complications were not included in one-third of studies. Body-contouring surgery was included in only 14%. Including postsurgical costs related to short-and longer term complications and cosmetic costs would decrease the intervention's cost-effectiveness. For example, the non-negligible percentage of reoperations (see part 7.6) have a negative impact

on the ICER by decreasing QoL in the period shortly after the reoperation and increasing incremental costs. Vice versa, including long-term costs related to a higher BMI would improve the cost-effectiveness of bariatric surgery.

A recently published editorial indicates that more recently conducted evaluations seem to be including some of these costs, referring to three decision models published in 2017 which have accounted for long-term surgical-related complications.[359, 362, 363] However, this editorial also underlines that "*what is not clear, is what specific complications have been considered, what sources of evidence have been used to populate the models, and how appropriate is the evidence for the populations being modeled.*"[395] Indeed, long-term information retrieved from existing databases might be based on very different procedures (e.g. banding is nowadays used to a lesser extend than before) and might thus not reflect the complications and AEs of currently used bariatric procedures. Nevertheless, the impact on both costs and benefits of potential long-term complications should not be ignored.

Finally, we would like to remark that also in this case, assuming a linear relationship between BMI and costs might be wrong. McCombie et al.[400] refer to results of the UK counterweight project[401] where researchers aim to quantify the influence of BMI on prescribing costs. The following figures show that an increasing cost is observed for each unit of increase in BMI. At a BMI of 40 kg/m2 drug prescription costs are about four times more than at a BMI of about 20 kg/m2 in men, and three times more in women.[401] This figure also suggests to pay caution if a linear relationship is assumed between BMI changes and drug costs, especially below a BMI of 30 kg/m2. McCombie et al.[400] also remark that "*there may have been permanent damage as a result of a period of obesity, the costs of which cannot entirely be reversed. Preventing weight gain in the first place is more likely to avoid the extra attributable costs.*" Using e.g. actual costs based on BMI after MBS avoids making strong assumptions about the relationship between BMI and costs which might not apply to lower BMI categories.

Figure 45 – Relationship between BMI and annual drug prescribing costs

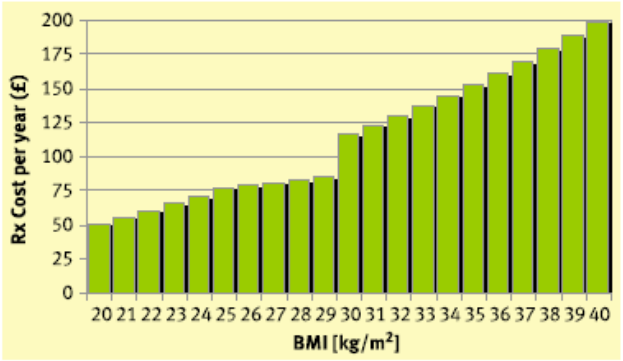


Figure 2 Increase in total annual drug prescribing costs by one-unit increments of BMI among men whose weight had been measured in primary care.[4]

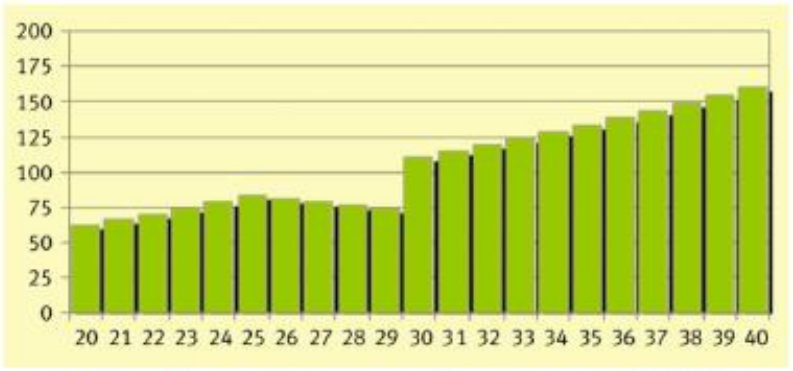


Figure 3 Total annual prescribing costs by one-unit increments in BMI among women whose weight had been measured in primary care.[4]

Source: McCombie et al.[400]

8.4.6 Impact on productivity

Indirect costs are also often omitted from the economic evaluations. The review of Campbell et al. identified that "*out-of-pocket costs to individuals, family members (travel time, caregiving) and indirect costs due to lost productivity were largely ignored.*"[304] Indeed, our review also shows that most studies are performed from a health care payer's perspective. In a wider societal perspective, impact on e.g. productivity would also be taken into account.

Next to the direct healthcare-related costs, Campbell et al.[304] also refers to the impact on productivity, family and relationships and stigmatization and discrimination of obese people. We performed a non-systematic search for literature investigating the impact of bariatric surgery on productivity and identified two recently published systematic reviews on this topic:

- Vayr F, Charras L, Savall F, Soulat J, Ritz P, Herin F. The Impact of Bariatric Surgery on Employment: A Systematic Review. Bariatric Surgical Practice and Patient Care. 2018;13(2):54-63.402
- Sharples AJ, Cheruvu CV. Systematic Review and Meta-Analysis of Occupational Outcomes after Bariatric Surgery. Obes Surg. 2017 Mar;27(3):774-81.[403]

In the introduction of these reviews, several studies are quoted providing support for the association between body weight and aspects related to productivity. Vayr et al. includes the following: "*A Canadian study revealed that obesity is associated with reduced workforce participation, regardless of associated comorbidities and sociodemographic factors.[404] Employment rate was higher in the normal weight group (80%) and was reduced depending on the class of obesity (79% in class I obesity, 75% in class II, and 66% in class III). A U.S. study reported that baseline obesity was associated with reduced employment throughout a 19-year follow-up (88% vs. 78% among men and 76% vs. 63% among women).[405] French authors described a significant difference between unemployment rate of nonobese and obese adults (9% vs. 11%, p <0.01).[406] Moreover, time spent unemployed for the adult working-age population was significantly higher for each kg/m2 deviation from the average body mass index (BMI) achieved at age 20.[406] … A Swedish study reported that BMI status was associated with the probability of being entitled to a disability pension.[407] … Employment rate of obese persons seems to be even lower for patients seeking bariatric surgery: 55–56% versus 85% in nonobese controls in U.S., Norwegian, and Spanish studies.[408-411]*"[402]

Sharples et al. confirm "*there is a clear link between obesity and unemployment. Multiple studies from different countries have demonstrated that unemployment and obesity are linked, although the direction of causality is not always obvious.[404, 406, 412-415]*"[403] Furthermore, they also stress the association between productivity and QoL. "*Obesity has been linked with reduced productivity in the workplace and is associated with higher levels of disability and absenteeism.[416, 417] … Studies have demonstrated that unemployment is negatively associated with quality of life, depression and generally poor health outcomes.[418-420] Obesity too is associated with many of the same issues, and when the two are combined, each is likely to exacerbate the other.[421-423] Indeed, the association between the two is likely to work in both directions; obesity does limit employment opportunities;[404, 412] however, unemployment itself seems to worsen obesity presumably, in part, due to worsening of depression and lack of motivation.[424, 425] Patients therefore enter a deteriorating cycle leading to deleterious physical and psychological consequences. Bariatric surgery is uniquely placed to tackle both of these issues with potentially great health and social benefits.*"[403]

Of course, productivity is related to more factors than body weight. For example, Caixa et al.[410] mention that obese individuals had less education than nonobese controls (43% vs. 72% with high school degree, respectively), limiting the access to employment. Only looking at associations between body weight and productivity does not provide a good estimate of the impact of bariatric surgery.

In what follows, we present the results of the two systematic reviews related to the impact on employment, absenteeism and presenteeism. We first present the results of the most recent review published by Vayr et al.[402] and complement this with the findings from the meta-analyses performed by Sharples et al.[403]

Vayr et al. performed a systematic literature search in PubMed and Web of Science and included studies published between January 2000 and April 2017. Eighteen relevant articles were identified. Four studies compared

occupational status between surgical patients and a control group.[426-429] The other 14 studies compared occupational status before and after bariatric surgery in the same population.[430-443] Half of the studies were performed in Europe and the other half in North America (US and Canada).[402] The literature search in the review of Sharples was performed using Medline, Embase, The Cochrane Library and NHS Evidence up to November 2015 and identified ten studies.

Employment status: most studies provide neutral or positive findings

- "A majority of authors report no major changes in prevalence of employment before and after bariatric surgery.[430, 431, 436, 441, 443] However, there were changes in employment status of patients: change in employment (starting a new job, increasing of working hours),[441] switching from unemployment to employment, or vice versa.[431]
- A few publications described nonetheless an improvement in employment rate with an increase from 12% to 32% in performing paid work after surgery.[434, 435, 440]
- Findings concerning unemployment rate after surgery vary according to studies: authors report an increase,[430] a decrease,[436] or no change[439] in the proportion of unemployment after surgery."[402]
- This is in line with the meta-analysis performed by Sharples et al.: "Five studies [431, 436, 439, 440, 442] looked at an unselected group of patients with a preoperative employment rate ranging from 34.1 to 64.4 %. Only one of these studies demonstrated a statistically significant increase in employment in the postoperative period.[440] Meta-analysis of these five studies does not suggest a significant improve in overall employment rates after surgery (RR 1.058, 95 % CI 0.979–1.144, p = 0.155, Q = 4.933, I2 = 18.9%) …"[403]
- "Two studies[428, 429] included only unemployed patients, and three further studies [431, 436, 442] performed a subset analysis on patients unemployed preoperatively. Pooled analysis of these studies demonstrates that 26.4% (95 % CI 21.6–31.5 %, Q = 5.429, I2 = 26.3%) of unemployed patients are able to return to work after bariatric surgery."[403]
- "Two studies[428, 429] sought to compare unemployed, obese patients undergoing bariatric surgery with unemployed, obese, non-surgical patients. Both studies demonstrated a greater chance of returning to work amongst those undergoing surgery. Pooling of this data suggests that those undergoing surgery are 3.24 (95 % CI 1.29–8.12, p = 0.012, Q = 0.492, I2 = 0.0 %) times more likely to return to work than nonsurgical controls."[403]

We remark that interpretation of results of these studies should be performed with caution. Both before-after studies as well as studies comparing outcomes between two different/matched populations are prone to bias. For example, only looking at unemployed patients does not take into account what might happen with employed patients. Comparing with non-surgical patients might be looking at completely different populations. Indeed, Sharples et al. remark that these studies were small and "*in one study[428] the groups were not comparable, the surgical group being less obese and more likely to be female. Nonetheless, the results are encouraging.*"[403]

Disability pension: mixed findings

- "The proportion of disability pension seems to remain steady,[430, 431, 438] or to be slightly reduced.[426]
- … In Norway, Andersen et al. found no significant change in the proportion of patients receiving disability pension in a 5-year prospective follow-up.[431] In Sweden, Gripeteg et al. suggest a reduced risk of needing a disability pension after bariatric surgery.[426]"[402]
- The review of Sharples et al. identified one study looking at the proportion of patients receiving disability benefits. This study "*showed a significant reduction* from *32.2 % of patients claiming benefits preoperatively to only 10.2 % claiming them after surgery.[440]*"[403]

Absenteeism: positive findings

- "Five studies out of 18 described the management of sick leave before and after surgery. The five studies report a significant decrease in absenteeism rate after bariatric surgery.[427, 430-432, 437"402] For example, in one study, "the rate of absenteeism among obese patients preoperatively was 3.5-fold higher throughout the study period compared with a Swedish reference population.[427] … In another study, authors conclude that obese workers are less productive due to fewer days at work. Whereas workers have on average 250–3 = 247 productive days per year in a reference population, obese workers have 250–33 = 217 productive days.[437"402]
- "Three studies[431, 432, 437] analysed the mean number of annual sick days taken by patients preoperatively and postoperatively. Each of these studies demonstrated a large decrease in mean sick days: from 56 to 28 days (p = 0.02),[431] from 33 to 1 day (no p value presented)[437] and from 12.5 to 6.3 days (p <0.05).[432] One of these studies also showed that the percentage of patients taking no sick days within a year rose from 25 to 41%.[431"403]

Presenteeism: only one study was identified studying this outcome

- "Prevalence of presenteeism was decreased after treatment, and at all postsurgery times.[430"402]

In summary the following results and conclusions were drawn by the most recent review by Vayr et al.:[402]

- Results: "… Publications found no major changes or an improvement in prevalence of employment after bariatric surgery, but an important decrease of sick leaves. Conversely, the proportion of disability pensions seems to remain steady or to be only slightly reduced. … "

  Conclusions: "Bariatric surgery seems to have a positive impact on occupational outcomes, despite some inconsistencies in findings."

This is in agreement with the findings of Sharples et al. who mention the reduction in sick days is relatively large in the studies which reported it and suggest that bariatric surgery has the potential to improve productivity due to the overall improvement in the health of these workers.[403] They conclude that "*there is limited evidence in the literature regarding occupational outcomes following bariatric surgery, and further studies are required before firm conclusions can be drawn. However, the existing evidence does suggest that bariatric surgery has a generally positive impact on occupational outcomes. This suggests that surgery may have wider economic, social and psychological benefits above and beyond its immediate health benefits.*"[403]

Key points

- **Most economic evaluations are performed from a health care payer's perspective. Productivity costs (unemployment, absenteeism, presenteeism) caused by obesity and its comorbidities are not included in this perspective.**
- **Based on the studies included in their review, Campbell et al. conclude there is a paucity of identified out-of-pocket costs, costs to family members and other sectors (such as work force participation/productivity, absenteeism and presenteeism) related to bariatric surgery.[304]**
- **Two recent systematic literature reviews studying the impact on productivity were identified. In most identified studies and a meta-analyses of five studies, no major changes in prevalence of employment after bariatric surgery are identified. However, while the majority of authors report no major changes in prevalence of employment, few publications described nonetheless an improvement in employment rate. Further studies are required before firm conclusions can be drawn. Furthermore, based on non-randomized studies, an important decrease of sick leaves is noticed.**

8.4.7 Silo thinking

The budgetary silo mentality refers to a focus of decision-makers on their own budget without taking sufficient account of the impact on another budget. In the case of bariatric surgery there is a risk that the reimbursement of this intervention will be charged to a certain budget while the potential benefits are for a different budget (drug use, productivity, etc.). We would like to briefly point out that we recommend looking first at what is beneficial for the intended target population and what is efficient for society and taking into account the global impact of reimbursing bariatric surgery.

8.4.8 Non-surgical alternatives and prevention

In the identified economic evaluations, the comparator was often described in very general terms such as 'no bariatric surgery' or 'standard care', without providing further details what this entails. However, we must not forget that patients already failed non-surgical approaches for weight loss. As noted by Picot et al., for patients with morbid obesity "*the non-surgical comparator consists primarily of monitoring rather than active treatment, because NICE guidance[444] specifies that patients offered bariatric surgery should have failed to achieve (or maintain) an adequate and clinically beneficial weight loss for at least six months on all appropriate non-surgical alternatives.*"[307] Nevertheless, although the scope of this report is on bariatric surgery, we do not want to ignore or diminish the importance of non-surgical alternatives and prevention.

Non-surgical alternatives

An evaluation of these so called "appropriate non-surgical alternatives" is out of scope of our research. The Canadian report by the Institute of Health Economics indicates that "*compared to no intervention, weight management programs or lifestyle modification were found to be cost-effective because the associated costs per additional health gains were considered good value for money. Importantly, however, there can be significant variation in the specific characteristics included in either lifestyle modification or weight management programs; this limits the generalizability of this finding.*"[313] The disadvantage is that when these non-surgical alternatives have no positive impact, they postpone the procedure and the related positive effects. In fact, Borisenko et al. criticize that "*England has insisted on mandatory preoperative weight loss programs for which no supporting evidence exists.*"[445] However, on an individual patient level, the advantage of such a preoperative weight loss program is that when succesful, the negative consequences of bariatric surgery are omitted.

In their study on adolescents, Bairdain et al. state that "*while we recognize that surgery plays an overall important long-term role, we do not negate the importance and value of continued attention to reduction of high-fat and high-sugar foods, as well as increasing physical activity. All of these factors play an integral role in long-term, successful weight loss, especially when it relates to adolescents' longevity.*"[345] In contrast, the study of Klebanoff et al. indicates that "*behavioral intervention is the first-line treatment for adolescents with severe obesity, but this type of intervention rarely leads to meaningful long-term weight loss in this population.[446] One recent study[447] indicated that behavioural treatment had no effect whatsoever on adolescents with severe obesity when assessed 1, 2, and 3 years after the intervention. While other studies have found that behavioural therapy results in less than 3% total body weight loss in adolescents with obesity,[448, 449] this small effect usually does not translate into meaningful change for individuals with very high baseline BMIs.*"[363] Being out of scope of this report and given the different opinions, it might be interesting to further investigate (the effectiveness of) the pre-operative weight-loss programs.

Prevention

An analysis of measures to prevent obesity is also out of scope. The population in our PICO exists of patients which already have overweight. However, when searching for relevant economic evaluations, we were confronted with a US publication comparing seven health care interventions on the obesity policy agenda: a sugar-sweetened beverage excise tax; elimination of the tax subsidy for advertising unhealthy food to children; restaurant menu calorie labeling; nutrition standards for school meals; nutrition standards for all other food and beverages sold in schools; improved early care and education; and increased access to adolescent bariatric surgery.[450] In their model "*three of the seven interventions—excise tax, elimination of the tax deduction, and nutrition standards for food and beverages sold in schools outside of meals—saved more in health care costs than they cost to implement. Each of the three interventions prevented 129,000–576,000 cases of childhood obesity in 2025. Adolescent bariatric*

surgery had a negligible impact on obesity prevalence. Our results highlight the importance of primary prevention for policy makers aiming to reduce childhood obesity."[450] On the other hand, Klebanoff et al. mention that "*experts in childhood and adolescent obesity focus primarily on public health interventions, such as taxes on sugar-sweetened beverages, calorie labeling on restaurant menus, and nutrition standards for food in schools. From an individual-patient perspective, though, bariatric surgery can result in life-altering weight loss, which not only leads to the resolution and prevention of disease but also allows patients to avoid the stigma, bullying, and isolation that often accompany severe obesity.[451]*"[363]

Focussing on bariatric surgery alone will not solve the problem of the increasing prevalence of obesity. As mentioned by Gulliford et al., "*as a 'downstream' procedure, bariatric surgery will not stem the global increase in obesity.*"[305] …"*the greatest opportunity for tackling the current obesity epidemic may be found outside primary care. Research to develop wider-reaching public health policies is needed to prevent obesity at the population level.*"[305] On the other hand, these authors also state that "*persistently high obesity rates and evidence from the literature[452] suggest that preventative and reactive treatment strategies are currently of limited use.*"[305] The authors state that "*development of more effective obesity prevention strategies is urgently required.*"[305] Although our study is focussing on obese patients, the potential role and importance of prevention should indeed not be forgotten and could be the subject of further research.

8.4.9 Out of scope elements

There are many other interesting research questions that we could ask ourselves in the context of bariatric surgery. Both the period before the bariatric procedure, the period after the procedure, and the comparators could be further examined in more detail. However, given the large amount of literature, it was decided to limit the scope to an evaluation of the bariatric procedure. As a result, we have not included studies that compare the different non-surgical options (no treatment/usual care, pharmacotherapy, lifestyle modification, weight management program, low-calorie diets, etc.) or preventive measures. Accelerating access to or delaying bariatric surgery was also beyond the remit of our research. Similarly as in the HTA report of Picot et al,[307] the impact of preintervention and postintervention education, counselling and support on the outcomes of the interventions were also considered out of scope. Some of these elements will be part of a Health Services Research (HSR) report KCE is currently working on.

9 OVERALL CONCLUSIONS AND RECOMMENDATIONS

We refer to the synthesis of this report for an overview of the findings, overall conclusions and policy recommendations.

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APPENDICES

APPENDIX 1. SEARCH STRATEGY FOR CLINICAL EFFECTIVENESS

Appendix 1.1. PICO

Keywords and search concepts were collected through experts' opinion and existing recent surveys and consultation of controlled vocabularies (Medical Subject headings = MeSH; Excerpta Medica = Emtree).

We excluded studies that made comparisons of open versus laparoscopic surgery, or in which the Scopinaro intervention or duodenal switch was the comparator. Comparisons of variations in similar surgical techniques were also excluded, except for the mini gastric bypass, a.k.a. one-anastomosis gastric bypass, a procedure that was explicitly asked by our external reviewers for consideration in the present report. Endoscopic techniques were considered out of scope since a preliminary evaluation learned that these techniques are not yet mature, with no RCTs being published so far.

Project number	**2017-05_HTA**
Project name	Bariatric surgery
Research question	What is the clinical effectiveness of bariatric surgery?
Structured search question(s) (PICO, SPICE, ECLIPSE...)	
P (patient)	patients with overweight or obesity
I (Intervention)	Any of the following bariatric surgery techniques: LAGB, RYGB, Sleeve gastrectomy. (NOT: scopinaro, not endoscopic)
C (comparison)	Diet. LAGB. RYGB. sleeve gastrectomy. (not scopinaro, not endoscopic, not comparisons of variations of the same basic technique)
O (outcome)	weight related parameters, T2DM remission parameters, hypertension, OSAS, Mortality, QoL, other hard endpoints such as infarction, stroke … Adverse events: separate search in separate chapter

S (study type)	**RCTs or SRs (2 separate search strategies for each study type as shown below)**

Appendix 1.2. Searched databases

Resource (Interface)	Set	Date of the search	Limits
Cochrane Database of Systematic Reviews (Cochrane Library - Wiley)	Issue 1 of 12, Jan 2018	2018-01-31	Subject headings only
Cochrane Central Register of Controlled Trials: (Cochrane Library - Wiley)	Issue 1 of 12, Jan 2018	2018-01-31	Subject headings only
MedLine (OVID)	Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to January 31, 2018	2018-02-05	Subject headings Systematic reviews
MedLine (OVID)	Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to February 21, 2018	2018-02-22	Subject headings only RCTs Year 2015-current
MedLine (OVID)	Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to February 14, 2018	2018-02-16	No Subject Headings Systematic reviews Year : 2017-current
MedLine (OVID)	Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to February 28, 2018	2018-03-01	No subject headings RCT special query Year 2017-current
Embase (Embase.com)	Embase database (1974 – present) MEDLINE database (1966 – present) Embase Classic (1947-1973)	2018-02-07	Subject Headings Systematic reviews special query Year 2017-current Not MedLine
Embase (Embase.com)	Embase database (1974 – present) MEDLINE database (1966 – present) Embase Classic (1947-1973)	2018-02-16	No Subject Headings RCT special query Not Medline
Embase (Embase.com)	Embase database (1974 – present) MEDLINE database (1966 – present) Embase Classic (1947-1973)	2018-02-22	Subject Headings RCT limit

Embase (Embase.com)	Embase database (1974 – present) MEDLINE database (1966 – present) Embase Classic (1947-1973)	2018-03-01	No Subject Headings RCT special query Year 2017-current
Embase (Embase.com)	Embase database (1974 – present) MEDLINE database (1966 – present) Embase Classic (1947-1973)	2018-03-01	No Subject Headings Year 2017-current

Appendix 1.3. Executed searches

Appendix 1.3.1. Cochrane Library

Date	2018-01-31
Database	Cochrane Database of Systematic Reviews: Issue 1 of 12, Jan 2018 (Cochrane Library - Wiley)
Strategy	1. MeSH descriptor: [Bariatric Surgery] explode all trees (1088) 2. Limit 1 to Cochrane reviews (4) 3. MeSH descriptor: [Gastrectomy] explode all trees (1008) 4. Limit 1 to Cochrane reviews (6)

Date	2018-01-31
Database	Cochrane Central Register of Controlled Trials: Issue 1 Jan 2018 (Cochrane Library - Wiley)
Strategy	1. MeSH descriptor: [Bariatric Surgery] explode all trees (1088) 2. Limit 1 to Trials (776) 3. MeSH descriptor: [Gastrectomy] explode all trees (1008) 4. Limit 3 to Trials (842)

Appendix 1.3.2. OVID MedLine

Subject Headings

Date	2018-02-05
Database	Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to January 31, 2018
Search Strategy	1 Overweight/ (19607) 2 exp Obesity/ (180954) 3 Bariatric Surgery/ (7104) 4 Gastric Bypass/ (7525) 5 GASTROPLASTY/ (3980) 6 exp Gastrectomy/ (31718) 7 3 or 4 or 5 or 6 (47404) 8 1 or 2 (188467) 9 7 and 8 (13836) 10 limit 9 to systematic reviews (694)

Date	2018-02-22

Database)	Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to February 21, 2018
Search Strategy	1 Overweight/ (19733) 2 exp Obesity/ (181698) 3 Bariatric Surgery/ (7156) 4 Gastric Bypass/ (7578) 5 GASTROPLASTY/ (3988) 6 exp Gastrectomy/ (31783) 7 3 or 4 or 5 or 6 (47553) 8 1 or 2 (189251) 9 7 and 8 (13930) 10 randomized controlled trial.pt. (454053) 11 controlled clinical trial.pt. (92169) 12 randomized.tw. (434605) 13 placebo.tw. (191709) 14 clinical trials as topic/ (182637) 15 randomly.tw. (286356) 16 trial?.ti. (239438) 17 10 or 11 or 12 or 13 or 14 or 15 or 16 (1163160) 18 exp animals/ not humans.sh. (4427654) 19 17 not 18 (1071974) 20 9 and 19 (1013) 21 limit 20 to yr=”2015 – 2018” (318)

Text words

Date	2018-02-16
Database	Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to February 14, 2018
Search Strategy	1 Overweight*.mp. (60173) 2 obesit*.mp. (269582) 3 1 or 2 (287007) 4 Bariatric*.mp. (16168) 5 (Stomach adj2 Stapling).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (14) 6 (Metabolic* adj2 Surg*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (895) 7 (Gastr* adj2 Bypass*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (11368) 8 Gastroplast*.mp. (4882) 9 4 or 5 or 6 or 7 or 8 (24845) 10 (Sleeve* adj2 gastrectom*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3661) 11 Gastrectomy.mp. (40188) 12 (Gastric adj2 surgery).mp. (6221) 13 10 or 11 or 12 (44527) 14 “Laparoscopic adjustable gastric banding”.mp. (1316)

	15 LAGB.mp. (1029) 16 (GASTRIC adj2 BANDING).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2867) 17 14 or 15 or 16 (3008) 18 "Roux-en-Y Gastric Bypass".mp. (5492) 19 (roux adj2 Y).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10540) 20 (roux adj4 bypass).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5717) 21 18 or 19 or 20 (10546) 22 9 or 13 or 17 or 21 (66544) 23 3 and 22 (19380) 24 limit 23 to yr="2017 –Current" (2028) 25 limit 24 to systematic reviews (121)

Date	2018-03-01
Database	Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to February 28, 2018
Search Strategy	1 Overweight*.mp. (60173) 2 obesit*.mp. (269582) **3 1 or 2** (287007) 4 Bariatric*.mp. (16168) 5 (Stomach adj2 Stapling).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (14) 6 (Metabolic* adj2 Surg*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (895) 7 (Gastr* adj2 Bypass*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (11368) 8 Gastroplast*.mp. (4882) **9 4 or 5 or 6 or 7 or 8** (24845) 10 (Sleeve* adj2 gastrectom*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3661) 11 Gastrectomy.mp. (40188) 12 (Gastric adj2 surgery).mp. (6221) **13 10 or 11 or 12 (44527)** 14 "Laparoscopic adjustable gastric banding".mp. (1316) 15 LAGB.mp. (1029) 16 (GASTRIC adj2 BANDING).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2867) **17 14 or 15 or 16** (3008) 18 "Roux-en-Y Gastric Bypass".mp. (5492) 19 (roux adj2 Y).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10540)

	20	(roux adj4 bypass).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5717)
	21	**18 or 19 or 20** (10546)
	22	9 or 13 or 17 or 21 (66544)
	23	3 and 22 (19380)
	24	randomized controlled trial.pt. (454636)
	25	controlled clinical trial.pt. (92192)
	26	randomized.tw. (434868)
	27	placebo.tw. (191787)
	28	clinical trials as topic/ (182748)
	29	randomly.tw. (286496)
	30	trial?.ti. (239646)
	31	**24 or 25 or 26 or 27 or 28 or 29 or 30** (1163813)
	32	23 and 31 (1433)
	33	limit 32 to yr="2017 -Current" (176)

Appendix 1.3.3. Embase.com

Subject headings

Date	2018-02-07		
Database	Embase (embase.com)		
Search Strategy	No.	Query Results	Results
	#1.	'obesity'/exp	431239
	#2.	'bariatric surgery'/exp	32002
	#3.	'gastric banding'/exp	6464
	#4.	'sleeve gastrectomy'/exp	8690
	#5.	'gastric bypass surgery'/exp	18080
	#6.	'gastroplasty'/exp	3717
	#7.	'gastrectomy'/exp	52855
	#8.	'roux-en-y gastric bypass'/exp	2272
	#9.	'metabolic surgery'/exp	71
	#10	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	85095
	#11	#1 AND #10	28362
	#12	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	322181
	#13	#10 AND #11	1040
	#14	#13 AND [embase]/lim	986

Date	2018-02-22

Database	Embase (embase.com)	
Search Strategy	No.	Query
	#1	'obesity'/exp
	#2	'bariatric surgery'/exp
	#3	'gastric banding'/exp
	#4	'sleeve gastrectomy'/exp
	#5	'gastric bypass surgery'/exp
	#6	'gastroplasty'/exp
	#7	'gastrectomy'/exp
	#8	'roux-en-y gastric bypass'/exp
	#9	'metabolic surgery'/exp
	#10	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
	#11	#1 AND #10
	#12	random*:ab,ti
	#13	placebo*:de,ab,ti
	#14	(double NEXT/1 blind*):ab,ti
	#15	#12 OR #13 OR #14
	#16	#11 AND #15
	#17	#11 AND [randomized controlled trial]/lim
	#18	#16 OR #17
	#19	(#16 OR #17) AND [2015-2018]/py

Text words

Date	2018-02-16	
Database	Embase.com	
Search Strategy	#1	,overweight*':ti,ab,kw OR ,obesit*':ti,ab,kw 338896
	#2	'bariatric*':ti,ab,kw OR (('stomach' NEAR/2 'stapling'):ti,ab,kw) OR (('metabolic*' NEAR/2 'surg*'):ti,ab,kw) OR (('gastr*' NEAR/2 'bypass*'):ti,ab,kw) OR 'gastroplast*':ti,ab,kw 37763
	#3	(('sleeve*' NEAR/2 'gastrectom*'):ti,ab,kw) OR 'gastrectomy':ti,ab,kw OR (('gastric' NEAR/2 'surgery'):ti,ab,kw) 43301
	#4	'laparoscopic adjustable gastric banding':ti,ab,kw OR 'lagb':ti,ab,kw OR (('gastric' NEAR/2 'banding'):ti,ab,kw) 5582
	#5	'roux-en-y gastric bypass':ti,ab,kw OR (('roux' NEAR/2 'y'):ti,ab,kw) OR (('roux' NEAR/4 'bypass'):ti,ab,kw) 16204
	#6	#2 OR #3 OR #4 OR #5 73677
	#7	#1 AND #6 21796
	#8	#1 AND #6 AND [2017-2018]/py 2671
	#9	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review' 324106
	#10	#8 AND #9 168
	#11	#10 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) 122
Date	2018-03-01	
Database (name + access ; e.g.: Medline OVID)	Embase.com	
Search Strategy	#1	,overweight*':ti,ab,kw OR ,obesit*':ti,ab,kw 338896

Results
431239
82003
6464
8690
18080
3717
53490
2678
71
86298
28729
1261140
410215
185478
1505605
2223
607
2288
704

(attention, for PubMed, check « Details »)	#2	'bariatric*':ti,ab,kw OR (('stomach' NEAR/2 'stapling'):ti,ab,kw) OR (('metabolic*' NEAR/2 'surg*'):ti,ab,kw) OR (('gastr*' NEAR/2 'bypass*'):ti,ab,kw) OR 'gastroplast*':ti,ab,kw 37763
	#3	(('sleeve*' NEAR/2 'gastrectom*'):ti,ab,kw) OR 'gastrectomy':ti,ab,kw OR (('gastric' NEAR/2 'surgery'):ti,ab,kw) 43301
	#4	'laparoscopic adjustable gastric banding':ti,ab,kw OR 'lagb':ti,ab,kw OR (('gastric' NEAR/2 'banding'):ti,ab,kw) 5582
	#5	'roux-en-y gastric bypass':ti,ab,kw OR (('roux' NEAR/2 'y'):ti,ab,kw) OR (('roux' NEAR/4 'bypass'):ti,ab,kw) 16204
	#6	#2 OR #3 OR #4 OR #5 73677
	#7	#1 AND #6 21796
	#8	#1 AND #6 AND [2017-2018]/py 2671

Appendix 1.4. Systematic Reviews selected for clinical effectiveness assessment

1	Ashrafian H, et al. 2016 Obes. Surg. 26(8):1697-1704 - Type 1 Diabetes Mellitus and Bariatric Surgery: A Systematic Review and Meta-Analysis
2	Cardoso L, et al. 2017 Diabetes Obes. Metab. 19(9):1223-1232 - and long-term mortality after bariatric surgery: A systematic review and meta-analysis
3	Cheng J, et al. 2016 Oncotarget 7(26):39216-39230 - The comprehensive summary of surgical versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomized controlled trials
4	Chow A, et al. 2016 Journal of Obesity 6170719(6170719 - A Systematic Review and Meta-Analysis of Outcomes for Type 1 Diabetes after Bariatric Surgery
5	Cohen R, et al. 2017 Obes. Surg. 27(10):2733-2739 - Roux-En-Y Gastric Bypass in Type 2 Diabetes Patients with Mild Obesity: a Systematic Review and Meta-analysis
6	Colquitt JL, et al. 2014 Cochrane Database of Systematic Reviews 8):- Surgery for weight loss in adults
7	Ells LJ, et al. 2015 Cochrane Database of Systematic Reviews 6):- Surgery for the treatment of obesity in children and adolescents
8	Ettleson MD, et al. 2017 Minerva Chirurgica 72(6):505-519 - Roux-en-Y gastric bypass versus sleeve gastrectomy: risks and benefits
9	Golzarand M, et al. 2017 Surg. Endosc. Interv. Tech. 31(11):4331-4345 - and very long-term effects of laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy on weight loss in adults
10	Juodeikis Z, et al. 2017 Surgery for Obesity & Related Diseases 13(4):693-699 - Long-term results after sleeve gastrectomy: A systematic review
11	Kang JH, et al. 2017 Medicine (Baltimore) 96(46):e8632 - Effectiveness of bariatric surgical procedures: A systematic review and network meta-analysis of randomized controlled trials
12	Li J, et al. 2016 Obes Surg 26(2):429-42 - Laparoscopic Roux-en-Y Gastric Bypass Versus Laparoscopic Sleeve Gastrectomy to Treat Morbid Obesity-Related Comorbidities: a Systematic Review and Meta-analysis
13	Mahawar KK, et al. 2016 Obes Surg 26(1):196-204 - Bariatric Surgery in Type 1 Diabetes Mellitus: A Systematic Review

14	Muller-Stich BP, et al. 2015 Ann Surg 261(3):421-9 - Surgical versus medical treatment of type 2 diabetes mellitus in nonseverely obese patients: a systematic review and meta-analysis
15	Osland E, et al. 2017 Obes Surg 27(5):1208-1221 - Changes in Non-Diabetic Comorbid Disease Status Following Laparoscopic Vertical Sleeve Gastrectomy (LVSG) Versus Laparoscopic Roux-En-Y Gastric Bypass (LRYGB) Procedures: a Systematic Review of Randomized Controlled Trials
16	Osland E, et al. 2017 Surg Endosc 31(4):1952-1963 - Diabetes improvement and resolution following laparoscopic vertical sleeve gastrectomy (LVSG) versus laparoscopic Roux-en-Y gastric bypass (LRYGB) procedures: a systematic review of randomized controlled trials
17	Osland E, et al. 2017 Surg Laparosc Endosc Percutan Tech 27(1):8-18 - Weight Loss Outcomes in Laparoscopic Vertical Sleeve Gastrectomy (LVSG) Versus Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) Procedures: A Meta-Analysis and Systematic Review of Randomized Controlled Trials
18	Paulus GF, et al. 2015 Obes Surg 25(5):860-78 - Bariatric surgery in morbidly obese adolescents: a systematic review and meta-analysis
19	Pedroso FE, et al. 2018 Surgery for Obesity & Related Diseases 10(10 - Weight loss after bariatric surgery in obese adolescents: a systematic review and meta-analysis
20	Puzziferri N, et al. 2014 JAMA 312(9):934-42 - Long-term follow-up after bariatric surgery: a systematic review
21	Qi L, et al. 2017 Surg. Obes. Relat. Dis. 13(12):2037-2055 - Effects of bariatric surgery on glycemic and lipid metabolism, surgical complication and quality of life in adolescents with obesity: a systematic review and meta-analysis
22	Quan Y, et al. 2015 Gastroenterol. Res. Pract. 2015(- Efficacy of Laparoscopic Mini Gastric Bypass for Obesity and Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis
23	Quintas-Neves M, et al. 2016 Rev Port Pneumol (Barc) 22(6):331-336 - Assessment of bariatric surgery efficacy on Obstructive Sleep Apnea (OSA)
24	Ricci C, et al. 2015 Obes Surg 25(3):397-405 - Long-term effects of bariatric surgery on type II diabetes, hypertension and hyperlipidemia: a meta-analysis and meta-regression study with 5-year follow-up
25	Sheng et al. The Long-Term Effects of Bariatric Surgery on Type 2 Diabetes Remission, Microvascular and Macrovascular Complications, and Mortality: a Systematic Review and Meta-Analysis. OBES SURG (2017) 27:2724–2732
26	Shoar S, et al. 2017 Obes. Surg. 27(12):3110-3117 - Long-Term Outcome of Bariatric Surgery in Morbidly Obese Adolescents: a Systematic Review and Meta-Analysis of 950 Patients with a Minimum of 3 years Follow-Up
27	Shoar S, et al. 2017 Surg. obes. relat. dis 13(2):170-180 - Long-term and midterm outcomes of laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass: a systematic review and meta-analysis of comparative studies
28	Switzer NJ, et al. 2016 Obes Surg 26(7):1616-21 - Sleeve Gastrectomy and Type 2 Diabetes Mellitus: a Systematic Review of Long-Term Outcomes
29	Wang. Comparison of safety and effectiveness between laparoscopic mini-gastric bypass and laparoscopic sleeve gastrectomy: A meta-analysis and systematic review.
30	Yan Y, et al. 2016 Medicine (Baltimore) 95(17):e3462 - Roux-en-Y Gastric Bypass Versus Medical Treatment for Type 2 Diabetes Mellitus in Obese Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
31	Zhou X, et al. 2016 Obes Surg 26(11):2590-2601 - Effects of Bariatric Surgery on Mortality, Cardiovascular Events, and Cancer Outcomes in Obese Patients: Systematic Review and Meta-analysis

APPENDIX 2. INDICATIONS FOR BARIATRIC SURGERY IN INT'L GUIDELINES

AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) in ADULTS 2018

https://www.awmf.org/leitlinien/detail/ll/088-001.html

Bei Patienten mit einem BMI ≥40 kg/m2 ohne Begleiterkrankungen und ohne Kontraindikationen ist nach Erschöpfung der konservativen Therapie nach umfassender Aufklärung eine adipositaschirurgische Operation indiziert. (Evidenzlevel und **Empfehlungsgrad 1 A**)

Patienten mit einem BMI ≥35 kg/m2 mit einer oder mehreren Adipositas-assoziierten Begleiterkrankungen wie Diabetes mellitus Typ 2, koronare Herzerkrankung, Herzinsuffizienz, Hyperlipidämie, arterieller Hypertonus, Nephropathie, Obstruktives Schlafapnoesyndrom (OSAS), Adipositas-Hypoventilationssyndrom, Pickwick Syndrom, nicht alkoholische Fettleber (NAFLD) oder nicht alkoholische Fettleberhepatitis (NASH), Pseudotumor cerebri, Gastroösophageale Refluxerkrankung (GERD), Asthma, chronisch venöse Insuffizienz, Harninkontinenz, immobilisierende Gelenkerkrankung, Einschränkungen der Fertilität oder polyzystisches Ovarialsyndrom sollte eine adipositaschirurgische Operation angeboten werden, wenn die konservative Therapie erschöpft ist. (**1A**)

Recommendations for patients with T2DM are copied ("nach American Diabetes Association") from ADA (cf. below).

AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) in ADOLESCENTS 2018 (draft)

https://www.awmf.org/leitlinien/detail/ll/088-001.html

Age definition: Die im Folgenden getroffenen Empfehlungen bzw. Statements beziehen auf Kinder und Jugendliche bis zu einem Alter von <18 Jahren. Da die Operation von Kindern eine Ausnahme darstellt, wird in der Folge überwiegend nur von Jugendlichen gesprochen.

Bei ausgeschöpfter oder aussichtsloser konservativer Therapie kann bei Kindern und Jugendlichen mit einer Adipositas BMI ≥35 kg/m² eine adipositaschirurgische oder metabolische Maßnahme in Erwägung gezogen werden, wenn mindestens eine somatische oder psychosoziale Komorbidität besteht. Ab einem BMI ≥50 kg/m² kann eine adipositaschirurgische oder metabolische Operation in Erwägung gezogen werden, auch wenn keine Komorbidität besteht. **(Expertenkonsens)**

American Diabetes Association (ADA) 2018 - endorsed by the European Association for the Study of Diabetes (EASD) ADULTS

WWW.DIABETES.ORG/DIABETESCARE ; Davies et al. Diabetologia. 2018 Dec;61(12):2461-2498

Metabolic surgery should be recommended as an option to treat type 2 diabetes in appropriate surgical candidates with BMI ≥40 kg/m2 (BMI ≥37.5 kg/m2 in Asian Americans), regardless of the level of glycemic control or complexity of glucose-lowering regimens, and in adults with BMI 35.0–39.9 kg/m2 (32.5–37.4 kg/m2 in Asian Americans) when hyperglycemia is inadequately controlled despite lifestyle and optimal medical therapy.

Metabolic surgery should be considered as an option for adults with type 2 diabetes and BMI 30.0 - 34.9 kg/m2 (27.5–32.4 kg/m2 in Asian Americans) if hyperglycemia is inadequately controlled despite optimal medical control by either oral or injectable medications including insulin).

American Diabetes Association (ADA) 2018 ADOLESCENTS

Metabolic surgery may be considered for the treatment of adolescents with type 2 diabetes who are markedly obese (BMI <35 kg/m²) and who have uncontrolled glycemia and/or serious comorbidities despite lifestyle and pharmacologic intervention.

American Society for Metabolic and Bariatric Surgery (ASMBS) 2018 PEDIATRIC

BMI ≥35 kg/m^2 or 120% of 95th percentile with clinically significant comorbid conditions such as obstructive sleep apnea (AHI >5), T2D, IIH, NASH, Blount's disease, SCFE, GERD or hypertension;

or BMI ≥40 kg/m2 or 140% of 95th percentile (whichever is lower)

Adolescents are defined by the World Health Organization's (WHO) definition of 10-19 years old, but younger children who meet the other criteria could be considered when benefit outweighs risk.

Dynamed Plus 2018

Bariatric surgery may be appropriate for patients with: body mass index (BMI) ≥40 kg/m2 without coexisting medical problems and without excessive surgical risk (Strong recommendation)

BMI ≥35 kg/m2 with at least 1 severe obesity-related comorbidity (Strong recommendation)

BMI ≥30 kg/m2 with at least 1 severe obesity-related comorbidity or type 2 diabetes (Weak recommendation)

Danish Health Authority 2017

https://www.sst.dk/da/udgivelser/2017/~/media/AB3129FA6FC4406AAD01F0087663AA1C.ashx

Bariatric surgery assessment should be offered to patients with a BMI above 40 kg/m2 (strong recommendation, moderate LoE). * Please note that the evidence is based on patients with obesity-related diseases, primarily type 2 diabetes. However, it is assessed that a beneficial effect on weight loss and increased physical quality of life will also apply to overweight patients without comorbidities.

Age limit: Bariatric surgery assessment should be offered to patients aged 18-25 years with a BMI above 40 kg/m2 (strong recommendation, moderate LoE). * Please note that the evidence is based on patients with obesity-related diseases, primarily type 2 diabetes.

DUODECIM 2017

https://www.ebpnet.be/nl/gp/pages/display.aspx?ebmid=ebm01025

Chirurgie kan worden overwogen als behandelingsoptie bij patiënten met een body mass index (BMI) groter dan 40 kg/m2, op voorwaarde dat de patiënt voordien met succes heeft deelgenomen aan een groepsprogramma voor de aanpak van het overgewicht (gewichtsverlies >7%).

Chirugie kan ook worden overwogen bij patiënten met een BMI van 35-40 kg/m2 wanneer obesitas geassocieerd is met diabetes type 2 of hypertensie, ernstige slaapapneu (CPAP-therapie) of een ernstige ziekte van het musculoskeletale systeem.

HAS 2016 ADOLESCENTS

https://www.has-sante.fr/portail/

IMC >35 kg/m2 avec au moins une des comorbidités sévères suivantes : diabète, syndrome d'apnées du sommeil ventilé, hypertension intracrânienne idiopathique, stéatohépatite ;

IMC >40 kg/m2 avec une comorbidité modérée (syndrome d'apnées du sommeil modéré, hypertension artérielle, dyslipidémie sévère, complications psychosociales liées à l'obésité, altération majeure de la qualité de vie) ;

stade de Tanner ≥IV (âge osseux ≥13 ans chez les filles et ≥15 ans chez les garçons) ;

JOINT INTERNATIONAL DIABETES ORGANISATIONS 2016

Rubino et al. Diabetes Care 2016;39:861-877

Metabolic surgery is recommended as an option to treat T2D in patients with (1) Class III obesity (BMI ≥40 kg/m²), regardless of the level of glycemic control or complexity of glucose lowering regimens and (2) with Class II obesity (BMI 35.0–39.9 kg/m²) with inadequately controlled hyperglycemia despite lifestyle and optimal medical therapy.

Metabolic surgery should be considered to be an option to treat T2D in patients with class I obesity (BMI 30.0–34.9 kg/m²) and inadequately controlled hyperglycemia despite optimal medical treatment by either oral or injectable medications (including insulin).

Given the lack of level-1 evidence involving the effects of metabolic surgery on T2D in adolescent patients, the DSS-II committee feels a recommendation for use of GI surgery in this population is inappropriate at present.

US ENDOCRINE SOCIETY 2016 - ADOLESCENTS (Co-sponsored by The European Society of Endocrinology and the Pediatric Endocrine Society)

We suggest bariatric surgery only under the following conditions: the patient has attained Tanner 4 or 5 pubertal development and final or near-final adult height, the patient has a BMI of >40 kg/m2 or has a BMI of >35 kg/m² and significant, extreme comorbidities extreme obesity and comorbidities persist despite compliance with a formal program of lifestyle modification, with or without pharmacotherapy

NICE 2014 ADULTS

https://pathways.nice.org.uk/pathways/obesity

Bariatric surgery is a treatment option for people with obesity if all of the following criteria are fulfilled: They have a BMI of 40 kg/m² or more, or between 35 kg/m2 and 40 kg/m² and other significant disease that could be improved if they lost weight. All appropriate non-surgical measures have been tried but the person has not achieved or maintained adequate, clinically beneficial weight loss. The person has been receiving or will receive intensive management in a tier 3 service. The person is generally fit for anaesthesia and surgery. The person commits to the need for long-term follow-up.

In addition to the criteria listed above, bariatric surgery is the option of choice (instead of lifestyle interventions or drug treatment) for adults with a BMI of more than 50 kg/m2 when other interventions have not been effective.

Offer an expedited assessment for bariatric surgery to people with a BMI of 35 and over who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

Consider an assessment for bariatric surgery for people with a BMI of 30–34.9 who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

NICE 2017 ADOLESCENTS

https://pathways.nice.org.uk/pathways/obesity

Surgical intervention is not generally recommended in children or young people. Bariatric surgery may be considered for young people only in exceptional circumstances, and if they have achieved or nearly achieved physiological maturity.

EASO 2013

http://easo.org/wp-content/uploads/2013/10/EASO-IFSO-EC-Guidelines-on-Metabolic-and-Bariatric-Surgery.pdf

Patients in age groups from 18 to 60 years: 1. With BMI ≥40 kg/m² 2. With BMI 35–40 kg/m² with co-morbidities in which surgically induced weight loss is expected to improve the disorder.

Patients with BMI ≥30 and <35 kg/m² with T2DM may be considered for bariatric surgery on an individual basis.

In children/adolescents if BMI >40 kg/m² (or 99.5th percentile for respective age) and at least one co-morbidity. Shows skeletal and developmental maturity.

US AACE/ACE Guidelines (2013)

https://www.aace.com/files/guidelines/ObesityExecutiveSummary.pdf

Patients with a BMI of ≥40 kg/m2 without coexisting medical problems and for whom the procedure would not be associated with excessive risk should be eligible for bariatric surgery (Grade A; BEL 1).

Patients with a BMI of ≥35 kg/m2 and 1 or more severe obesity-related complications, including type 2 diabetes, hypertension, obstructive sleep apnea, obesity-hypoventilation syndrome, Pickwickian syndrome, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, pseudotumor cerebri, gastroesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life may also be considered for a bariatric surgery procedure.

Patients with BMI of 30 to 34.9 kg/m2 with diabetes or metabolic syndrome may also be considered for a bariatric procedure.

NEDERLANDS HUISARTSEN GENOOTSCHAP (NHG) 2010

https://www.nhg.org/standaarden/volledig/nhg-standaard-obesitas#idp584880

De huisarts kan een patiënt verwijzen voor bariatrische chirurgie als de BMI ≥40 kg/m^2 is of tussen 35 en 40 kg/m^2 én er is comorbiditeit én de gangbare niet-chirurgische behandelingen zijn geprobeerd, maar hebben niet geresulteerd in gewichtsverlies of -behoud.

De huisarts kan bij een patiënt met een BMI >50 kg/m2 bariatrische chirurgie als eerste behandeling overwegen.

Chirurgische interventies bij (morbide) obesitas bij kinderen en adolescenten zullen alleen in een onderzoekssetting plaatsvinden.

HAS 2009 ADULTS

https://www.has-sante.fr/portail/

La chirurgie bariatrique est indiquée par décision collégiale, prise après discussion et concertation pluridisciplinaires (accord professionnel), chez des patients adultes réunissant l'ensemble des conditions suivantes : • patients avec un IMC ≥40 kg/m2 ou bien avec un IMC ≥35 kg/m2 associé à au moins une comorbidité susceptible d'être améliorée après la chirurgie (notamment maladies cardio-vasculaires dont HTA, syndrome d'apnées hypopnées obstructives du sommeil et autres troubles respiratoires sévères, désordres métaboliques sévères, en particulier diabète de type 2, maladies ostéo-articulaires invalidantes, stéatohépatite non alcoolique) (grade B) ; • en deuxième intention après échec d'un traitement médical, nutritionnel, diététique et psychothérapeutique bien conduit pendant 6-12 mois (grade B) ; en l'absence de perte de poids suffisante ou en l'absence de maintien de la perte de poids (grade B) ; • patients bien informés au préalable (accord professionnel), ayant bénéficié d'une évaluation et d'une prise en charge préopératoires pluridisciplinaires (grade C) ; • patients ayant compris et accepté la nécessité d'un suivi médical et chirurgical à long terme (accord professionnel) ; • risque opératoire acceptable (accord professionnel).

En l'absence de données établies sur une population plus large et à plus long terme, on ne peut recommander pour l'instant la chirurgie bariatrique chez des sujets diabétiques avec IMC entre 30 et 35 kg/m2 (accord professionnel).

APPENDIX 3. SOURCES FOR EVIDENCE ON CLINICAL EFFECTIVENESS OUTCOMES

Outcome	SR evidence source	RCT evidence data, not available from SRs
Weight related parameters	Cheng et al.[87]	IKRAMUDDDIN_2018,[74], MINGRONE_2015,[75] SCHAUER_2017,[13] WENTWORTH_2017,[77] OBRIEN_2013.[76]
Type 2 diabetes remission	Cheng et al.[87], Yan et al.[102]	WENTWORTH_2017,[77] SCHAUER_2017,[13] MINGRONE_2015,[75] IKRAMUDDIN_2018[73, 74], COURCOULAS_2015.
Micro- and macrovascular	None	WENTWORTH_2017,[77] SCHAUER_2017,[13] MINGRONE_2015.[75]
Arterial hypertension	Cheng et al.[87]	IKRAMUDDDIN_2018,[74], SCHAUER_2017,[13] WENTWORTH_2017,[77] SCHIAVON.[72]
Serum lipids	Cheng et al.[87]	IKRAMUDDDIN_2018,[74], SCHAUER_2017,[13] MINGRONE_2015.[75]
OSAS	Quintas-Neves et al.,[54] Wong et al.[453]	DIXON_2012,[61] Feigel-Guiller[62]
QoL	NA	CUMMINGS_2016,[97] DING_2015,[59] HALPERIN_2014,[63] DIXON_2012,[61] OBRIEN_2006,[67] MINGRONE_2015,[75] SCHAUER_2017,[13] SCHAUER_2014,[98] WENTWORTH_2017,[77]
Mortality	CARDOSO et al. [89]	
Bariatric surgery in adolescents	NA	OBRIEN_2010,[68] Observational studies: Teen-LABS,[84] AMOS[85] and FABS-5+[86]
Bariatric surgery in T2DM and BMI<35	NA	COURCOULAS_2014,[57] LIANG_2013,[65] PARIKH_2014,[69] WENTWORTH_2014,[71] DING_2015,[59] DIXON_2008,[60] HALPERIN_2014,[63] MINGRONE_2012,[66] SCHAUER_2012,[70] COURCOULAS_2015,[73] IKRAMUDDIN_2018,[74] WENTWORTH_2017,[77] MINGRONE_2015,[75] SCHAUER_2017.[13]

APPENDIX 4. GRADE LEVEL OF EVIDENCE FOR THE MOST CRITICAL OUTCOMES

Surgical treatment versus medical treatment in obese adults

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Control	**With Intervention**		**Risk with Control** / **Risk difference with Intervention** (95% CI)
Short-term mortality (CRITICAL OUTCOME)										
4030 pts 38 RCTs 30 days	No serious RoB	No inconsistency	No Indirectness	No imprecision	Not detected	⨁⨁⨁⨁ **HIGH**	NA	11/4030 0.18% (0.04-0.38%)		
Long-term mortality (CRITICAL OUTCOME) : see GRADING table hereunder										
see separate grading table										
Quality of life 1 year after surgery (generic instruments) (CRITICAL OUTCOME)										
131 pts 3 RCTs 1 year	Serious risk of bias[1]	No inconsistency	No Indirectness	Serious imprecision[2]	Not detected	⨁⨁⨀⨀ **LOW**			No significant difference	
Quality of life 2 year after surgery (generic instruments) (CRITICAL OUTCOME)										
140 pts 2 RCTs	Serious risk of bias[1]	No inconsistency	No Indirectness[3]	Serious imprecision[2]	Not detected	⨁⨁⨀⨀ **LOW**			May be better after surgery for some components SF 36 (Physical role, general	

							health, energy)
Quality of life 5 year after surgery (generic instruments) (CRITICAL OUTCOME)							
261 pts 3 RCTs	Serious risk of bias[1]	No inconsistency	No Indirectness	Serious imprecision[2]	Not detected	⊕⊕⊖⊖ **LOW**	May be better after surgery for some components SF 36 (general health, energy)
Quality of life 10 year after surgery (generic instruments) (CRITICAL OUTCOME)							
80 pts 1 RCT	Very serious risk of bias[4]	No inconsistency	No Indirectness	Serious imprecision[2]	Not detected	⊕⊖⊖⊖ **VERY LOW**	No significant difference

[1] *Significant and/or unbalanced loss of FU*
[2] *Optimal information size not reached*
[3] *Although one study was in patients with obstructive sleep apnea only, and the second study in patients with BMI 30-35 kg/m2, we decided not to rate down for indirectness in view of the overall judgement of the quality of evidence.*
[4] *Significant loss of FU and cross-over, no ITT*

Quality appraisal (GRADE) for three SR-MA on the effects of bariatric surgery on LT-mortality risk.

Quality assessment									Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Overall quality of evidence** (= confidence in effect size)	**Relative effect** (95% CI)	**Event rates (%)**		**ARR (absolute risk reduction)**	**NNT (number needed-to-treat)**
									Intervention	**Control**		
	Long term survival (≥2 y follow-up) patients with BMI ≥35 kg/m2, ≥18 y (CRITICAL OUTCOME), Cardoso et al. 2017											
113 275 pts 8 obs. Studies* ≥2 years	No serious RoB	No inconsistency	No Indirectness	No imprecision	Not detected	Large effect size, consistency with other data[1]	⊕⊕⊕⊖ **MODERATE** [1]	HR 0.57 (0.47-0.69) (adjusted)	NA	NA		
	Long term survival (≥2 y follow-up) with patient eligible BMI as from 30 kg/m2, ≥18 y (CRITICAL OUTCOME), Zhou et al. 2016											
224 187 pts 20 studies[$] ≥1 year; (adjusted OR based on 10 studies)	No serious RoB	No inconsistency	No Indirectness[3]	No imprecision	Not detected	Large effect size[2] Idem for adjusted analysis on 10 trials and different sensitivity analyses[4]	⊕⊕(⊕)⊖ **LOW-to-MODERATE** [1,2]	Unadjusted OR 0.38 (0.29-0.50) Adjusted OR 0.55 (0.46-0.65)	4.5%	8.5%	4%	25

	Long-term mortality risk, follow-up ≥2 y, only studies with ≥100 subjects (CRITICAL OUTCOME) Kwok et al. 2014											
29 208 pts 14 cohort trials£ ≥2 year; (adjusted OR based on 10 studies)	4 studies at moderate-high RoB; 10 studies at moderate or lower RoB	No inconsistency	No indirectness	No imprecision	Not detected	Large effect size[3]	⊕⊕(⊕)⊖ **LOW-to-MODERATE**[4]	- Pooled adjusted OR 0.60 (0.49-74), 10 studies[5] - Adjusted OR 0.67 (0.59-077) after exclusion of 4 studies[6]	4.0% 3.8%	8.3% 8.3%	4.3% 4.5%	23 22

These three SR-MA had some overlap, explained by the slightly different eligibility criteria and their different time of periods.
Overall the consolidated level of evidence according to GRADE was considered to be low-to-moderate for the outcome long-term mortality (risk reduction).
RoB: risk of bias
**see Cardoso et al. 2017*
$see Zhou et al. 2016
£see Kwok et al. 2014
[1,2] Reason's for rating up: large effect size obtained in SR-MA, and consistency with other data/observations
[4] Included studies were eligible to include patients with BMI ≥30 which could theoretically point to in-directness. However looking at the mean BMI values of the included patients in the total of 32 studies, only 2 trials had mean BMI values between 34-35, a few studies did not report mean BMI, but all other trials had mean BMI values above or far above 35 or above 40. Therefore decision has been justified not to rate down. Arguments for possible rating up are: 1) large effect size observed in these SR-MA and consistency with other data/observations and 2) the fact that results remain consistent after adjustment and performance of different sensitivity analyses: for all the outcomes analyzed on adjusted estimates (based on 10 studies), no significant difference was observed when comparing: non-RCT vs. cohort trials, BMI < vs. ≥40, analysis according to FU period <5 vs. ≥5years. Apart from large effect on relative reduction in mortality, absolute risk difference in mortality was large
[5] Pooled adjusted OR 0.60 (0.49-74), based on 10 studies, moderate heterogeneity (I^2 = 64%)
[6] Adjusted OR 0.67 (0.59-077) after exclusion of 4 studies with moderate-high risk of bias, low heterogeneity (I^2 = 25%)
When considering only adjusted relative risk estimates, there is limited overlap between the SR-MA by Cardoso et al. and Zhou et al.: of the 6 studies relied on for the adjusted analysis in the SR-MA by Cardoso, 4 studies overlapped with the SR by Zhou, while 2 studies were not included by Zhou et al. as they were published after the search period applied by Cardoso et al.

APPENDIX 5. SEARCH STRATEGY FOR CLINICAL SAFETY

Search for studies

Appendix 5.1. Identification of studies

We followed the KCE Process Book for conducting the search[i].

The research question was transformed into a PICOS structured search question, we did not limit the search by adding specific outcomes.

Keywords and search concepts were collected through expert's knowledge and analysis of keywords and subject headings from articles retrieved after preliminary literature searches.

The following resources were searched:

Resource (Interface)	Set	Date of the search	Limits
HTA Database (CRD)	complete	2018-07-03	none
MedLine (OVID)	Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to June 20, 2018>	2018-06-27	Year: 2008-current Subject headings
MedLine (OVID)	Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to June 27, 2018>	2018-07-05	Year: 2017-current No Subject headings
Embase (Embase.com)	Embase database (1974 – present)	2018-07-10	Year: 2008-current Not MedLine

[i] http://processbook.kce.fgov.be/

	MEDLINE database (1966 – present) Embase Classic (1947-1973)		Subject Headings
Embase (Embase.com)	Embase database (1974 – present) MEDLINE database (1966 – present) Embase Classic (1947-1973)	2018-07-11	Year: 2017-current Not MedLine No Subject Headings
Cochrane Database of Systematic Reviews (Cochrane Library - Wiley)	: Issue 7 of 12, July 2018	2018-07-13	Subject headings only
Cochrane Central Register of Controlled Trials (Cochrane Library - Wiley)	Issue 6 of 12, June 2018	2018-07-16	Subject headings only

A search strategy was developed by assistance of a medical information specialist and adapted to each database. We used existing special queries such as Systematic reviews for MedLine (OVID MedLine); Systematic reviews for Embase, adapted from Wilczynski & Haynes (2007), Randomised Control Trials for Medline from the Cochrane Handbook (v.5.1.0), Randomized Controlled trials for Embase adapted from Wong et al. (2006) <REF KCE PROCESS BOOK>.

Search in those resources was supplemented by collecting suggested references from different sources (external experts, exploratory searches in the bibliographical databases, identification of cited references and looking into the bibliography of key references).

All identified references were imported in Endnote X.8, the duplicate search results were detected based on title match during the import process in EndNote, and supplemented by manual identification after sorting on Title.

Appendix 5.1.1. Selection of studies

Considering the large amount of identified studies, some choices were made in order to reduce the amount of references to assess:

- Case Reports were not included in the assessment tool (that result in the PRISMA flow)
- Studies published earlier than 2013 were excluded without any screening (Exclusion “Period (censored <2013)”)
- Remaining studies were first screened on title and abstract using the PICO in - and exclusion criteria; irrelevant studies were discarded.
- The full text of the retained studies was then sought. If no full text was available, the study was excluded for the final evaluation. When several full-text were available on the same sub-topic, full-text were retrieved and assessed until saturation on this specific sub-topic.

Appendix 5.1.2. Search strategies

Appendix 5.1.2.1. HTA database

Date	2018-07-03
Database	HTA database (CRD)
Search strategy	1. MeSH DESCRIPTOR Bariatric Surgery EXPLODE ALL TREES IN HTA [73] 2. ((bariatric*)) and (Full publication record:ZDT) IN HTA [149]
Note	

Appendix 5.1.2.2. OVID MedLine

Subject Headings

Date	2018-06-27
Database	Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to June 20, 2018>
Search Strategy (attention, for PubMed, check « Details »)	1 Overweight/ (20548) 2 exp Obesity/ (186323) 3 1 or 2 (194150) 4 Bariatric Surgery/ (7645) 5 Gastric Bypass/ (7876) 6 Gastroplasty/ (4050) 7 4 or 5 or 6 (17878) 8 bariatrics/ (245) 9 bariatric medicine/ (62) 10 8 or 9 (304) 11 3 and 10 (238) 12 7 or 11 (18033) 13 exp animals/ not humans.sh. (4467410) 14 12 not 13 (17577) **15 limit 14 to yr="2008 -Current" (12899)** 16 Meta-Analysis/ (89489) 17 15 and 16 (198) 18 limit 15 to systematic reviews (783) 19 randomized controlled trial.pt. (462868) 20 controlled clinical trial.pt. (92461) 21 randomized.ab. (414641) 22 placebo.ab. (189814) 23 drug therapy.fs. (2025420) 24 randomly.ab. (292756) 25 trial.ab. (431276) 26 groups.ab. (1807519) 27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (4227107) 28 15 and 27 (2862) 29 exp Cohort Studies/ (1751920) 30 15 and 29 (4492) 31 Observational Study/ (48819) 32 Observational Studies as Topic/ (3070) 33 31 or 32 (51861) 34 15 and 33 (298) 35 Case Reports/ (1883690) 36 15 and 35 (1485)
Comment	From Cohort Studies results (#30), only the 1500 most recent were exported

Text words

Date	2018-07-05
Database	Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to June 27, 2018>
Search Strategy (attention, for PubMed, check « Details »)	1 Overweight*.tw. (58016) 2 obesit*.tw. (200783) 3 1 or 2 (227247) 4 (Stomach adj2 Stapling).tw. (12) 5 (Metabolic* adj2 Surg*).tw. (857) 6 (Gastr* adj2 Bypass*).tw. (9736) 7 Gastroplast*.tw. (1879) 8 Gastrectomy.tw. (23913) 9 (Gastric adj2 surgery).tw. (6313) 10 "Laparoscopic adjustable gastric banding".tw. (1325) 11 LA?GB.tw. (1082) 12 (GASTRIC adj2 BANDING).tw. (2863) 13 "Roux-en-Y Gastric Bypass".tw. (5658) 14 (roux adj2 Y).tw. (9722) 15 (roux adj2 bypass).tw. (102) 16 RY?GB.tw. (2124) 17 (Sleeve* adj2 gastrectom*).tw. (3830) 18 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (40769) 19 3 and 18 (6973) 20 "weight loss surgery".tw. (669) 21 (obesity adj2 surg$).tw. (1921) 22 19 or 20 or 21 (8706) **23 limit 22 to yr="2017 -Current" (1264)** 24 meta-analysis.mp. (144963) 25 23 and 24 (37) 26 limit 23 to systematic reviews (76) 27 random$.mp. (1203258) 28 groups.ab. (1809712) 29 placebo.ab. (190007) 30 trial.ab. (431983) 31 27 or 28 or 29 or 30 (2849220) 32 23 and 31 (316) 33 cohort.tw. (422030) 34 23 and 33 (159) 35 (observational adj2 stud*).tw. (98041) 36 23 and 35 (43) 37 (case? adj2 report$).tw. (504429) 38 23 and 37 (53)

Appendix 5.1.2.3. Embase.com

Subject headings

Date	2018-07-10		
Database	Embase (embase.com) - current		
Search Strategy (attention, for PubMed, check « Details »)	No.	Query	Results
	1	'bariatric surgery'/de	25756
	2	'gastric banding'/de	6709
	3	'sleeve gastrectomy'/exp	9963
	4	#1 OR #2 OR #3	33703
	5	'obesity'/exp	448047
	6	'gastric bypass surgery'/de	16774
	7	'roux-en-y gastric bypass'/exp	3409
	8	'gastroplasty'/exp	3821
	9	'gastrectomy'/exp	55067
	10	'metabolic surgery'/exp	77
	11	#6 OR #7 OR #8 OR #9 OR #10	71675

12	#5 AND #11	17668
13	#4 OR #12	40613
14	**#13 AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)**	**19950**
15	'meta-analysis'/exp OR 'meta-analysis'	218902
16	#14 AND #15	401
17	'systematic review'/exp OR 'systematic review'	224675
18	#14 AND #17	533
19	random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)	1549568
20	#14 AND #19	1525
21	'cohort analysis'/exp OR (cohort NEXT/1 stud*)	440247
22	#14 AND #21	900
23	'observational study'/exp OR (observational NEXT/1 stud*)	184205
24	#14 AND #23	398
25	'case report'/exp OR (case NEXT/1 report*)	2393512
26	#14 AND #25	1256

Text words

Date	20180711		
Database	Embase (embase.com)		
Search Strategy (attention, for PubMed, check « Details »)	No.	Query	Results
	1	overweight*:ti,ab,kw	87744
	2	obesit*:ti,ab,kw	318049
	3	#1 OR #2	333962
	4	(stomach NEXT/2 stapling):ti,ab,kw	15
	5	(metabolic* NEXT/2 surg*):ti,ab,kw	1488
	6	(gastr* NEXT/2 bypass*):ti,ab,kw	18661
	7	gastroplast*:ti,ab,kw	2795
	8	gastrectomy:ti,ab,kw	36414
	9	(gastric NEXT/2 surgery):ti,ab,kw	7645
	10	'laparoscopic adjustable gastric banding':ti,ab,kw	2204
	11	lagb:ti,ab OR 'la gb':ti,ab,kw	2136
	12	(gastric NEXT/2 banding):ti,ab,kw	5238
	13	'roux-en-y gastric bypass':ti,ab,kw	10635
	14	(roux NEXT/2 y):ti,ab,kw	16853
	15	(roux NEXT/2 bypass):ti,ab,kw	44
	16	rygb:ti,ab,kw OR 'ry gb':ti,ab,kw	4966
	17	(sleeve* NEXT/2 gastrectom*):ti,ab,kw	9867
	18	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	61859
	19	#3 AND #18	15268
	20	'weight loss surgery':ti,ab,kw	1252
	21	(obesity NEXT/2 surg*):ti,ab,kw	2922

22	#19 OR #20 OR #21	17563
23	**#22 AND (2017:py OR 2018:py) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)**	**1989**
24	'meta analysis':ti,ab,kw	145708
25	#23 AND #24	50
26	'systematic review*':ti,ab,kw	150528
27	#23 AND #26	56
28	random*:ti,ab,kw OR placebo*:ti,ab,kw OR ((double NEXT/1 blind*):ti,ab,kw)	1426863
29	#23 AND #28	162
30	(cohort NEXT/1 stud*):ti,ab,kw	228823
31	#23 AND #30	98
32	(observational NEXT/1 stud*):ti,ab,kw	127518
33	#23 AND #32	40
34	(case NEXT/1 report*):ti,ab,kw	447228
35	#23 AND #34	93

Appendix 5.1.2.4. Cochrane Library

Date	20180713
Database (name + access ; e.g.: Medline OVID)	Cochrane Database of Systematic Reviews: : Issue 7 of 12, July 2018 (Cochrane Library - Wiley)
	1 MeSH descriptor: [Bariatric Surgery] this term only (1) 2 MeSH descriptor: [Gastric Bypass] this term only (2) 3 MeSH descriptor: [Gastroplasty] this term only (2) **4 1 OR 2 OR 3 (4)** 5 MeSH descriptor: [Bariatrics] this term only (0) 6 MeSH descriptor: [Bariatric Medicine] this term only (0)

Date	2018-07-13
Database	Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018 (Cochrane Library - Wiley)
	1. MeSH descriptor: [Bariatric Surgery] this term only (212) 2. MeSH descriptor: [Gastric Bypass] this term only (387) 3. MeSH descriptor: [Gastroplasty] this term only (169) **4. #1 or #2 or #3 (712)** 5. MeSH descriptor: [Bariatrics] this term only (0) 6. MeSH descriptor: [Bariatric Medicine] this term only (0)

APPENDIX 6. RELATED TO CHAPTER 7

Table 50 – Overview of associated bariatric surgery codes

code	category	description (short)
779096	apnea	CPAP
779100	apnea	CPAP
241776	bariatric surgery; bariatric reintervention	Mason/Sleeve
241780	bariatric surgery; bariatric reintervention	Mason/Sleeve
241791	bariatric surgery; bariatric reintervention	Mason/Sleeve
241802	bariatric surgery; bariatric reintervention	Mason/Sleeve
241813	bariatric surgery; bariatric reintervention	Gastric banding
241824	bariatric surgery; bariatric reintervention	Gastric banding
241835	bariatric surgery; bariatric reintervention	Scopinaro, gastric bypass, duodenal switch
241846	bariatric surgery; bariatric reintervention	Scopinaro, gastric bypass, duodenal switch
241850	bariatric surgery; bariatric reintervention	Scopinaro, gastric bypass, duodenal switch
241861	bariatric surgery; bariatric reintervention	Scopinaro, gastric bypass, duodenal switch
241533	bariatric reintervention; Proxy undo gastric band	Resection of the stomach
241544	bariatric reintervention; Proxy undo gastric band	Resection of the stomach
241555	bariatric reintervention	Degastro-gastrectomy
241566	bariatric reintervention	Degastro-gastrectomy
241581	bariatric reversal intervention;	Reconversion of the gastroduodenal transit after previous gastrectomy
241570	bariatric reversal intervention	Reconversion of the gastroduodenal transit after previous gastrectomy
243633	bariatric reversal intervention	Explorative laparotomy
243644	bariatric reversal intervention	Explorative laparotomy

220231	bariatric reversal intervention; Proxy undo gastric band	Removal of internal strange body from tissues
220242	bariatric reversal intervention; Proxy undo gastric band	Removal of internal strange body from tissues
243611	bariatric reversal intervention; Proxy undo gastric band	Surgery after perforation of abdominal organ other than appendix
243622	bariatric reversal intervention; Proxy undo gastric band	Surgery after perforation of abdominal organ other than appendix
243331	bariatric reversal intervention; Proxy undo gastric band	Surgery due to intestinal obstruction
243342	bariatric reversal intervention; Proxy undo gastric band	Surgery due to intestinal obstruction
241032	Hiatal hernia	Diaphragmhernia or hiatal hernia from abdominal side
241043	Hiatal hernia	Diaphragmhernia or hiatal hernia from abdominal side
244716	Hiatal hernia	Vagotomy with or without stomach drain, associated with complete anti-reflux treatment
244720	Hiatal hernia	Vagotomy with or without stomach drain, associated with complete anti-reflux treatment
243331	Obstruction	Surgery due to intestinal obstruction (excl. Strangulated Hernia)
243342	Obstruction	Surgery due to intestinal obstruction (excl. Strangulated Hernia)
243316	Obstruction	Treatment of small intestinal obstruction by adhesiolysis as by Noble, Childs or Baker, including gastrostomy
243320	Obstruction	Treatment of small intestinal obstruction by adhesiolysis as by Noble, Childs or Baker, including gastrostomy
241452	Other adverse events	Total gastrectomy with oesofago-jejunal anastomosis or subtotal gastrectomy with recovery of transit by interposition of an intestinal segment
241463	Other adverse events	Total gastrectomy with oesofago-jejunal anastomosis or subtotal gastrectomy with recovery of transit by interposition of an intestinal segment
241931	Other adverse events	Treatment of an incisional hernia (including redo after treatment of a primary incisional hernia and parastomal hernias)
241942	Other adverse events	Treatment of an incisional hernia (including redo after treatment of a primary incisional hernia and parastomal hernias)

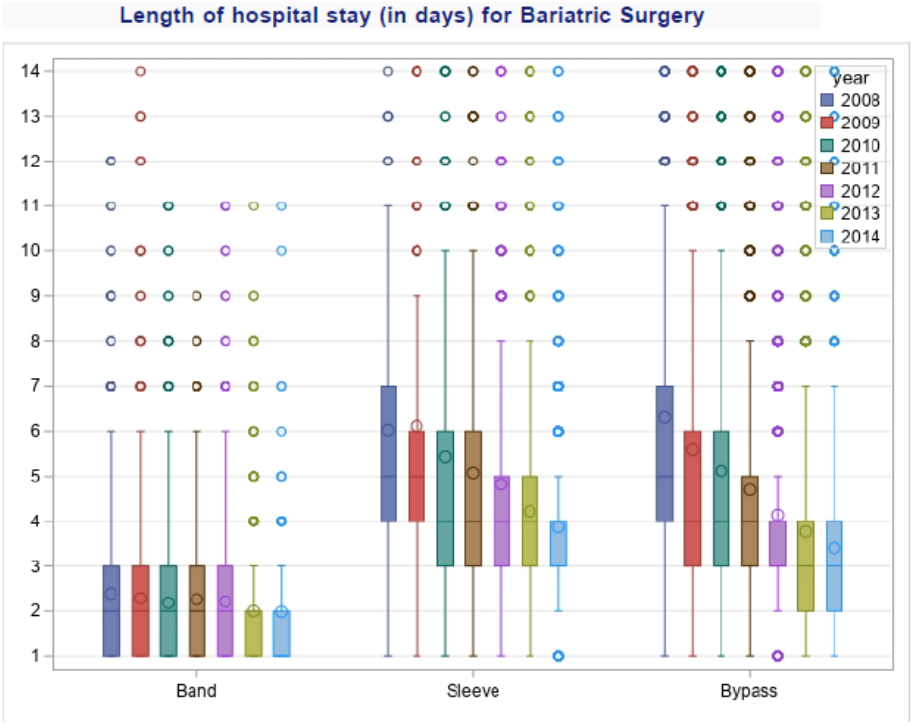
Table 51 – Diabetic medication classification

Type	Code	Name	ATC
Oral	O1	**METFORMIN - Biguanide class**	**A10BA**02
Oral	O2	**SULFONYL UREA derivates (SU)**, with inclusion of repaglinide	**A10BB**01
			A10BB02
			A10BB03
			A10BB04
			A10BB05
			A10BB06
			A10BB07
			A10BB08
			A10BB09
			A10BB10
			A10BB11
			A10BB12
		repaglinide	**A10BX02**
Oral	O3	**THIAZOLIDINEDIONES (glitazones or TZD);** only Pioglitazone	**A10BG**03
Oral	O4	**SGLT2-inhibitors**	**A10BK**01
			A10BK02
			A10BK03
Oral	O5	**DPP4-inhibitors**	**A10BH**01

			A10BH02
			A10BH03
			A10BH04
			A10BH05
Oral	O6	**Fixed dose combinations**	**A10BD**01
			A10BD02
			A10BD03
			A10BD04
			A10BD05
			A10BD06
			A10BD07
			A10BD08
			A10BD09
			A10BD10
			A10BD11
			A10BD12
			A10BD13
			A10BD14
			A10BD15
			A10BD16
			A10BD17
			A10BD18
			A10BD19
			A10BD20
			A10BD21
			A10BD22

Inject	I1	**GLP-1 analogues**	**A10BJ**01
			A10BJ02
			A10BJ03
			A10BJ04
			A10BJ05
			A10BJ06
Inject	I2	**INSULINS**	A10AB…
			A10AC…
			A10AD…
			A10AE…

Figure 46 – Boxplot hospital stay duration by bariatric surgery type



Note: Not all extremely outlying stays are graphically represented (max. 14 days) in order to allow a clear focus on the main interquartile range (IQR) of the boxplots.
*Note: Circles within the box represent the mean. Lower box border = 25th percentile. Middle straight line within box = median = 50th percentile. Upper box border = 75th percentile. Upper whisker = max observation below upper fence (red: upper fence equals 1.5*IQR above 75th percentile). Lower whisker = min observation lower fence (red: lower fence equals 1.5*IQR under 25th percentile). Circles outside box and whiskers are outliers.*

Table 52 – Mean reimbursed cost & mean length of hospital stay for bariatric surgery

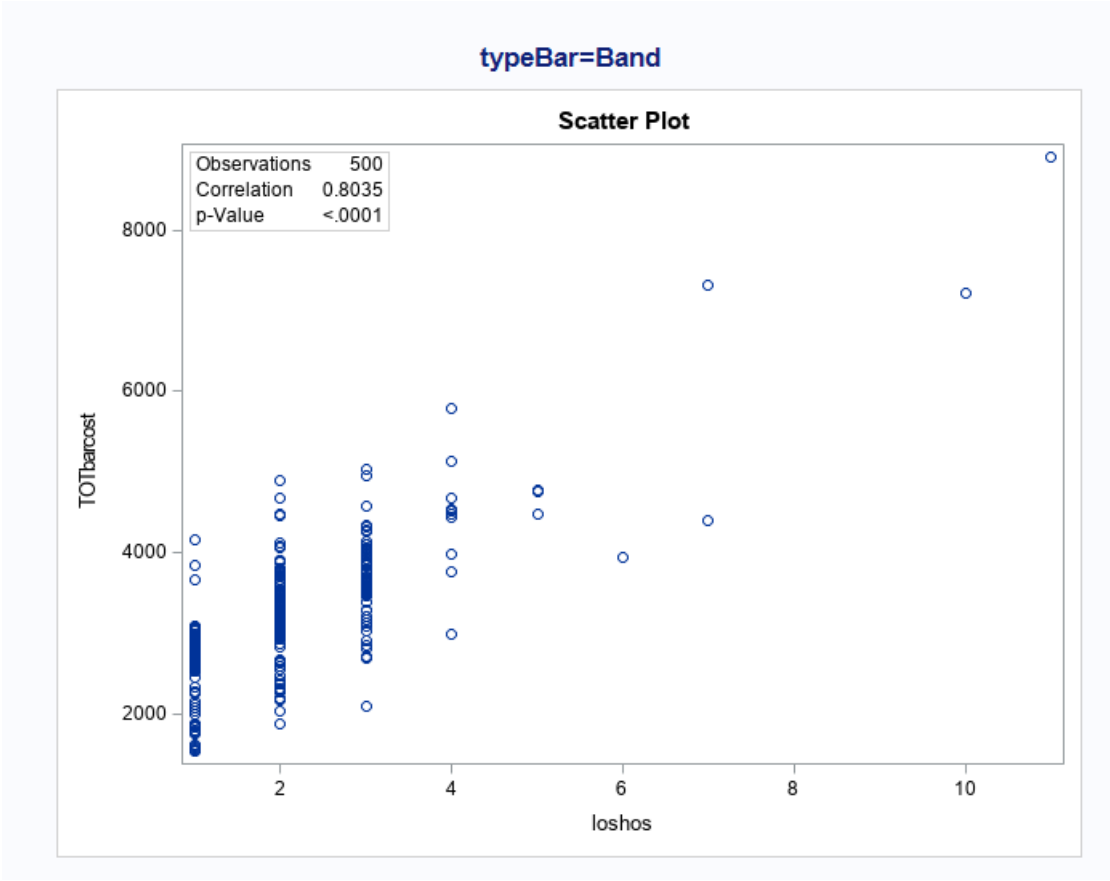
	MEAN COST REIMBURSED			MEAN LENGTH STAY		
YEAR	Band	Sleeve	Bypass	Band	Sleeve	Bypass
2008	3 212	4 949	5 993	2	6	6
2009	3 305	5 195	5 812	2	6	6
2010	3 249	5 000	5 608	2	5	5
2011	3 370	4 994	5 616	2	5	5
2012	3 459	4 924	5 368	2	5	4
2013	3 389	4 783	5 360	2	4	4
2014	3 521	4 413	5 037	2	4	3

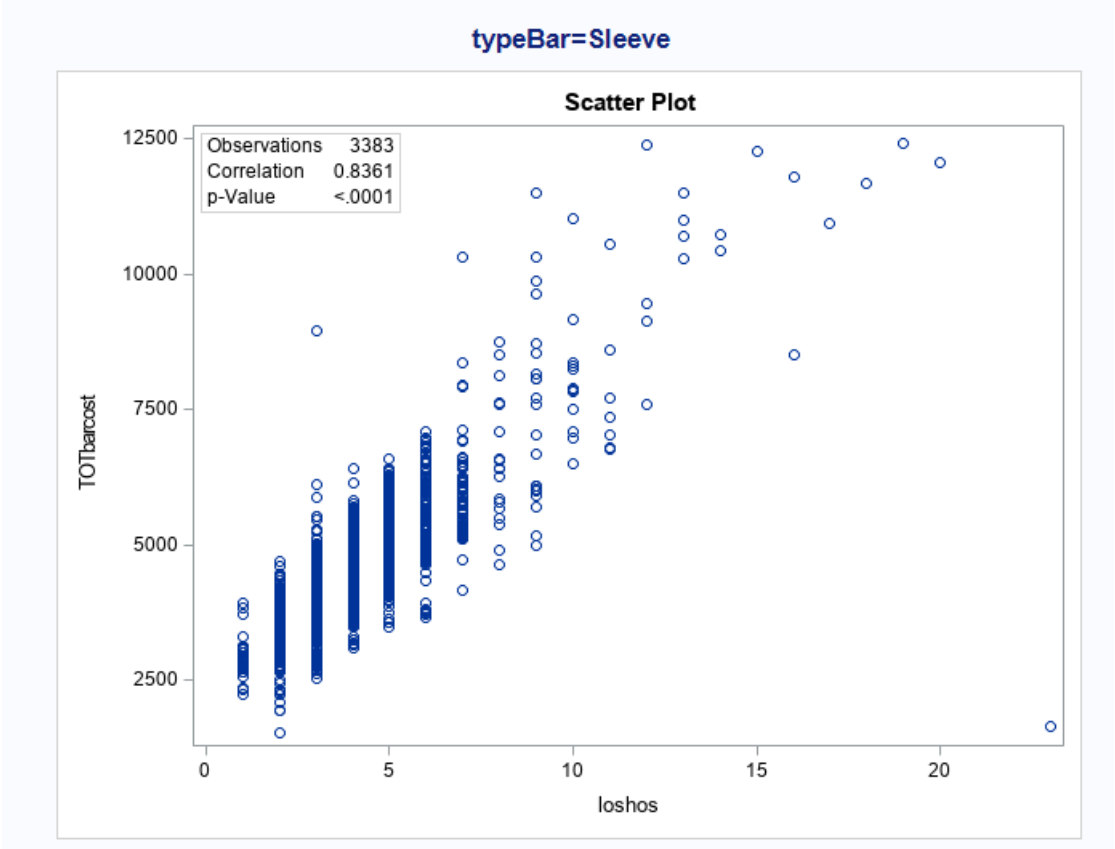
Table 53 – Dispersion measures for reimbursed bariatric surgery costs, by year and surgery type

year	type	N	5th Pctl	10th Pctl	Lower Quartile	Median	Upper Quartile	90th Pctl	95th Pctl	Mean	Std Dev	Std Error	Lower 95%	Upper 95%
2008	***Band***	1 692	2 111	2 462	2 810	3 150	3 527	3 992	4 365	3 212	865	21	3 171	3 253
	Bypass	3 784	3 953	4 117	4 438	5 046	6 141	7 325	8 805	5 993	6 084	99	5 800	6 187
	Sleeve	446	2 907	3 154	3 646	4 239	5 004	5 905	7 180	4 949	4 661	221	4 516	5 383
2009	***Band***	1 632	2 362	2 553	2 893	3 225	3 567	4 029	4 391	3 305	1 003	25	3 256	3 353
	Bypass	5 169	3 936	4 199	4 494	5 064	6 066	7 228	8 298	5 812	3 861	54	5 707	5 917
	Sleeve	818	3 172	3 414	3 886	4 377	5 105	6 169	8 361	5 195	4 105	144	4 914	5 477
2010	***Band***	1 342	2 272	2 522	2 875	3 153	3 546	4 057	4 442	3 249	909	25	3 201	3 298
	Bypass	6 049	3 867	4 154	4 452	4 995	5 911	6 952	7 921	5 608	4 505	58	5 494	5 721
	Sleeve	1 203	3 003	3 368	3 844	4 365	5 083	6 038	6 674	5 000	6 463	186	4 635	5 366

2011	***Band***	1 088	2 284	2 528	2 799	3 184	3 651	4 160	4 658	3 370	1 618	49	3 274	3 466
	Bypass	7 772	4 002	4 149	4 498	5 037	5 810	6 813	7 750	5 616	3 867	44	5 530	5 702
	Sleeve	1 604	3 235	3 419	3 823	4 426	5 274	6 260	7 171	4 994	4 162	104	4 790	5 198
2012	***Band***	885	2 374	2 556	2 893	3 197	3 605	4 215	4 764	3 459	2 520	85	3 293	3 625
	Bypass	8 307	3 889	4 044	4 430	4 905	5 620	6 599	7 429	5 368	3 614	40	5 291	5 446
	Sleeve	2 075	3 180	3 390	3 801	4 385	5 224	6 092	7 034	4 924	3 502	77	4 774	5 075
2013	***Band***	606	2 520	2 581	2 937	3 193	3 629	4 353	4 754	3 389	980	40	3 311	3 467
	Bypass	8 471	3 947	4 048	4 403	4 909	5 616	6 450	7 140	5 360	3 794	41	5 280	5 441
	Sleeve	2 620	3 251	3 455	3 832	4 323	4 969	5 982	6 749	4 783	5 265	103	4 581	4 984
2014	***Band***	501	2 180	2 549	2 687	2 821	3 383	3 875	4 273	3 522	10 500	469	2 600	4 443
	Bypass	8 590	3 742	3 937	4 153	4 608	5 226	6 068	6 729	5 037	3 330	36	4 966	5 107
	Sleeve	3 413	3 087	3 294	3 600	4 045	4 715	5 383	6 033	4 413	2 251	39	4 338	4 489

Figure 47 – Relation between reimbursed bariatric cost (under €12 500) and length of hospital stay (max. 31 days), by surgery type (in 2014)




typeBar=Sleeve
Scatter Plot
Observations 3383
Correlation 0.8361
p-Value <.0001
TOTbarcost
12500
10000
7500
5000
2500
0
5
10
15
20
loshos

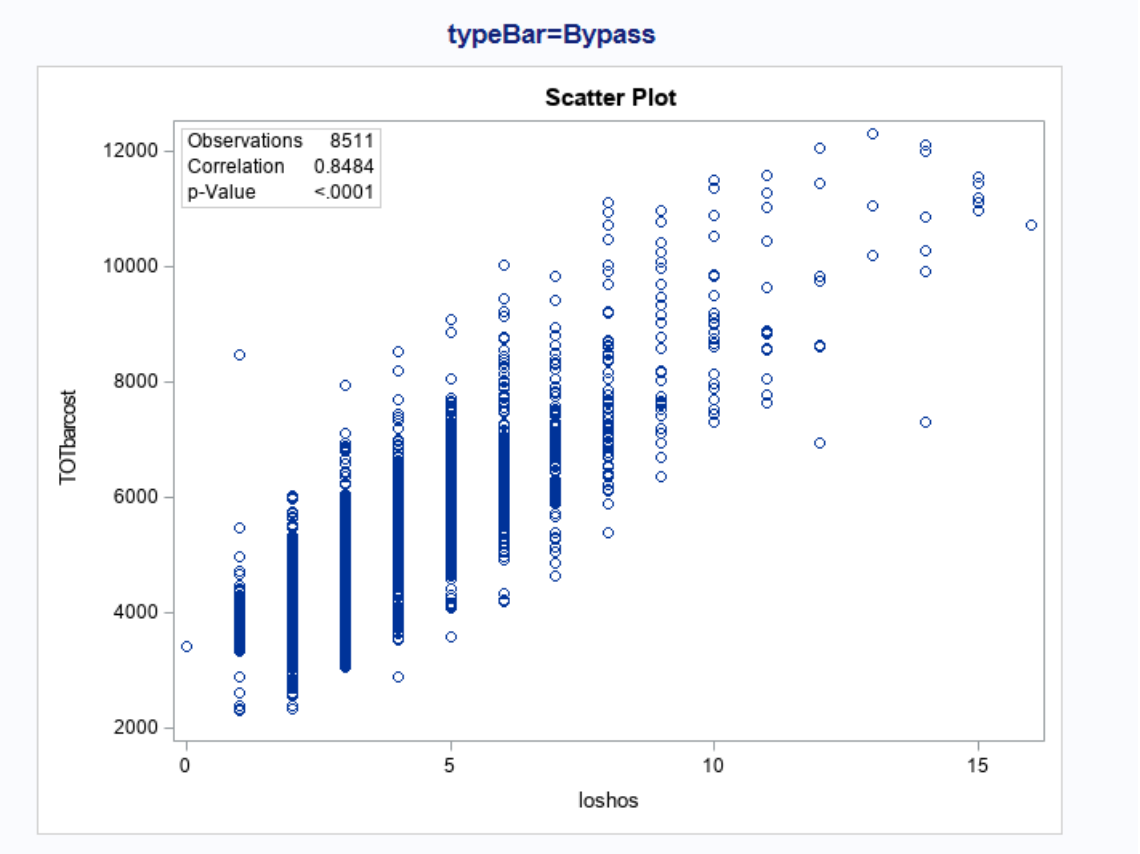

typeBar=Bypass
Scatter Plot
Observations 8511
Correlation 0.8484
p-Value <.0001
TOTbarcost
12000
10000
8000
6000
4000
2000
0
5
10
15
loshos

Table 54 – Median bariatric reimbursed cost component (RIZIV – INAMI), by year and surgery type

Type	year		HospCost	SurgeonCost	ImplantCost	PharmaCost	ClinBioCost	BloodCost
Band	2008	Median	859	970	1 178	175	3	0
Band	2009	Median	889	1 020	1 178	164	2	0
Band	2010	Median	867	991	1 180	155	1	0
Band	2011	Median	892	1 029	1 180	147	0	0
Band	2012	Median	912	1 024	1 180	136	0	0
Band	2013	Median	875	1 036	1 180	123	0	0
Band	2014	Median	503	1 033	1 143	125	0	0
Bypass	2008	Median	1 765	1 907	1 218	202	15	0
Bypass	2009	Median	1 700	1 966	1 218	192	14	0
Bypass	2010	Median	1 666	1 889	1 229	180	12	0
Bypass	2011	Median	1 681	1 945	1 229	169	11	0
Bypass	2012	Median	1 584	1 892	1 229	151	9	0
Bypass	2013	Median	1 530	1 896	1 229	137	9	0
Bypass	2014	Median	1 260	1 895	1 191	132	9	0
Sleeve	2008	Median	1 728	1 262	1 049	202	17	0
Sleeve	2009	Median	1 765	1 365	1 049	189	17	0
Sleeve	2010	Median	1 746	1 340	1 059	175	15	0
Sleeve	2011	Median	1 742	1 392	1 059	167	11	0
Sleeve	2012	Median	1 772	1 361	1 059	152	10	0
Sleeve	2013	Median	1 734	1 364	1 059	140	9	0
Sleeve	2014	Median	1 468	1 377	1 026	135	9	0

Table 55 – Mean RIZIV- INAMI reimbursed cost components for bariatric surgery by year and surgery type

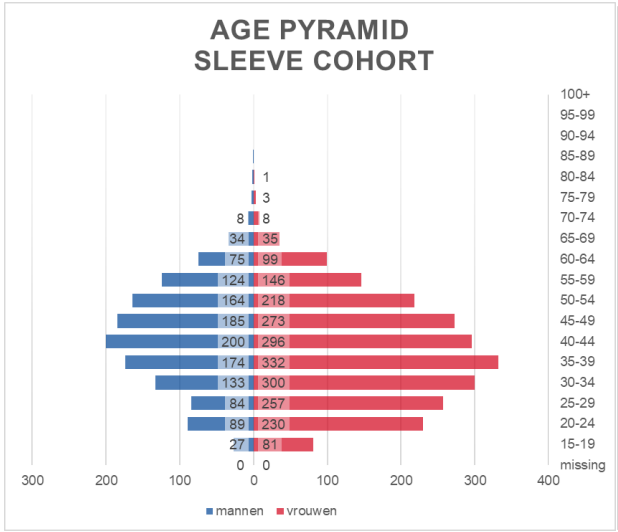
Type	year		HospStayCost	SurgPrestCost	ImplantCost	PharmaCost	ClinBioCost	BloodCost
Band	2008	Mean	**947**	1 000	1 076	180	9	0
Band	2009	Mean	**987**	1 053	1 084	170	9	1
Band	2010	Mean	**973**	1 010	1 095	160	8	3
Band	2011	Mean	**1 081**	1 056	1 062	162	8	1
Band	2012	Mean	**1 121**	1 060	1 103	165	7	3
Band	2013	Mean	**1 066**	1 048	1 115	151	6	2
Band	2014	Mean	**927**	1 186	1 063	306	26	14
Bypass	2008	Mean	**2 392**	2 114	1 073	342	45	29
Bypass	2009	Mean	**2 201**	2 162	1 113	275	41	19
Bypass	2010	Mean	**2 114**	2 049	1 160	236	34	15
Bypass	2011	Mean	**2 032**	2 108	1 185	244	30	17
Bypass	2012	Mean	**1 931**	2 039	1 150	211	23	14
Bypass	2013	Mean	**1 839**	2 082	1 189	209	25	17
Bypass	2014	Mean	**1 566**	2 068	1 169	204	21	9
Sleeve	2008	Mean	**2 223**	1 414	970	278	51	14
Sleeve	2009	Mean	**2 298**	1 527	1 020	295	42	14
Sleeve	2010	Mean	**2 224**	1 481	1 029	217	38	11
Sleeve	2011	Mean	**2 161**	1 500	1 042	238	33	20
Sleeve	2012	Mean	**2 209**	1 458	1 010	209	28	11
Sleeve	2013	Mean	**2 054**	1 454	1 033	208	24	10
Sleeve	2014	Mean	**1 762**	1 436	999	191	20	6

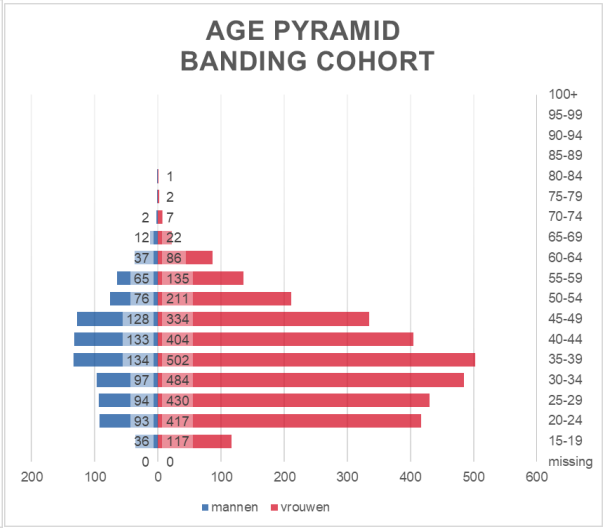
Note: For corresponding table based on *median* information (instead of *mean*), cf. Appendix 6 Table 54.

Table 56 – Quarterly year evolution of bariatric surgery in Belgium (2009 – 2016) by surgery type

Year	Quarter	Sleeve	Banding	Bypass
2009	Q1	193	433	1289
	Q2	207	420	1247
	Q3	192	409	1219
	Q4	229	387	1281
2010	Q1	290	333	1463
	Q2	263	380	1416
	Q3	309	333	1427
	Q4	321	300	1595
2011	Q1	414	310	1930
	Q2	394	296	1906
	Q3	364	236	1789
	Q4	411	230	1874
2012	Q1	498	259	2148
	Q2	467	225	1874
	Q3	511	200	1942
	Q4	570	189	2048
2013	Q1	680	175	2282
	Q2	595	148	2036
	Q3	647	119	1859
	Q4	694	121	1915
2014	Q1	858	137	2175
	Q2	806	112	1966
	Q3	790	110	1967
	Q4	873	110	2050
2015	Q1	959	95	2162
	Q2	896	86	2011
	Q3	864	94	1853
	Q4	1032	91	2001
2016	Q1	1309	99	2268
	Q2	1165	83	2117
	Q3	1083	80	1965
	Q4	1091	70	2052

Figure 48 – Age pyramid by bariatric surgery type (sleeve, banding and bypass), cohort (2009 – 2011)





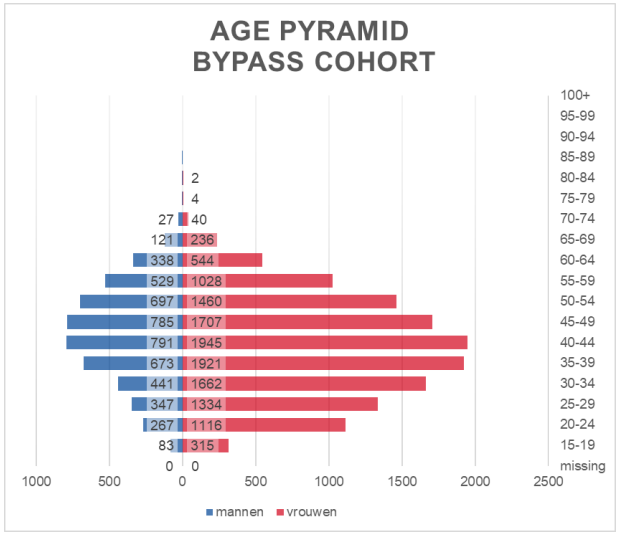


Table 57 – log linear decomposition test effects of bariatric cohort (t_1 and t_2) by age, gender, and surgery type.

***** LOG-LINEAR DECOMPOSITION saturated model ACTG *****

Effect	Wald value	df	Probability
Age (A)	*4713.75*	*11*	*0.000*
Cohort (C)	*44.95*	*1*	*0.000*
Type (T)	*9285.10*	*2*	*0.000*
Gender (G)	*1681.73*	*1*	*0.000*
AC	*48.63*	*11*	*0.000*
AT	*414.03*	*22*	*0.000*
CT	*515.39*	*2*	*0.000*
AG	*457.16*	*11*	*0.000*
CG	2.86	1	0.091
TG	*143.76*	*2*	*0.000*
ACT	28.52	22	0.159
ACG	10.63	11	0.475
ATG	25.95	22	0.254
CTG	1.52	2	0.467
ACTG	21.56	22	0.486

Table 58 – log linear decomposition parameters for bariatric cohort (t_1 and t_2) by age, gender, and surgery type

saturated model * Age (12 classes)* Cohort (orig, fut) * Type (Sleeve, Banding, Bypass) * Gender (M, F)

***LEM: log-linear and event history analysis with missing data.**

Developed by Jeroen Vermunt (c), Tilburg University, The Netherlands.

***** STATISTICS *****

X-squared = -0.0000 (0.0000)

L-squared = -0.0000 (0.0000)

Cressie-Read = -0.0000 (0.0000)

Dissimilarity index = 0.0000

Degrees of freedom = 0

Log-likelihood = -260538.73321

Number of parameters = 143 (+1)

Sample size = 60185.0

BIC(L-squared) = -0.0000

AIC(L-squared) = -0.0000

BIC(log-likelihood) = 522651.2069

AIC(log-likelihood) = 521363.4664

***** LOG-LINEAR PARAMETERS *****

*** TABLE ACTG ***

effect beta std err z-value exp(beta) Wald df prob

main	5.2082		182.7626			
A						
1	-0.8199	0.0381	-21.509	0.4405		
2	0.3836	0.0228	16.837	1.4675		
3	0.4715	0.0226	20.837	1.6024		
4	0.6205	0.0217	28.579	1.8599		
5	0.7677	0.0214	35.929	2.1548		
6	0.8563	0.0201	42.523	2.3544		
7	0.7752	0.0202	38.354	2.1710		
8	0.5374	0.0225	23.920	1.7115		
9	0.2182	0.0254	8.575	1.2439		
10	-0.2673	0.0311	-8.589	0.7655		
11	-1.1561	0.0476	-24.275	0.3147		
12	-2.3871		0.0919	4713.75	11	0.000
C						
1	-0.0722	0.0108	-6.704	0.9303		
2	0.0722		1.0749	44.95	1	0.000
T						
1	-0.1472	0.0141	-10.439	0.8631		
2	-0.9888	0.0188	-52.468	0.3720		
3	1.1360		3.1143	9285.10	2	0.000
G						
1	-0.4418	0.0108	-41.009	0.6429		
2	0.4418		1.5555	1681.73	1	0.000
AC						
1 1	0.0518	0.0381	1.359	1.0532		
1 2	-0.0518		0.9495			
2 1	-0.0033	0.0228	-0.147	0.9967		
2 2	0.0033		1.0033			
3 1	-0.0021	0.0226	-0.092	0.9979		
3 2	0.0021		1.0021			
4 1	0.0528	0.0217	2.431	1.0542		
4 2	-0.0528		0.9486			
5 1	0.1218	0.0214	5.702	1.1296		
5 2	-0.1218		0.8853			
6 1	0.0289	0.0201	1.435	1.0293		
6 2	-0.0289		0.9715			
7 1	0.0224	0.0202	1.108	1.0226		
7 2	-0.0224		0.9779			
8 1	-0.0067	0.0225	-0.296	0.9934		
8 2	0.0067		1.0067			
9 1	-0.0059	0.0255	-0.230	0.9942		
9 2	0.0059		1.0059			
10 1	-0.0187	0.0311	-0.602	0.9814		
10 2	0.0187		1.0189			
11 1	-0.1603	0.0476	-3.365	0.8519		

11 2	0.1603		1.1739				
12 1	-0.0807		0.9225				
12 2	0.0807		1.0841	48.63	11	0.000	
AT							
1 1	-0.0846	0.0534	-1.583	0.9189			
1 2	0.3755	0.0626	5.997	1.4558			
1 3	-0.2910		0.7475				
2 1	-0.0249	0.0315	-0.792	0.9754			
2 2	0.3205	0.0379	8.467	1.3778			
2 3	-0.2956		0.7441				
3 1	-0.0830	0.0313	-2.652	0.9203			
3 2	0.2324	0.0380	6.116	1.2616			
3 3	-0.1494		0.8612				
4 1	-0.0392	0.0290	-1.353	0.9615			
4 2	0.1297	0.0375	3.462	1.1385			
4 3	-0.0905		0.9135				
5 1	-0.0166	0.0278	-0.596	0.9836			
5 2	0.0156	0.0376	0.413	1.0157			
5 3	0.0010		1.0010				
6 1	-0.0231	0.0265	-0.873	0.9771			
6 2	-0.0464	0.0353	-1.316	0.9546			
6 3	0.0696		1.0720				
7 1	-0.0361	0.0269	-1.342	0.9646			
7 2	-0.0297	0.0352	-0.845	0.9707			
7 3	0.0658		1.0680				
8 1	0.0127	0.0294	0.431	1.0128			
8 2	-0.1865	0.0396	-4.706	0.8299			
8 3	0.1738		1.1898				
9 1	0.0119	0.0333	0.357	1.0120			
9 2	-0.2063	0.0449	-4.593	0.8136			
9 3	0.1944		1.2145				
10 1	0.0335	0.0406	0.825	1.0341			
10 2	-0.1901	0.0550	-3.458	0.8269			
10 3	0.1566		1.1695				
11 1	0.0765	0.0614	1.245	1.0795			
11 2	-0.2991	0.0849	-3.525	0.7415			
11 3	0.2227		1.2494				
12 1	0.1730		1.1888				
12 2	-0.1156		0.8909				
12 3	-0.0574		0.9442	414.03	22	0.000	
CT							
1 1	-0.3062	0.0141	-21.712	0.7362			
1 2	0.3961	0.0188	21.016	1.4860			
1 3	-0.0899		0.9140				
2 1	0.3062		1.3583				
2 2	-0.3961		0.6729				
2 3	0.0899		1.0941	515.39	2	0.000	
AG							
1 1	-0.2021	0.0381	-5.303	0.8170			

1 2	0.2021		1.2240			
2 1	-0.2308	0.0228	-10.129	0.7939		
2 2	0.2308		1.2596			
3 1	-0.2171	0.0226	-9.592	0.8049		
3 2	0.2171		1.2424			
4 1	-0.1849	0.0217	-8.515	0.8312		
4 2	0.1849		1.2031			
5 1	-0.1210	0.0214	-5.663	0.8860		
5 2	0.1210		1.1286			
6 1	-0.0014	0.0201	-0.067	0.9986		
6 2	0.0014		1.0014			
7 1	0.0662	0.0202	3.275	1.0684		
7 2	-0.0662		0.9359			
8 1	0.1037	0.0225	4.615	1.1092		
8 2	-0.1037		0.9015			
9 1	0.1684	0.0254	6.616	1.1834		
9 2	-0.1684		0.8450			
10 1	0.1952	0.0311	6.274	1.2156		
10 2	-0.1952		0.8226			
11 1	0.2028	0.0476	4.257	1.2248		
11 2	-0.2028		0.8165			
12 1	0.2210		1.2474			
12 2	-0.2210		0.8017	457.16	11	0.000
CG						
1 1	0.0182	0.0108	1.692	1.0184		
1 2	-0.0182		0.9819			
2 1	-0.0182		0.9819			
2 2	0.0182		1.0184	2.86	1	0.091
TG						
1 1	0.1637	0.0141	11.608	1.1779		
1 2	-0.1637		0.8490			
2 1	-0.1337	0.0188	-7.096	0.8748		
2 2	0.1337		1.1431			
3 1	-0.0300		0.9705			
3 2	0.0300		1.0304	143.76	2	0.000
ACT						
1 1 1	0.0153	0.0534	0.286	1.0154		
1 1 2	0.0221	0.0626	0.353	1.0223		
1 1 3	-0.0373		0.9633			
1 2 1	-0.0153		0.9849			
1 2 2	-0.0221		0.9782			
1 2 3	0.0373		1.0381			
2 1 1	-0.0745	0.0315	-2.365	0.9283		
2 1 2	0.0388	0.0379	1.025	1.0396		
2 1 3	0.0356		1.0363			
2 2 1	0.0745		1.0773			
2 2 2	-0.0388		0.9619			
2 2 3	-0.0356		0.9650			
3 1 1	-0.0790	0.0313	-2.522	0.9241		

3 1 2	0.0584	0.0380	1.537	1.0602
3 1 3	0.0205			1.0207
3 2 1	0.0790			1.0822
3 2 2	-0.0584			0.9432
3 2 3	-0.0205			0.9797
4 1 1	-0.0196	0.0290	-0.675	0.9806
4 1 2	0.0321	0.0375	0.857	1.0326
4 1 3	-0.0125			0.9875
4 2 1	0.0196			1.0198
4 2 2	-0.0321			0.9684
4 2 3	0.0125			1.0126
5 1 1	-0.0734	0.0278	-2.637	0.9293
5 1 2	0.1098	0.0376	2.918	1.1161
5 1 3	-0.0365			0.9642
5 2 1	0.0734			1.0761
5 2 2	-0.1098			0.8960
5 2 3	0.0365			1.0371
6 1 1	-0.0502	0.0265	-1.895	0.9510
6 1 2	0.0639	0.0353	1.810	1.0660
6 1 3	-0.0137			0.9864
6 2 1	0.0502			1.0515
6 2 2	-0.0639			0.9381
6 2 3	0.0137			1.0138
7 1 1	-0.0291	0.0269	-1.082	0.9713
7 1 2	0.0205	0.0352	0.582	1.0207
7 1 3	0.0086			1.0087
7 2 1	0.0291			1.0295
7 2 2	-0.0205			0.9798
7 2 3	-0.0086			0.9914
8 1 1	0.0163	0.0294	0.555	1.0164
8 1 2	-0.0462	0.0396	-1.167	0.9548
8 1 3	0.0299			1.0304
8 2 1	-0.0163			0.9838
8 2 2	0.0462			1.0473
8 2 3	-0.0299			0.9705
9 1 1	-0.0048	0.0333	-0.144	0.9952
9 1 2	-0.0096	0.0449	-0.213	0.9905
9 1 3	0.0144			1.0145
9 2 1	0.0048			1.0048
9 2 2	0.0096			1.0096
9 2 3	-0.0144			0.9857
10 1 1	0.0263	0.0406	0.647	1.0266
10 1 2	-0.0346	0.0550	-0.629	0.9660
10 1 3	0.0083			1.0083
10 2 1	-0.0263			0.9741
10 2 2	0.0346			1.0352
10 2 3	-0.0083			0.9918
11 1 1	0.0983	0.0615	1.599	1.1033
11 1 2	-0.1398	0.0849	-1.647	0.8696
11 1 3	0.0415			1.0423
11 2 1	-0.0983			0.9064
11 2 2	0.1398			1.1500

11 2 3	-0.0415		0.9594			
12 1 1	0.1743		1.1904			
12 1 2	-0.1155		0.8910			
12 1 3	-0.0589		0.9428			
12 2 1	-0.1743		0.8400			
12 2 2	0.1155		1.1224			
12 2 3	0.0589		1.0606	28.52	22	0.159

ACG

1 1 1	0.0238	0.0381	0.626	1.0241
1 1 2	-0.0238		0.9764	
1 2 1	-0.0238		0.9764	
1 2 2	0.0238		1.0241	
2 1 1	0.0076	0.0228	0.335	1.0077
2 1 2	-0.0076		0.9924	
2 2 1	-0.0076		0.9924	
2 2 2	0.0076		1.0077	
3 1 1	-0.0236	0.0226	-1.044	0.9767
3 1 2	0.0236		1.0239	
3 2 1	0.0236		1.0239	
3 2 2	-0.0236		0.9767	
4 1 1	-0.0161	0.0217	-0.744	0.9840
4 1 2	0.0161		1.0163	
4 2 1	0.0161		1.0163	
4 2 2	-0.0161		0.9840	
5 1 1	0.0419	0.0214	1.962	1.0428
5 1 2	-0.0419		0.9589	
5 2 1	-0.0419		0.9589	
5 2 2	0.0419		1.0428	
6 1 1	0.0244	0.0201	1.213	1.0247
6 1 2	-0.0244		0.9759	
6 2 1	-0.0244		0.9759	
6 2 2	0.0244		1.0247	
7 1 1	0.0032	0.0202	0.157	1.0032
7 1 2	-0.0032		0.9968	
7 2 1	-0.0032		0.9968	
7 2 2	0.0032		1.0032	
8 1 1	-0.0210	0.0225	-0.934	0.9792
8 1 2	0.0210		1.0212	
8 2 1	0.0210		1.0212	
8 2 2	-0.0210		0.9792	
9 1 1	-0.0046	0.0255	-0.180	0.9954
9 1 2	0.0046		1.0046	
9 2 1	0.0046		1.0046	
9 2 2	-0.0046		0.9954	
10 1 1	-0.0378	0.0311	-1.216	0.9629
10 1 2	0.0378		1.0386	
10 2 1	0.0378		1.0386	
10 2 2	-0.0378		0.9629	
11 1 1	0.0036	0.0476	0.075	1.0036
11 1 2	-0.0036		0.9964	
11 2 1	-0.0036		0.9964	

11 2 2	0.0036		1.0036			
12 1 1	-0.0014		0.9986			
12 1 2	0.0014		1.0014			
12 2 1	0.0014		1.0014			
12 2 2	-0.0014		0.9986	10.63	11	0.475

ATG

1 1 1	-0.0724	0.0534	-1.356	0.9301
1 1 2	0.0724		1.0751	
1 2 1	0.0768	0.0626	1.227	1.0798
1 2 2	-0.0768		0.9261	
1 3 1	-0.0044		0.9956	
1 3 2	0.0044		1.0044	
2 1 1	-0.0509	0.0315	-1.617	0.9504
2 1 2	0.0509		1.0522	
2 2 1	0.0950	0.0379	2.510	1.0997
2 2 2	-0.0950		0.9094	
2 3 1	-0.0441		0.9568	
2 3 2	0.0441		1.0451	
3 1 1	-0.0799	0.0313	-2.551	0.9232
3 1 2	0.0799		1.0831	
3 2 1	0.0553	0.0380	1.454	1.0568
3 2 2	-0.0553		0.9462	
3 3 1	0.0246		1.0249	
3 3 2	-0.0246		0.9757	
4 1 1	0.0265	0.0290	0.916	1.0269
4 1 2	-0.0265		0.9738	
4 2 1	-0.0298	0.0375	-0.794	0.9707
4 2 2	0.0298		1.0302	
4 3 1	0.0032		1.0032	
4 3 2	-0.0032		0.9968	
5 1 1	0.0100	0.0278	0.359	1.0100
5 1 2	-0.0100		0.9901	
5 2 1	-0.0517	0.0376	-1.374	0.9496
5 2 2	0.0517		1.0531	
5 3 1	0.0417		1.0426	
5 3 2	-0.0417		0.9591	
6 1 1	0.0032	0.0265	0.121	1.0032
6 1 2	-0.0032		0.9968	
6 2 1	-0.0413	0.0353	-1.169	0.9596
6 2 2	0.0413		1.0421	
6 3 1	0.0381		1.0388	
6 3 2	-0.0381		0.9627	
7 1 1	-0.0093	0.0269	-0.345	0.9908
7 1 2	0.0093		1.0093	
7 2 1	0.0007	0.0352	0.020	1.0007
7 2 2	-0.0007		0.9993	
7 3 1	0.0086		1.0086	
7 3 2	-0.0086		0.9914	
8 1 1	-0.0041	0.0294	-0.139	0.9959
8 1 2	0.0041		1.0041	
8 2 1	0.0025	0.0396	0.063	1.0025

8 2 2	-0.0025		0.9975	
8 3 1	0.0016		1.0016	
8 3 2	-0.0016		0.9984	
9 1 1	-0.0186	0.0333	-0.558	0.9816
9 1 2	0.0186		1.0188	
9 2 1	0.0407	0.0449	0.905	1.0415
9 2 2	-0.0407		0.9602	
9 3 1	-0.0221		0.9782	
9 3 2	0.0221		1.0223	
10 1 1	0.0272	0.0406	0.670	1.0276
10 1 2	-0.0272		0.9731	
10 2 1	-0.0308	0.0550	-0.560	0.9697
10 2 2	0.0308		1.0312	
10 3 1	0.0035		1.0035	
10 3 2	-0.0035		0.9965	
11 1 1	0.0290	0.0615	0.472	1.0295
11 1 2	-0.0290		0.9714	
11 2 1	0.0024	0.0849	0.028	1.0024
11 2 2	-0.0024		0.9976	
11 3 1	-0.0314		0.9691	
11 3 2	0.0314		1.0319	
12 1 1	0.1392		1.1493	
12 1 2	-0.1392		0.8701	
12 2 1	-0.1198		0.8871	
12 2 2	0.1198		1.1273	
12 3 1	-0.0194		0.9808	
12 3 2	0.0194		1.0196	25.95 22 0.254

CTG

1 1 1	0.0095	0.0141	0.674	1.0096
1 1 2	-0.0095		0.9905	
1 2 1	0.0025	0.0188	0.131	1.0025
1 2 2	-0.0025		0.9975	
1 3 1	-0.0120		0.9881	
1 3 2	0.0120		1.0120	
2 1 1	-0.0095		0.9905	
2 1 2	0.0095		1.0096	
2 2 1	-0.0025		0.9975	
2 2 2	0.0025		1.0025	
2 3 1	0.0120		1.0120	
2 3 2	-0.0120		0.9881	1.52 2 0.467

ACTG

1 1 1 1	-0.0483	0.0534	-0.904	0.9529
1 1 1 2	0.0483		1.0495	
1 1 2 1	0.0670	0.0626	1.069	1.0693
1 1 2 2	-0.0670		0.9352	
1 1 3 1	-0.0187		0.9815	
1 1 3 2	0.0187		1.0189	
1 2 1 1	0.0483		1.0495	
1 2 1 2	-0.0483		0.9529	
1 2 2 1	-0.0670		0.9352	

1 2 2 2	0.0670			1.0693
1 2 3 1	0.0187			1.0189
1 2 3 2	-0.0187			0.9815
2 1 1 1	0.0497	0.0315	1.577	1.0509
2 1 1 2	-0.0497			0.9516
2 1 2 1	-0.0673	0.0379	-1.777	0.9349
2 1 2 2	0.0673			1.0696
2 1 3 1	0.0176			1.0178
2 1 3 2	-0.0176			0.9825
2 2 1 1	-0.0497			0.9516
2 2 1 2	0.0497			1.0509
2 2 2 1	0.0673			1.0696
2 2 2 2	-0.0673			0.9349
2 2 3 1	-0.0176			0.9825
2 2 3 2	0.0176			1.0178
3 1 1 1	0.0117	0.0313	0.375	1.0118
3 1 1 2	-0.0117			0.9883
3 1 2 1	-0.0200	0.0380	-0.526	0.9802
3 1 2 2	0.0200			1.0202
3 1 3 1	0.0083			1.0083
3 1 3 2	-0.0083			0.9918
3 2 1 1	-0.0117			0.9883
3 2 1 2	0.0117			1.0118
3 2 2 1	0.0200			1.0202
3 2 2 2	-0.0200			0.9802
3 2 3 1	-0.0083			0.9918
3 2 3 2	0.0083			1.0083
4 1 1 1	0.0181	0.0290	0.624	1.0183
4 1 1 2	-0.0181			0.9821
4 1 2 1	-0.0180	0.0375	-0.482	0.9821
4 1 2 2	0.0180			1.0182
4 1 3 1	-0.0000			1.0000
4 1 3 2	0.0000			1.0000
4 2 1 1	-0.0181			0.9821
4 2 1 2	0.0181			1.0183
4 2 2 1	0.0180			1.0182
4 2 2 2	-0.0180			0.9821
4 2 3 1	0.0000			1.0000
4 2 3 2	-0.0000			1.0000
5 1 1 1	-0.0037	0.0278	-0.131	0.9964
5 1 1 2	0.0037			1.0037
5 1 2 1	0.0253	0.0376	0.671	1.0256
5 1 2 2	-0.0253			0.9751
5 1 3 1	-0.0216			0.9786
5 1 3 2	0.0216			1.0218
5 2 1 1	0.0037			1.0037
5 2 1 2	-0.0037			0.9964
5 2 2 1	-0.0253			0.9751
5 2 2 2	0.0253			1.0256
5 2 3 1	0.0216			1.0218
5 2 3 2	-0.0216			0.9786
6 1 1 1	0.0280	0.0265	1.057	1.0284

6 1 1 2	-0.0280		0.9724	
6 1 2 1	0.0175	0.0353	0.495	1.0176
6 1 2 2	-0.0175		0.9827	
6 1 3 1	-0.0455		0.9555	
6 1 3 2	0.0455		1.0465	
6 2 1 1	-0.0280		0.9724	
6 2 1 2	0.0280		1.0284	
6 2 2 1	-0.0175		0.9827	
6 2 2 2	0.0175		1.0176	
6 2 3 1	0.0455		1.0465	
6 2 3 2	-0.0455		0.9555	
7 1 1 1	-0.0043	0.0269	-0.161	0.9957
7 1 1 2	0.0043		1.0043	
7 1 2 1	0.0052	0.0352	0.148	1.0052
7 1 2 2	-0.0052		0.9948	
7 1 3 1	-0.0009		0.9991	
7 1 3 2	0.0009		1.0009	
7 2 1 1	0.0043		1.0043	
7 2 1 2	-0.0043		0.9957	
7 2 2 1	-0.0052		0.9948	
7 2 2 2	0.0052		1.0052	
7 2 3 1	0.0009		1.0009	
7 2 3 2	-0.0009		0.9991	
8 1 1 1	0.0294	0.0294	1.001	1.0298
8 1 1 2	-0.0294		0.9710	
8 1 2 1	-0.0409	0.0396	-1.033	0.9599
8 1 2 2	0.0409		1.0418	
8 1 3 1	0.0115		1.0116	
8 1 3 2	-0.0115		0.9885	
8 2 1 1	-0.0294		0.9710	
8 2 1 2	0.0294		1.0298	
8 2 2 1	0.0409		1.0418	
8 2 2 2	-0.0409		0.9599	
8 2 3 1	-0.0115		0.9885	
8 2 3 2	0.0115		1.0116	
9 1 1 1	0.0235	0.0333	0.704	1.0237
9 1 1 2	-0.0235		0.9768	
9 1 2 1	-0.0150	0.0449	-0.335	0.9851
9 1 2 2	0.0150		1.0152	
9 1 3 1	-0.0084		0.9916	
9 1 3 2	0.0084		1.0084	
9 2 1 1	-0.0235		0.9768	
9 2 1 2	0.0235		1.0237	
9 2 2 1	0.0150		1.0152	
9 2 2 2	-0.0150		0.9851	
9 2 3 1	0.0084		1.0084	
9 2 3 2	-0.0084		0.9916	
10 1 1 1	-0.0731	0.0406	-1.800	0.9295
10 1 1 2	0.0731		1.0759	
10 1 2 1	0.0065	0.0550	0.118	1.0065
10 1 2 2	-0.0065		0.9935	
10 1 3 1	0.0666		1.0689	

10 1 3 2	-0.0666		0.9355	
10 2 1 1	0.0731		1.0759	
10 2 1 2	-0.0731		0.9295	
10 2 2 1	-0.0065		0.9935	
10 2 2 2	0.0065		1.0065	
10 2 3 1	-0.0666		0.9355	
10 2 3 2	0.0666		1.0689	
11 1 1 1	0.0004	0.0615	0.007	1.0004
11 1 1 2	-0.0004		0.9996	
11 1 2 1	0.0431	0.0849	0.507	1.0440
11 1 2 2	-0.0431		0.9579	
11 1 3 1	-0.0435		0.9574	
11 1 3 2	0.0435		1.0444	
11 2 1 1	-0.0004		0.9996	
11 2 1 2	0.0004		1.0004	
11 2 2 1	-0.0431		0.9579	
11 2 2 2	0.0431		1.0440	
11 2 3 1	0.0435		1.0444	
11 2 3 2	-0.0435		0.9574	
12 1 1 1	-0.0314		0.9691	
12 1 1 2	0.0314		1.0319	
12 1 2 1	-0.0032		0.9968	
12 1 2 2	0.0032		1.0032	
12 1 3 1	0.0346		1.0352	
12 1 3 2	-0.0346		0.9660	
12 2 1 1	0.0314		1.0319	
12 2 1 2	-0.0314		0.9691	
12 2 2 1	0.0032		1.0032	
12 2 2 2	-0.0032		0.9968	
12 2 3 1	-0.0346		0.9660	
12 2 3 2	0.0346		1.0352	21.56 22 0.486

Table 59 – log linear decomposition parameters for bariatric comorbidities (OSAS, Hypertension, Diabetes) by BMI class (35-39; 40+)

***LEM: log-linear and event history analysis with missing data.**

Developed by Jeroen Vermunt (c), Tilburg University, The Netherlands.

Saturated model

*** BMI (35-39, 40+) * OSAS (0,1) * HYP (0,1) * DIAB (0,1)**

***** STATISTICS *****

X-squared = -0.0000 (0.0000)
L-squared = -0.0000 (0.0000)
Cressie-Read = -0.0000 (0.0000)
Dissimilarity index = 0.0000
Degrees of freedom = 0
Log-likelihood = -37128.96206
Number of parameters = 15 (+1)
Sample size = 20532.0
BIC(L-squared) = -0.0000
AIC(L-squared) = -0.0000
BIC(log-likelihood) = 74406.8702
AIC(log-likelihood) = 74287.9241

***** LOG-LINEAR PARAMETERS *****

*** TABLE BOHD ***

effect	*beta*	*std err*	*z-value*	*exp(beta)*	*Wald*	*df*	*prob*
main	6.1369			462.6308			
B							
1	-0.5598	0.0171	-32.754	0.5713			
2	0.5598			1.7503	1072.84	1	0.000
O							
1	1.0844	0.0171	63.433	2.9576			
2	-1.0844			0.3381	4023.74	1	0.000
H							
1	0.0285	0.0171	1.665	1.0289			
2	-0.0285			0.9719	2.77	1	0.096
D							
1	0.4901	0.0171	28.672	1.6325			
2	-0.4901			0.6125	822.06	1	0.000
BO							
1 1	-0.0375	0.0171	-2.197	0.9632			
1 2	0.0375			1.0383			
2 1	0.0375			1.0383			
2 2	-0.0375			0.9632	4.83	1	0.028

BH						
1 1	0.0832	0.0171	4.866	1.0867		
1 2	-0.0832			0.9202		
2 1	-0.0832			0.9202		
2 2	0.0832			1.0867	23.68	1 0.000
OH						
1 1	0.1375	0.0171	8.045	1.1474		
1 2	-0.1375			0.8715		
2 1	-0.1375			0.8715		
2 2	0.1375			1.1474	64.72	1 0.000
BD						
1 1	-0.1394	0.0171	-8.155	0.8699		
1 2	0.1394			1.1496		
2 1	0.1394			1.1496		
2 2	-0.1394			0.8699	66.51	1 0.000
OD						
1 1	0.0785	0.0171	4.595	1.0817		
1 2	-0.0785			0.9245		
2 1	-0.0785			0.9245		
2 2	0.0785			1.0817	21.11	1 0.000
HD						
1 1	0.2901	0.0171	16.971	1.3366		
1 2	-0.2901			0.7482		
2 1	-0.2901			0.7482		
2 2	0.2901			1.3366	288.00	1 0.000
BOH						
1 1 1	-0.0541	0.0171	-3.164	0.9474		
1 1 2	0.0541			1.0556		
1 2 1	0.0541			1.0556		
1 2 2	-0.0541			0.9474		
2 1 1	0.0541			1.0556		
2 1 2	-0.0541			0.9474		
2 2 1	-0.0541			0.9474		
2 2 2	0.0541			1.0556	10.01	1 0.002
BOD						
1 1 1	-0.1590	0.0171	-9.305	0.8530		
1 1 2	0.1590			1.1724		
1 2 1	0.1590			1.1724		
1 2 2	-0.1590			0.8530		
2 1 1	0.1590			1.1724		
2 1 2	-0.1590			0.8530		
2 2 1	-0.1590			0.8530		
2 2 2	0.1590			1.1724	86.58	1 0.000
BHD						
1 1 1	-0.0029	0.0171	-0.167	0.9972		

1 1 2	0.0029		1.0029		
1 2 1	0.0029		1.0029		
1 2 2	-0.0029		0.9972		
2 1 1	0.0029		1.0029		
2 1 2	-0.0029		0.9972		
2 2 1	-0.0029		0.9972		
2 2 2	0.0029		1.0029	0.03	1 0.867
OHD					
1 1 1	0.0362	0.0171	2.119	1.0369	
1 1 2	-0.0362		0.9644		
1 2 1	-0.0362		0.9644		
1 2 2	0.0362		1.0369		
2 1 1	-0.0362		0.9644		
2 1 2	0.0362		1.0369		
2 2 1	0.0362		1.0369		
2 2 2	-0.0362		0.9644	4.49	1 0.034
BOHD					
1 1 1 1	-0.0476	0.0171	-2.783	0.9536	
1 1 1 2	0.0476		1.0487		
1 1 2 1	0.0476		1.0487		
1 1 2 2	-0.0476		0.9536		
1 2 1 1	0.0476		1.0487		
1 2 1 2	-0.0476		0.9536		
1 2 2 1	-0.0476		0.9536		
1 2 2 2	0.0476		1.0487		
2 1 1 1	0.0476		1.0487		
2 1 1 2	-0.0476		0.9536		
2 1 2 1	-0.0476		0.9536		
2 1 2 2	0.0476		1.0487		
2 2 1 1	-0.0476		0.9536		
2 2 1 2	0.0476		1.0487		
2 2 2 1	0.0476		1.0487		
2 2 2 2	-0.0476		0.9536	7.74	1 0.005

Table 60 – Test differences in pre -operative medication use depending on bariatric surgery type

Pre op medication	*χ^2 -value (df)*	*p- value*
180 Metformin	6.90 (2)	0.032
Insulin	48.58 (2)	0.000
90 antidiabetic	33.81 (2)	0.000
90 antidepressant	16.68 (2)	0.000
90 lipid lowering	75.27 (2)	0.000
cardiovascular	115.94 (2)	0.000

Table 61 – Medication group ATC definitions.

Medication group	Description
Single Metformin use	Metformin (A10BA02) use equivalent of 180 daily doses or more in the year before surgery, without any other antidiabetics.
Insulin use	Insulin use in the year before surgery.
Antidiabetic medication	Use equivalent of 90 daily doses or more oral antidiabetic medication or GLP 1 analogues (cf. Table 8 in appendix for complete ATC code list) in the year before surgery.
Antidepressant medication	Antidepressant medication (ATC N06A) equivalent of 90 daily doses or more in the year before surgery.
Lipid lowering medication	Lipid lowering medication (C10****) equivalent of 90 daily doses or more in the year before surgery.
Cardiovascular medication group	Use of 90 daily doses or more of at least one of the following medication groups: C2 –anti hypertensives; C3 – diuretics; C7 - beta blocking agents; C8 -calcium channel blockers; C9 - renin angiotensin agents.

Table 62 – Reference: evolution medication use in matched control groups

name		START	1P	2P	3P	4P	5P	START	1P	2P	3P	4P	5P
Insuline	RQ_1	51 000	48 268	47 439	46 908	46 494	45 466	**100%**	**95%**	**93%**	**92%**	**91%**	**89%**
Diabetesmedication excl insuline	RQ_2	39 672	34 388	32 680	31 232	29 890	27 856	**100%**	**87%**	**82%**	**79%**	**75%**	**70%**
Antidepressives	RQ_3	444 276	334 637	308 651	295 920	288 345	276 312	**100%**	**75%**	**69%**	**67%**	**65%**	**62%**
Lipid lowering agents	RQ_4	117 060	105 667	103 336	100 502	97 448	92 635	**100%**	**90%**	**88%**	**86%**	**83%**	**79%**
Cardiovascular medication	RQ_5	199 203	183 314	180 125	177 690	175 378	170 169	**100%**	**92%**	**90%**	**89%**	**88%**	**85%**

Insuline use, no min

min 90 DDD antidiabetics, NO insuline

min 90 DDD antidepressives

min 90 DDD lipid lowering agents

90 DDD of at least 1 group (C02, C03, C07, C08, C09)

Table 63 – Patient selection redo/ undo/ adverse event analyses

Patient selection redo/ undo/ adverse events analyses:	
a.	**EXCLUDE patients with earlier bariatrics**: exclude those with surgery in 2007-2008 based on the nomenclature codes (sleeve: 241776-241780, 241791-241802, gastric banding:241813-241824, gastric bypass 241835-241846,241850-241861).
b.	**KEEP (as a separate group) patients without clear evidence of earlier bariatrics, but with surgical treatments related to bariatric interventions before the 'first' bariatric procedure** (redo's (resections 241533-241544, degastro-gastrectomies 241555-241566) undo's (reconversions 241570-241581, removal of strange tissue 220231-220242, surgery after perforations 243611-242622, laparotomies 243633-243644, or adverse events (surgeries after obstructions 243331-243342, hernia's 241032-241043, 241931-241942, vagotomies 244716-244720, gastrectomies (241452-241463)) in the period 2007-2011.
c.	**KEEP (as a separate group) patients with clear evidence of bariatrics (no earlier bariatrics, no other related issues before 'first' bariatry).** These were flagged as 'proxy first' patients.

Table 64 – Test differences in bariatric post op REDO operations after 5 yr by surgery type

LEM: log-linear and event history analysis with missing data.
Developed by Jeroen Vermunt (c), Tilburg University, The Netherlands.
Version 1.0 (September 18, 1997).

****saturated model *** 5 YEARS POST REDO**
**** Type (Sleeve, Banding, Bypass) * Redo (Yes, No)**

```
*** STATISTICS ***
*** LOG-LINEAR PARAMETERS ***
  effect           beta  std err  z-value   exp(beta)     Wald  df  prob
  main           7.0822                   1.19E+0003
  T
   1            -0.3795   0.0291  -13.021      0.6842
   2             0.1858   0.0242    7.682      1.2042
   3             0.1936                        1.2137   192.93   2 0.000
  R
   1            -1.5606   0.0206  -75.749      0.2100
   2             1.5606                        4.7616  5737.91   1 0.000
  TR
   1 1           0.2002   0.0291    6.869      1.2217
   1 2          -0.2002                        0.8185
   2 1           0.7110   0.0242   29.383      2.0360
   2 2          -0.7110                        0.4912
   3 1          -0.9112                        0.4020
   3 2           0.9112                        2.4873  1058.13   2 0.000
```

Figure 49 – Extracts Belgian official text (30.08.2007) concerning bariatric surgery, with additions in 2008, 2010 and 2013

Note: the version "K.B. 30.08.2007" (active from 1.10.2007) was replaced by "K.B. 29.4.2008" (active from 1.6.2008), abolishing the notion "with special title in endocrinology – diabetology specialism"



44984 MONITEUR BELGE — 30.08.2007 — BELGISCH STAATSBLAD

Vu l'accord de Notre Ministre du Budget, donné le 11 avril 2007;

Vu l'avis 42.795/1 du Conseil d'Etat, donné le 14 juin 2007;

Sur la proposition de Notre Ministre des Affaires sociales et de la Santé publique,

Nous avons arrêté et arrêtons :

Article 1er. L'article 14 *d*), de l'annexe à l'arrêté royal du 14 septembre 1984 établissant la nomenclature des prestations de santé en matière d'assurance obligatoire soins de santé et indemnités, modifié par les arrêtés royaux des 14 novembre 1984, 23 mai 1985, 22 juillet 1988, 10 juillet 1990, 22 janvier 1991, 7 juin 1995, 9 octobre 1998, 26 mars 2003, 27 mars 2003, 22 avril 2003 et 20 juin 2005, est complété comme suit :

« Traitement de l'obésité morbide

241776-241780

Gastroplastie de réduction par laparotomie (Mason, Sleeve) (pour le traitement de l'obésité morbide) ..... N 400

241791-241802

Gastroplastie de réduction par laparoscopie (Mason, Sleeve) (pour le traitement de l'obésité morbide) ..... N 400

241813-241824

Gastroplastie de réduction par placement d'un anneau gastrique adaptable ("gastric banding") par laparoscopie (pour le traitement de l'obésité morbide) ..... N 400

241835-241846

Gastroplastie de réduction associée à une dérivation bilio-pancréatique ou gastro-jéjunale (Scopinaro, bypass gastrique, switch duodénal) par laparotomie (pour le traitement de l'obésité morbide) ..... N 650

241850-241861

Gastroplastie de réduction associée à une dérivation bilio-pancréatique ou gastro-jéjunale (Scopinaro, bypass gastrique, switch duodénal) par laparoscopie (pour le traitement de l'obésité morbide) ..... N 650

Ces prestations ne sont remboursables qu'aux conditions suivantes :

1° « BMI » ≥ 40;

2° à partir de 18 ans jusqu'à 60 ans;

3° avoir suivi pendant au moins 1 an un traitement par un régime documenté sans obtenir de résultat stable;

4° après une concertation bariatrique multidisciplinaire effectuée au préalable à laquelle participent conjointement et au moins outre le médecin spécialiste en chirurgie, un médecin spécialiste en médecine interne porteur d'un titre professionnel particulier en endocrinologie-diabétologie, et un médecin spécialiste en psychiatrie, ou un psychologue clinique. Le rapport de cette concertation explicitant l'indication opératoire doit être signé par les trois participants des disciplines précitées. Le rapport de la concertation ainsi que les données relatives au traitement par régime se retrouvent dans le dossier médical. ».

Gelet op de akkoordbevinding van Onze Minister van Begroting van 11 april 2007;

Gelet op advies 42.795/1 van de Raad van State, gegeven op 14 juni 2007;

Op de voordracht van Onze Minister van Sociale Zaken en Volksgezondheid,

Hebben Wij besloten en besluiten Wij :

Artikel 1. Artikel 14 *d*), van de bijlage bij het koninklijk besluit van 14 september 1984 tot vaststelling van de nomenclatuur van de geneeskundige verstrekkingen inzake verplichte verzekering voor geneeskundige verzorging en uitkeringen, gewijzigd bij de koninklijke besluiten van 14 november 1984, 23 mei 1985, 22 juli 1988, 10 juli 1990, 22 januari 1991, 7 juni 1995, 9 oktober 1998, 26 maart 2003, 27 maart 2003, 22 april 2003 en 20 juni 2005, wordt aangevuld als volgt :

« Behandeling van morbide obesitas

241776-241780

Reducerende gastroplastie (Mason, Sleeve) (ter behandeling van morbide obesitas), door laparotomie ..... N 400

241791-241802

Reducerende gastroplastie (Mason, Sleeve) (ter behandeling van morbide obesitas), door laparoscopie ..... N 400

241813-241824

Reducerende gastroplastie door plaatsen van een aanpasbare maagring ("gastric banding") (ter behandeling van morbide obesitas), door laparoscopie ..... N 400

241835-241846

Reducerende gastroplastie met bileopancreatische of gastro-jejunale diversie (Scopinaro, gastric bypass, duodenal switch) (ter behandeling van morbide obesitas), door laparotomie ..... N 650

241850-241861

Reducerende gastroplastie met bileopancreatische of gastro-jejunale diversie (Scopinaro, gastric bypass, duodenal switch) (ter behandeling van morbide obesitas), door laparoscopie ..... N 650

Deze verstrekkingen zijn slechts aanrekenbaar op de volgende voorwaarden :

1° "BMI" ≥ 40;

2° vanaf 18 jaar tot en met 60 jaar;

3° minstens gedurende 1 jaar een gedocumenteerde dieetbehandeling hebben gevolgd zonder blijvend succes;

4° na het uitvoeren van een multidisciplinair bariatrisch overleg waar naast de geneesheer-specialist in de chirurgie tevens terminsle een geneesheer-specialist in de inwendige geneeskunde met een bijzonder beroepstitel in de endocrinologie-diabetologie en een geneesheer-specialist in de psychiatrie of een klinisch psycholoog aan hebben deelgenomen. Het verslag van dit overleg met de gezamenlijke indicatiestelling tot chirurgische ingreep wordt ondertekend door de drie deelnemers van de vermelde disciplines. Het verslag van het overleg bevindt zich samen met de gegevens over de dieettherapie in het medisch dossier. ».

Artikel 1. In artikel 14, *d)*, van de bijlage bij het koninklijk besluit van 14 september 1984 tot vaststelling van de nomenclatuur van de geneeskundige verstrekkingen inzake verplichte verzekering voor geneeskundige verzorging en uitkeringen, laatstelijk gewijzigd bij het koninklijk besluit van 29 april 2008, onder het opschrift « Behandeling van morbide obesitas », worden de volgende wijzigingen aangebracht :

1° in het opschrift "Behandeling van morbide obesitas" wordt het woord "morbide" geschrapt;

2° in de omschrijving van de verstrekkingen 241776-241780, 241791-241802, 241813-241824, 241835-241846 en 241850-241861, wordt het woord "morbide" geschrapt;

3° de eerste voorwaarde voor terugbetaling van de betreffende verstrekkingen wordt vervangen als volgt :

« 1° op het moment van de chirurgische indicatiestelling BMI ≥ 40 ofwel BMI ≥ 35 in combinatie met minstens één van volgende criteria :

a) met geneesmiddelen behandelde diabetes;

b) therapieresistente hypertensie gedefinieerd als een bloeddruk >140/90mmHg, ondanks behandeling gedurende minstens 1 jaar met een gelijktijdige inname van 3 antihypertensiva;

c) slaapapneusyndroom geobjectiveerd door middel van polysomnografisch onderzoek uitgevoerd in een centrum met een overeenkomst zoals bedoeld in artikel 22, 6° en 23, § 3, van de wet voor geneeskundige verzorging en uitkeringen van 14 juli 1994, betreffende de diagnose en behandeling van het obstructief slaapapneusyndroom;

d) heringreep na complicatie of onvoldoende resultaat van een vorige bariatrische ingreep; »;

4° de voorwaarden voor terugbetaling van de betreffende verstrekkingen worden aangevuld als volgt :

« 5° voorafgaand aan de ingreep maakt de behandelend geneesheer een standaardformulier ter notificatie over aan de adviserend geneesheer van de verzekeringsinstelling. De modaliteiten van dit notificatieformulier worden vastgesteld door het Verzekeringscomité;

Article 1er. A l'article 14, *d)*, de l'annexe à l'arrêté royal du 14 septembre 1984 établissant la nomenclature des prestations de santé en matière d'assurance obligatoire soins de santé et indemnités, modifié en dernier lieu par l'arrêté royal du 29 avril 2008, sous l'intitulé «Traitement de l'obésité morbide», sont apportées les modifications suivantes :

1° dans l'intitulé "Traitement de l'obésité morbide", le mot "morbide" est supprimé;

2° dans le libellé des prestations 241776-241780, 241791-241802, 241813-241824, 241835-241846 et 241850-241861, le mot "morbide" est supprimé;

3° la première condition de remboursement des prestations concernées est remplacée comme suit :

« 1° au moment de l'indication chirurgicale BMI ≥ 40 ou BMI ≥ 35 en combinaison avec au moins un des critères suivants :

a) diabète traité par médicaments;

b) hypertension résistant au traitement définie comme une pression sanguine > 140/90mmHg, malgré un traitement pendant 1 an au moyen d'une prise simultanée de 3 antihypertenseurs;

c) syndrome d'apnée du sommeil objectivé au moyen d'un examen polysomnographique réalisé dans un centre ayant conclu une convention comme stipulé à l'article 22, 6° et 23, § 3, de la loi relative à l'assurance obligatoire soins de santé et indemnités du 14 juillet 1994, en ce qui concerne le diagnostic et le traitement du syndrome d'apnée obstructive du sommeil;

d) réintervention après complication ou résultat insuffisant d'une intervention bariatrique précédente;";

4° les conditions de remboursement des prestations concernées sont complétées comme suit :

« 5° préalablement à l'intervention, le médecin traitant transmet un formulaire standard de notification au médecin-conseil de l'organisme assureur. Les modalités de ce formulaire de notification sont fixées par le Comité de l'assurance;

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6° per ziekenhuis wordt tevens een register bijgehouden van alle bariatrische ingrepen. De modaliteiten van deze registratie worden vastgesteld door het Verzekeringscomité. »

6° un registre de l'ensemble des interventions bariatriques est tenu par hôpital. Les modalités de cet enregistrement sont fixées par le Comité de l'assurance. »

Sur la proposition de la Ministre des Affaires sociales,

Nous avons arrêté et arrêtons :

Article 1er. A l'article 14, *d)*, de l'annexe à l'arrêté royal du 14 septembre 1984 établissant la nomenclature des prestations de santé en matière d'assurance obligatoire soins de santé et indemnités, modifié en dernier lieu par l'arrêté royal du 24 octobre 2011, dans les conditions de remboursement qui suivent la prestation 241850-241861, le 5° est remplacé par ce qui suit :

« 5° le médecin traitant transmet un formulaire standard de notification par courrier personnel au médecin-conseil de l'organisme assureur. Les modalités de ce formulaire de notification sont fixées par le Comité de l'assurance. L'intervention de l'assurance pour les prestations relatives au traitement de l'obésité est due uniquement si le médecin-conseil de l'organisme assureur est en possession d'une notification valide; ».

Op de voordracht van de Minister van Sociale Zaken,

Hebben Wij besloten en besluiten Wij :

Artikel 1. In artikel 14, *d)*, van de bijlage bij het koninklijk besluit van 14 september 1984 tot vaststelling van de nomenclatuur van de geneeskundige verstrekkingen inzake verplichte verzekering voor geneeskundige verzorging en uitkeringen, laatstelijk gewijzigd bij het koninklijk besluit van 24 oktober 2011, in de voorwaarden voor terugbetaling die volgen op de verstrekking 241850-241861, wordt 5° als volgt vervangen :

« 5° de behandelend geneesheer maakt in een persoonlijke brief een standaardformulier ter notificatie over aan de adviserend geneesheer van de verzekeringsinstelling. De modaliteiten van dit notificatieformulier worden vastgesteld door het Verzekeringscomité. De verzekerings-tegemoetkoming voor de verstrekkingen betreffende de behandeling van obesitas is enkel verschuldigd als de adviserend geneesheer van de verzekeringsinstelling in het bezit is van een geldige notificatie; ».

Table 65 – log linear decomposition parameters for 5yr rehospitalisation rates by age, gender and bariatric surgery type

LEM: log-linear and event history analysis with missing data.
Developed by Jeroen Vermunt (c), Tilburg University, The Netherlands.

****saturated model *** 5 YEARS POST OP**
****** Type (Sleeve, Banding, Bypass) * Gender (Male, Female) * Age (Young, Old) * Issues (Yes, No)**

***** STATISTICS *****
Number of iterations = 2
Converge criterion = 0.0000000000
X-squared = 0.0000 (0.0000)
L-squared = 0.0000 (0.0000)
Cressie-Read = 0.0000 (0.0000)
Dissimilarity index = 0.0000
Degrees of freedom = 0
Log-likelihood = -62299.27193
Number of parameters = 23 (+1)
Sample size = 24585.0
BIC(L-squared) = 0.0000
AIC(L-squared) = 0.0000
BIC(log-likelihood) = 124831.0714
AIC(log-likelihood) = 124644.5439

***** LOG-LINEAR PARAMETERS *****
*** TABLE TGAI [or P(TGAI)] ***

effect	beta	std err	z-value	exp(beta)	Wald	df	prob
main	6.2273			506.3878			
T							
1	-0.6217	0.0202	-30.813	0.5370			
2	-0.3415	0.0180	-18.973	0.7107			
3	0.9632			2.6201	4432.55	2	0.000
G							
1	-0.4997	0.0125	-39.900	0.6067			
2	0.4997			1.6482	1592.00	1	0.000
A							
1	-0.0409	0.0125	-3.266	0.9599			
2	0.0409			1.0418	10.67	1	0.001

```
I
 1             -0.7801   0.0125  -62.293       0.4584
 2              0.7801                         2.1817  3880.38   1 0.000
TG
 1 1            0.1703   0.0202    8.437       1.1856
 1 2           -0.1703                         0.8434
 2 1           -0.1586   0.0180   -8.809       0.8533
 2 2            0.1586                         1.1719
 3 1           -0.0117                         0.9884
 3 2            0.0117                         1.0118    86.81   2 0.000
TA
 1 1           -0.0602   0.0202   -2.984       0.9416
 1 2            0.0602                         1.0621
 2 1            0.1738   0.0180    9.653       1.1898
 2 2           -0.1738                         0.8405
 3 1           -0.1136                         0.8927
 3 2            0.1136                         1.1203   125.33   2 0.000
GA
 1 1           -0.1323   0.0125  -10.563       0.8761
 1 2            0.1323                         1.1414
 2 1            0.1323                         1.1414
 2 2           -0.1323                         0.8761   111.58   1 0.000
TI
 1 1           -0.1648   0.0202   -8.165       0.8481
 1 2            0.1648                         1.1792
 2 1            0.2823   0.0180   15.679       1.3261
 2 2           -0.2823                         0.7541
 3 1           -0.1175                         0.8892
 3 2            0.1175                         1.1247   265.57   2 0.000
GI
 1 1           -0.0749   0.0125   -5.984       0.9278
 1 2            0.0749                         1.0778
 2 1            0.0749                         1.0778
 2 2           -0.0749                         0.9278    35.81   1 0.000
AI
 1 1            0.0021   0.0125    0.169       1.0021
 1 2           -0.0021                         0.9979
 2 1           -0.0021                         0.9979
 2 2            0.0021                         1.0021     0.03   1 0.866
TGA
 1 1 1         -0.0142   0.0202   -0.704       0.9859
```



```
 1 1 2          0.0142                          1.0143
 1 2 1          0.0142                          1.0143
 1 2 2         -0.0142                          0.9859
 2 1 1          0.0041    0.0180     0.226      1.0041
 2 1 2         -0.0041                          0.9959
 2 2 1         -0.0041                          0.9959
 2 2 2          0.0041                          1.0041
 3 1 1          0.0101                          1.0102
 3 1 2         -0.0101                          0.9899
 3 2 1         -0.0101                          0.9899
 3 2 2          0.0101                          1.0102      0.66   2 0.720
TGI
 1 1 1          0.0057    0.0202     0.284      1.0058
 1 1 2         -0.0057                          0.9943
 1 2 1         -0.0057                          0.9943
 1 2 2          0.0057                          1.0058
 2 1 1         -0.0447    0.0180    -2.482      0.9563
 2 1 2          0.0447                          1.0457
 2 2 1          0.0447                          1.0457
 2 2 2         -0.0447                          0.9563
 3 1 1          0.0389                          1.0397
 3 1 2         -0.0389                          0.9618
 3 2 1         -0.0389                          0.9618
 3 2 2          0.0389                          1.0397     10.79   2 0.005
TAI
 1 1 1         -0.0389    0.0202    -1.929      0.9618
 1 1 2          0.0389                          1.0397
 1 2 1          0.0389                          1.0397
 1 2 2         -0.0389                          0.9618
 2 1 1          0.0215    0.0180     1.194      1.0217
 2 1 2         -0.0215                          0.9787
 2 2 1         -0.0215                          0.9787
 2 2 2          0.0215                          1.0217
 3 1 1          0.0175                          1.0176
 3 1 2         -0.0175                          0.9827
 3 2 1         -0.0175                          0.9827
 3 2 2          0.0175                          1.0176      3.80   2 0.150
GAI
 1 1 1         -0.0073    0.0125    -0.585      0.9927
 1 1 2          0.0073                          1.0073
 1 2 1          0.0073                          1.0073
```

```
 1 2 2        -0.0073                      0.9927
 2 1 1         0.0073                      1.0073
 2 1 2        -0.0073                      0.9927
 2 2 1        -0.0073                      0.9927
 2 2 2         0.0073                      1.0073     0.34   1 0.559
TGAI
 1 1 1 1      -0.0000   0.0202   -0.000    1.0000
 1 1 1 2       0.0000                     1.0000
 1 1 2 1       0.0000                     1.0000
 1 1 2 2      -0.0000                     1.0000
 1 2 1 1       0.0000                     1.0000
 1 2 1 2      -0.0000                     1.0000
 1 2 2 1      -0.0000                     1.0000
 1 2 2 2       0.0000                     1.0000
 2 1 1 1      -0.0160   0.0180   -0.887    0.9842
 2 1 1 2       0.0160                     1.0161
 2 1 2 1       0.0160                     1.0161
 2 1 2 2      -0.0160                     0.9842
 2 2 1 1       0.0160                     1.0161
 2 2 1 2      -0.0160                     0.9842
 2 2 2 1      -0.0160                     0.9842
 2 2 2 2       0.0160                     1.0161
 3 1 1 1       0.0160                     1.0161
 3 1 1 2      -0.0160                     0.9842
 3 1 2 1      -0.0160                     0.9842
 3 1 2 2       0.0160                     1.0161
 3 2 1 1      -0.0160                     0.9842
 3 2 1 2       0.0160                     1.0161
 3 2 2 1       0.0160                     1.0161
 3 2 2 2      -0.0160                     0.9842     1.62   2 0.444
```

Table 66 – Selection bariatric surgery, RIZIV reimbursed, by year and typology

year	N	type
2008	1 692	Band
2008	3 784	Bypass
2008	446	Sleeve
2008	4	multipleBariatric
2009	1 632	Band
2009	5 169	Bypass
2009	818	Sleeve
2010	1 342	Band
2010	6 049	Bypass
2010	1 203	Sleeve
2010	4	multipleBariatric
2011	1 088	Band
2011	7 772	Bypass
2011	1 604	Sleeve
2011	4	multipleBariatric
2012	885	Band
2012	8 307	Bypass
2012	2 075	Sleeve
2012	8	multipleBariatric
2013	606	Band
2013	8 471	Bypass
2013	2 620	Sleeve
2013	6	multipleBariatric
2014	501	Band
2014	8 589	Bypass
2014	3 413	Sleeve
2014	1	3 types
2014	1	multipleBariatric

APPENDIX 7. SEARCH STRATEGY: ECONOMIC PART

Appendix 7.1. HTA reports

On April 23, 2018, we searched for HTA reports on bariatric surgery including an economic evaluation of this intervention and/or a review of such evaluations. In the first place, the Centre for Reviews and Dissemination (CRD) HTA database was searched (Table 67). In addition, the websites of HTA institutes were searched using the free text 'bariatric'. This was done using the Google 'site:'-search limiting search results to those linked to the website of the selected HTA institutes. This was performed on the website of the International Network of Agencies for Health Technology Assessment (INAHTA) members, as well as a selection of non-member websites (see Table 68).

Table 67 – Search strategy and results for CRD HTA

Date	**23 April 2018**		
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Bariatric Surgery EXPLODE ALL TREES	314
	2	* IN HTA	17351
	3	#1 AND #2	73 references
Note	/		

Table 68 – List of INAHTA member websites searched for HTA reports

Abbreviation	Institute	Country
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland

Abbreviation	Institute	Country
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya	Spain
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
ASSR	Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care)	Italy
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CDE	Center for Drug Evaluation	Taiwan
CEDIT	Comité d'Évaluation et de Diffusion des Innovations Technologiques	France
CEM	Inspection générale de la sécurité sociale (IGSS), Cellule d'expertise médicale	Luxembourg
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CONITEC	National Committee for Technology Incorporation	Brazil
CMeRC	Department of Internal Medicine	South Africa
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS	Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
DEFACTUM	Social & Health Services and Labour Market	Denmark
G-BA	The German Health Care System and the Federal Joint Committee	Germany
GÖG	Gesundheit Österreich	Austria
HAD-MSP	Health Assessment Division, Ministry of Public Health	Uruguay
HAS	Haute Autorité de Santé	France
HCT-NHSRC	Division of Healthcare Technology, National Health Systems Resource Center	India
HealthPACT	Health Policy Advisory Committee on Technology	Australia
HIQA	Health Information and Quality Authority	Ireland
HIS	Healthcare Improvement Scotland	United Kingdom

Abbreviation	Institute	Country
HQO	Evidence Development and Standards Branch	Canada
IACS	Health Sciences Institute in Aragon	Spain
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IETS	Instituto de Evaluación Tecnológica en Salud	Colombia
IHE	Institute of Health Economics	Canada
INASanté	National Instance for Accreditation in Health Care	Tunisia
INESSS	Institut national d'excellence en santé et en services sociaux	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA	Ludwig Boltzmann Institut für Health Technology Assessment	Austria
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NECA	National Evidence-based healthcare Collaboration Agency	Korea
NIHR	National Institute for Health Research	United Kingdom
NIPH	Norwegian Institute of Public Health	Norway
OSTEBA	Basque Office for Health Technology Assessment	Spain
RCHD-CS	Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development, Centre of Standardization, HTA department	Kazakhstan
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UVT	HTA Unit in A. Gemelli University Hospital	Italy
ZIN	Zorginstituut Nederland	The Netherlands
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands
Selection of non-member websites		

Abbreviation	Institute	Country
CHE	Centre for Health Economics	United Kingdom
EUnetHTA	European Network for HealthTechnology Assessment	Europe
NICE	National Institute for Health and Care Excellence	United Kingdom
PHARMAC	Pharmaceutical Management Agency	New Zealand

Table 69 – List of retrieved HTA reports

References
HTA reports identified through CRD HTA (n=16)
Gulliford M, Charlton J, Booth H, Fildes A, Khan O, Reddy M, et al. Costs and outcomes of increasing access to bariatric surgery for obesity: cohort study and cost-effectiveness analysis using electronic health records. Health Services and Delivery Research Report: NIHR Health Services and Delivery Research programme; 2016.[305]
Institute for Clinical Economic Review. Bariatric surgery. Report. Boston: Institute for Clinical and Economic Review (ICER); 2015.[306]
Göthberg G, Bergh C, Dahlgren J, Daxberg E, Gronowitz E, Nordenström J, et al. Bariatric surgery in adolescents with severe obesity. Report. Gothenburg: The Regional Health Technology Assessment Centre (HTA-centrum); 2014.[392]
CADTH. Bariatric surgical procedures for obese and morbidly obese patients: a review of comparative clinical and cost-effectiveness, and guidelines. Report. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2014.[310]
ASERNIP-S. Centralisation of bariatric surgery: policy implications. Report. Australia: Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S); 2014.[454]
Kelly J. What is the relative clinical effectiveness, cost effectiveness and safety of different bariatric surgery techniques (gastric bypass, gastric banding and sleeve gastrectomy)? Report. Glasgow: Healthcare Improvement Scotland; 2012.[455]
Institute of Health Economics. Bariatric treatments for adult obesity. Report. Edmonton: Institute of Health Economics (IHE); 2012.[313]
NHS Quality Improvement Scotland. Bariatric surgery in adults. Report. Glasgow: Quality Improvement Scotland (NHS QIS); 2010.[314]
Picot J, Jones J, Colquitt J, Gospodarevskaya E, Loveman E, Baxter L, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. HTA Technology Assessment Report: NIHR Health Technology Assessment programme; 2009.[307]

Medical Advisory Secretariat. Bariatric surgery for people with diabetes and morbid obesity: an evidence-based analysis. Report. Toronto: Medical Advisory Secretariat (MAS); 2009.[456]
Bockelbrink A, Stoeber Y, Roll S, Vauth C, Willich S, Greiner W. Evaluation of medical and health economic effectiveness of bariatric surgery (obesity surgery) versus conservative strategies in adult patients with morbid obesity. Report. Cologne: German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DAHT@DIMDI); 2008.[457]
NHS Quality Improvement Scotland. Surgery for obesity. Report. Glasgow: Quality Improvement Scotland (NHS QIS); 2007.[458]
Boudreau R, Hodgson A. Laparoscopic adjustable gastric banding for weight loss in obese adults: clinical and economic review. Report. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2007.[339]
Medical Advisory Secretariat. Bariatric surgery: an evidence-based analysis. Report. Toronto: Medical Advisory Secretariat (MAS); 2005.[459]
Chen J, McGregor M. The gastric banding procedure: an evaluation. Report. Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC); 2004.[460]
Scottish Health Purchasing Information Centre. Gastric surgery for obesity. Review. Aberdeen: Scottish Health Purchasing Information Centre (SHPIC); 1998. [461]
Extra HTA reports identified through searching websites HTA institutes (n=9)
FAAHMS. Public investment in bariatric surgery – powerpoint presentation. 2017.
CADTH. Bariatric Surgery for the Long-Term Treatment of Obesity: A Review of the Clinical Effectiveness and Cost-Effectiveness. 2016.
CADTH. Bariatric Surgery for the Long-Term Treatment of Obesity – powerpoint presentation. 2016.
ZINL. Standpunt bariatrische chirurgie. 2014.
NICE. Costing report: obesity. Implementing the NICE guideline on obesity (CG189). 2014.
NICE. Obesity: Identification, assessment and management of overweight and obesity in children, young people and adults. 2014.
CADTH. Bariatric Surgery for Morbidly Obese Patients: Cost-Effectiveness. 2007.
IHE. Working paper: costing of alternative interventions for the treatment of morbid obesity. 2006.
INESS. Surgical treatment of morbid obesity. 2006.

Appendix 7.2. Supplementary primary economic evaluations

Table 70 – Search strategy and results for Medline (OVID)

Date	**29 October 2018**		
Date covered	2015-2018 (search performed in database 'Ovid MEDLINE(R) 2014 to October Week 2 2018')		
Search Strategy	1	Economics/	500
	2	"costs and cost analysis"/	3739
	3	Cost allocation/	46
	4	Cost-benefit analysis/	12453
	5	Cost control/	1055
	6	Cost savings/	1969
	7	Cost of illness/	5484
	8	Cost sharing/	373
	9	"deductibles and coinsurance"/	210
	10	Medical savings accounts/	41
	11	Health care costs/	7508
	12	Direct service costs/	120
	13	Drug costs/	2547
	14	Employer health costs/	28
	15	Hospital costs/	1914
	16	Health expenditures/	3361
	17	Capital expenditures/	38
	18	Value of life/	223
	19	Exp economics, hospital/	2967
	20	Exp economics, medical/	377
	21	Economics, nursing/	84
	22	Economics, pharmaceutical/	261
	23	Exp "fees and charges"/	2087

	24	Exp budgets/	1108
	25	(low adj cost).mp.	9774
	26	(high adj cost).mp.	2281
	27	(health?care adj cost$).mp.	2763
	28	(fiscal or funding or financial or finance).tw.	24410
	29	(cost adj estimate$).mp.	355
	30	(cost adj variable).mp.	6
	31	(unit adj cost$).mp.	421
	32	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	48535
	33	Or/1-32	105116
	34	Bariatric Surgery/	3257
	35	Gastric Bypass/	2244
	36	roux-en-y.ti,ab.	2136
	37	RYGB.ti,ab.	768
	38	gastric banding.ti,ab.	473
	39	LAGB.ti,ab.	221
	40	sleeve gastrectom*.ti,ab.	1549
	41	bariatric surg*.ti,ab.	3811
	42	(surg* adj5 bariatric).ti,ab.	3905
	43	(metabol* adj5 surg*).ti,ab.	698
	44	(obesity adj5 surg*).ti,ab.	1013
	45	or/34-44	7591
	46	33 and 45	236
	47	limit 46 to yr="2015 -Current"	178 references
Note	/		

Table 71 – Search strategy and results for Embase

Date	**31 October 2018**		
Date covered	2015-2018		
Search Strategy	1	'socioeconomics'/exp	348440
	2	'cost benefit analysis'/exp	78591
	3	'cost effectiveness analysis'/exp	135583
	4	'cost of illness'/exp	17683
	5	'cost control'/exp	63014
	6	'economic aspect'/exp	1538838
	7	'financial management'/exp	393008
	8	'health care cost'/exp	267561
	9	'health care financing'/exp	12808
	10	'health economics'/exp	788588
	11	'hospital cost'/exp	34668
	12	'finance'/exp OR 'funding'/exp OR fiscal OR financial	249841
	13	'cost minimization analysis'/exp	3181
	14	cost*:de,cl,ab,ti	937523
	15	estimate*:de,cl,ab,ti	1053180
	16	variable*:de,cl,ab,ti	980716
	17	unit:de,cl,ab,ti	596137
	18	('#14' NEAR/1 '#15') OR ('#15' NEAR/1 '#14')	119737
	19	('#14' NEAR/1 '#16') OR ('#16' NEAR/1 '#14')	293693
	20	('#14' NEAR/1 '#17') OR ('#17' NEAR/1 '#14')	57923
	21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20	2036692
	22	'bariatric surgery'/exp	35704
	23	'gastric bypass surgery'/exp	20265

	24	'roux en y':ti,ab	16244
	25	'rygb':ti,ab	5061
	26	'gastric banding'/exp	6815
	27	'gastric banding':ti,ab	5089
	28	'lagb':ti,ab	2161
	29	'sleeve gastrectomy'/exp	10334
	30	'sleeve gastrectomy':ti,ab	9881
	31	'bariatric surg*':ti,ab	24466
	32	*surg*:ti,ab*	*(2374797)*
	33	*bariatric*:ti,ab*	*(28768)*
	34	*('#32' NEAR/5 '#33') OR ('#33' NEAR/5 '#32')*	*(48550)*
	35	*metabol*:ti,ab*	*(1362303)*
	36	*('#32' NEAR/5 '#35') OR ('#35' NEAR/5 '#32')*	*(55818)*
	37	*obesity:ti,ab*	*(305202)*
	38	*('#32' NEAR/5 '#37') OR ('#37' NEAR/5 '#32')*	*(308234)*
	39	*#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #34 OR #36 OR #38*	*(453824)*
	40	*#21 AND #39*	*(29541)*
	41	*#21 AND #39 AND [2015-2018]/py*	*(6449 references)*
	42	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	52332
	43	#21 AND #42	3572
	44	#21 AND #42 AND [2015-2018]/py	1331 references
Note	The initial search strategy identified 6449 references (see line 41). From a practical point of view, this was considered too much and the search strategy was strengthened by deleting lines 32-40. The new search strategy identified 1331 references which were further selected.		

Table 72 – Results of search strategy for extra primary economic evaluations

Database	
Medline (OVID)	178
Embase	1331
Total (incl. duplicates)	**1509**
Duplicates	101
Total (excl. duplicates)	**1408**