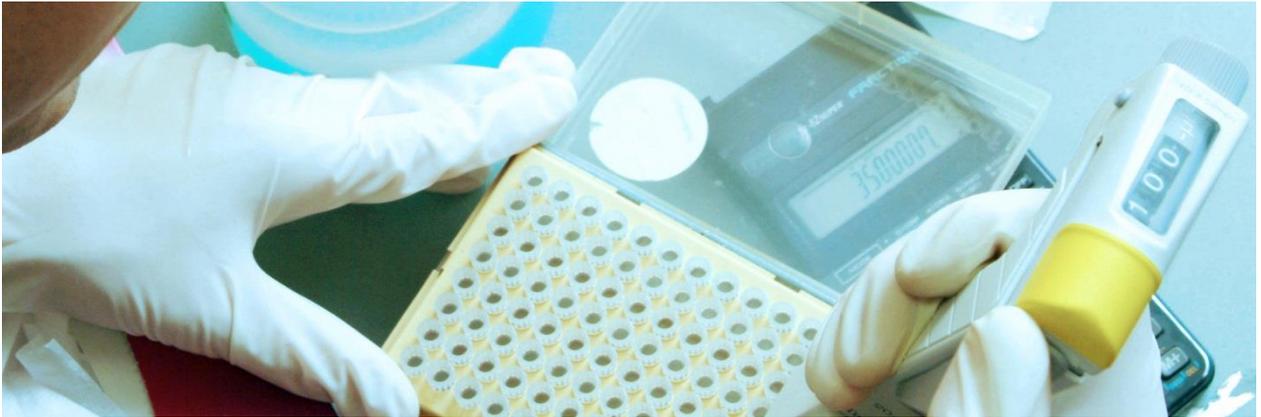


# Bariatric surgery vs. conservative treatment for obesity and overweight



Report of the Appraisal Committee of the Swiss Medical Board

October 18<sup>th</sup>, 2016

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# Foreword

The Swiss Medical Board (SMB) analyzes and assesses therapeutic and diagnostic interventions from the medical, economic, ethical and legal points of view. A particular focus is on the cost-utility ratio of interventions covered by statutory health insurance. The conclusions drawn from these analyses allow to establish recommendations for healthcare providers and policy makers. An additional aim is to help optimize the allocation of resources in healthcare.

The general procedure for SMB Reports is as follows: The governing body (Trägerverein/ Association responsible) decides on the subject to be assessed after a broad consultation. A scoping process allows to refine the questions to be answered. Representatives of medical societies and other stakeholders are invited to comment on the drafted questions. The Assessment Team then conducts a qualitative and quantitative search of the research evidence available covering the domains (i) clinical effectiveness and safety, (ii) health economic analyses, (iii) legal issues and (iv) ethical issues. It establishes an Assessment Report summarizing and critically assessing this evidence. Once this report is finalized, the stakeholders are again invited to participate in a hearing and given the opportunity for comments. Based on the Assessment Report, the preceding scoping documents and the feedback by stakeholders, the Appraisal Committee appraises the evidence synthesized in the assessment report, decides whether it includes additional evidence in its appraisal and establishes recommendations. The Appraisal Committee's approach is guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The SMB governing body disseminates its reports to interested parties and ensures communication with them.

The present Appraisal Report was prepared between January and July 2016 and is based on the following documents:

- Assessment Report "Bariatric surgery vs. conservative treatment for obesity and overweight" (version of January 29th, 2016),
- Scoping Document Bariatric surgery (version of June 25th, 2015),
- Stakeholder Document: Minutes of hearing of March 31<sup>st</sup>, 2016 and written statements.

The final version of the Assessment Report as well as the Scoping and Stakeholder Documents are available on the SMB website ([www.medical-board.ch](http://www.medical-board.ch)).

In the scoping phase for the present Appraisal Report, it was decided to consider evidence from randomized controlled trials (RCTs) only. Given the limitations of this evidence, the Appraisal Committee decided to also consider long-term follow-up and safety data such as peri-operative mortality and rates of complications and reoperations from well-conducted observational studies. In addition, recently published reports from international health technology assessment (HTA) agencies were reviewed. For this purpose, the Scientific Secretariat conducted an additional literature search.

# 1. Context and questions

Individuals with severe obesity defined as body mass index (BMI)  $\geq 35 \text{ kg/m}^2$  (also called 'class II obesity') have a high prevalence of concomitant chronic diseases such as type 2 diabetes, hypertension, hypercholesterolemia, osteoarthritis and mental health disorders.<sup>1,2</sup> These chronic conditions lead to a substantial increase in morbidity<sup>1</sup> and mortality.<sup>3</sup> For individuals who are overweight (defined as BMI  $\geq 25$  to  $< 30 \text{ kg/m}^2$ ) or have class I obesity (BMI  $\geq 30$  to  $< 35 \text{ kg/m}^2$ ), the prevalence of chronic diseases is increased, especially type 2 diabetes and hypertension. When considering individuals with class I obesity in general, the morbidity from heart disease is increased.<sup>1</sup> However, in individuals who are overweight or with class I obesity, the increase in heart disease and mortality is mostly apparent among those who have co-morbid conditions such as type 2 diabetes and hypertension.<sup>5</sup> BMI alone does not seem to determine whether an individual is at increased risk of cardiovascular disease or mortality.<sup>3</sup>

In Switzerland, the estimated healthcare cost due to obesity was CHF 5755 Mio. in 2006 and CHF 7990 Mio. in 2011.<sup>6</sup> In 2012, 30.8% of the Swiss resident population were overweight and 10.3% were obese (BMI  $\geq 30 \text{ kg/m}^2$ ).<sup>7</sup>

Lifestyle interventions and pharmacotherapy have failed to show a long-term effect on quality of life and health among individuals with severe obesity.<sup>8</sup> Bariatric surgery has increasingly been discussed as representing a promising intervention to improve long-term outcomes and quality of life in individuals with obesity.<sup>2,9-11</sup> Swiss statutory health insurance (Obligatorische Krankenpflegeversicherung) covers certain types of bariatric surgery in individuals with BMI  $\geq 35 \text{ kg/m}^2$ .<sup>6,12</sup> In Switzerland, a total of 4167 bariatric surgeries were performed in 2014. Roux-en-Y gastric bypass was the most frequently used technique with about 82.5% of all interventions, followed by sleeve gastrectomy with 15.7%, adjustable gastric banding with 0.8% and biliopancreatic diversion (with or without duodenal switch) with 0.7%.<sup>13</sup>

Roux-en-Y gastric bypass involves surgical rearrangements of the stomach and small intestine limiting caloric intake and absorption (Figure 1, panel c). With sleeve gastrectomy the size of the stomach is reduced to a sleeve-like small pouch (Figure 1, panel b). With adjustable gastric banding an adjustable ring is put around the stomach, which allows only the ingestion of small food portions (Figure 1, panel a). For biliopancreatic diversion with duodenal switch, the size of the stomach is reduced and then connected to the lower part of the small intestine. (Figure 1, panel d).

**Figure 1. Commonly performed bariatric surgery procedures. (A) Adjustable gastric band; (B) sleeve gastrectomy; (C) Roux-en-Y gastric bypass; (D) biliopancreatic diversion with duodenal switch.**

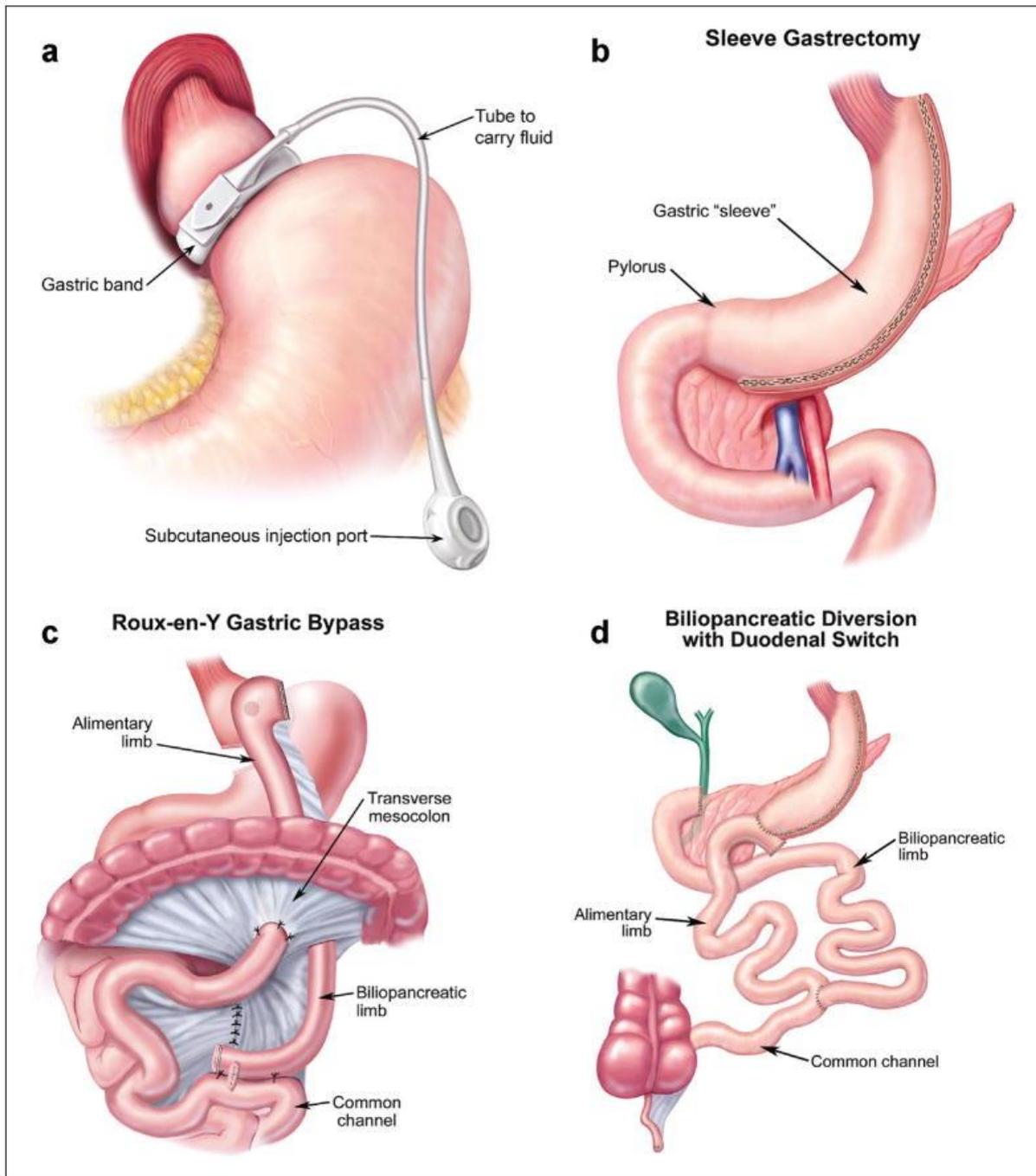


Illustration from Atlas of Metabolic and Weight Loss Surgery, Jones et al. *Cine-Med*, 2010. Copyright of the book and illustrations is retained by *Cine-Med*.

The effect of bariatric surgery on weight loss and reduction of co-morbid conditions such as hypertension and type 2 diabetes might be mediated through various mechanisms.<sup>2,14</sup> While Roux-en-Y gastric bypass might work by mechanical means, i.e., food restriction and malabsorption, recent evidence points to more complex hormonal and neuronal changes such as reduced insulin release and an increase in energy consumption.<sup>14</sup> However, a strict diet following

bariatric surgery appears to be decisive to achieve the intended long-term benefits regarding body weight and co-morbid conditions. Failure to comply with dietary recommendations may lead patients to “bypass the bypass”, which is one explanation for some of the observed failures of bariatric surgery.

Observational data from long-term follow-up suggest a substantial reduction in overall mortality, cardiovascular diseases, type 2 diabetes and hypertension with bariatric surgery.<sup>2,9,15-17</sup> As with any medical intervention, there are downsides and secondary effects involved.<sup>2</sup> In the short term (first year after surgery), there are potential direct complications from surgery and the early adaptation to the new lifestyle imposed by it. In the long term (>3 years), bariatric surgery is associated with nutritional deficiencies in case of poor adherence to dietary recommendations. Adequate diet requires patients to follow instructions including the number of meals to be taken daily, adequate protein intake and the use of vitamin and mineral supplements.<sup>18</sup> Deficiencies in calcium intake can lead to long-term bone loss and osteoporosis, iron deficiencies to anemia, vitamin deficiencies to various neurological, hematological and hormonal consequences.<sup>2,18</sup> Other potential adverse effects following bariatric surgery have been found such as an increased risk of alcohol misuse and suicide.<sup>19-21</sup> While bariatric surgery in women in child-bearing age is associated with a reduction of subsequent rates of gestational diabetes, it was also associated with an increased risk of small-for-gestational-age infants and, possibly, with an increased risk of stillbirth and neonatal death.<sup>22</sup> This highlights the need for (i) adequate information for the women concerned and (ii) dedicated teams of healthcare professionals following and counseling women in child-bearing age after bariatric surgery, in particular to prevent nutritional deficiencies and to manage abdominal complaints.<sup>23</sup>

This Appraisal Report examines the evidence on the safety and the effectiveness, the cost-utility as well as the legal and ethical implications of bariatric surgery compared to conservative treatment. Neither the underlying Assessment Report nor this Appraisal Report reviews the evidence on interventions for *preventing* obesity. Both reports focus on bariatric surgery for *adults* and exclude evidence from studies in children and adolescents of less than 18 years. For these age groups, a separate review would be needed, in particular in the light of recent reports on the effects of bariatric surgery in adolescents.<sup>24</sup> The RCTs included in the Assessment Report for clinical safety and effectiveness were limited to three years of follow-up and therefore of limited use to assess long-term outcomes. In addition, the number of participants included in these trials to assess the safety of bariatric surgery was small. Consequently, the Appraisal Committee agreed on an additional literature search, which was performed by its Scientific Secretariat. The Appraisal Committee considered long-term follow-up data and safety data such as peri-operative mortality and rates of complications and reoperations, which were gathered from observational studies. Published reports from international HTA agencies were also reviewed. In order to label the respective source of evidence discussed in Section 2 (Evidence and interpretation) of the Appraisal Report, we indicated subheadings with one asterisk (\*) if data from the Assessment Report were used and with two (\*\*) if data from the additional search were used.

In accordance with the preceding scoping, the Assessment Report did not consider co-morbidities such as type 2 diabetes as a criterion to appraise the evidence from individuals with BMI <35 kg/m<sup>2</sup>. However, given that being overweight or with class I obesity alone does not confer a significant additional risk of cardiovascular events or mortality compared to normal weight populations, the Appraisal Committee took into consideration co-morbidities such as hypertension and type 2 diabetes in the present recommendations in line with a recently published HTA report.<sup>25</sup>

## 2. Evidence and interpretation

### 2.1. Clinical effectiveness and safety

*Evidence from RCTs included in the Assessment Report \**

The Assessment Team updated a systematic review of the randomized evidence on the effectiveness of bariatric surgery vs. non-surgical treatments for obesity published in 2013<sup>10</sup> and included studies published up to July 2015. Five studies were added to the 11 reviewed in the earlier article. Clinical outcomes up to 2 to 3 years of follow-up such as weight loss, hypertension, type 2 diabetes and adverse events were the main focus of the Assessment Team. The GRADE methodology was used to summarize the findings and assess the quality of the evidence. Subgroup analyses included testing for differences in effectiveness and safety between individuals with BMI  $\geq 35$  and  $< 35$  kg/m<sup>2</sup> and between different types of bariatric surgery, mostly between Roux-en-Y gastric bypass and adjustable gastric banding.

Sixteen RCTs fulfilled the inclusion criteria and 10 RCTs reported outcomes after 2 to 3 years. Most RCTs included individuals with specific co-morbidities such as type 2 diabetes, sleep apnea and a mix of co-morbidities. Overall, trials excluded relevant patient subgroups. For instance, most trials excluded participants with currently active chronic diseases such as cardiovascular, neurological, gastrointestinal or neoplastic diseases. Individuals with currently active eating disorder, drug or alcohol abuse were often specifically excluded. Some studies also excluded those with significant psychiatric co-morbid conditions. Results from RCTs therefore mostly apply to selected populations.

When compared to conservative treatment, bariatric surgery appeared beneficial for the critical outcome “change of body weight”, with a reported reduction of 18% on average (95% confidence interval (CI): 15% to 21%). This evidence was considered of moderate quality (Table 1). Bariatric surgery was also significantly associated with an improvement in the physical functioning component of quality of life, a reduction in the mean HbA1c concentration in the blood, higher diabetes remission rates and a reduction in proportions of patients with dyslipidemia and hypertension. Few studies reported on these outcomes, and the quality of the evidence was considered to be low. Bariatric surgery was not significantly associated with an improvement in the mental health component of quality of life, with sleep apnea and other clinical outcomes such as all-cause mortality and stroke. The effect on components of health-related quality of life was only assessed in 108 participants from two RCTs, and there were too few clinical events to compare outcomes between groups. The estimated relative risk of serious adverse events including reoperations suggested more than a doubling (68/1000 vs. 162/1000) with surgery, although results were not statistically significant. While seven studies reported on reoperations, only three studies reported serious adverse outcomes; of these, one study had drop out of more than 20% of participants and another of more than 10%, which raises considerable uncertainty around these estimates.

The subgroup analyses in participants with BMI  $\geq 35$  kg/m<sup>2</sup> and those with BMI  $< 35$  kg/m<sup>2</sup> suggest that estimates of effectiveness for most outcomes such as weight loss, type 2 diabetes and hypertension remission point in the same direction. However, only one study included participants (all with type 2 diabetes) who were overweight (BMI  $\geq 25$  to 30 kg/m<sup>2</sup>).<sup>26</sup> This study was designed specifically to test the hypothesis that bariatric surgery could be a treatment option for individuals recently diagnosed with type 2 diabetes. The studies including participants with BMI  $\geq 30$  to  $< 35$  kg/m<sup>2</sup> were mostly designed to test the effect of bariatric surgery on type 2 diabetes and all but one<sup>27</sup> had diabetes mellitus as an inclusion criterion. This one study used additional co-morbidities such as hypertension and sleep apnea as inclusion criteria.<sup>27</sup> Thus, the evidence from RCTs for individuals with BMI  $< 35$  kg/m<sup>2</sup> essentially applies to those with obesity

and type 2 diabetes or other co-morbidities. The Assessment Report did not consider co-morbidities such as type 2 diabetes and hypertension when summarizing the evidence on the effect of bariatric surgery in individuals with BMI <35 kg/m<sup>2</sup>. We suggest that the benefit of bariatric surgery in patients with type 2 diabetes or hypertension be explored separately. In the light of these additional selection criteria, a careful interpretation of the evidence included in the Assessment Report for individuals with BMI <35 kg/m<sup>2</sup> is warranted.

The second subgroup analysis in the Assessment Report explored differences in effectiveness between types of surgery performed. Based on the included studies, no definite answer was possible. The pooled estimate from four RCTs, testing the effectiveness of Roux-en-Y gastric bypass, suggested a 21% reduction in mean weight. This compares with a 15% reduction estimated from the five RCTs on adjustable gastric banding. Two other studies tested biliopancreatic diversion and sleeve gastrectomy.<sup>28,29</sup> The mean weight loss was 22% (29% in one study<sup>29</sup> and 17% in the other<sup>28</sup>). This subgroup analysis is of limited relevance given that studies directly comparing different types of bariatric surgery without a control group with conservative management were excluded from the Assessment Report.<sup>30,31</sup> Two small RCTs included in the Appraisal Report have addressed the comparative effectiveness of Roux-en-Y gastric bypass and adjustable gastric banding. These studies were included in a recent Cochrane systematic review.<sup>11</sup> They suggest that Roux-en-Y gastric bypass was more effective than adjustable gastric banding, but was associated with higher rates of complications at 5-year follow-up.

**Table 1. Summary of findings of RCTs included in the Assessment Report; outcomes after 2 to 3 years of follow-up according to GRADE (adapted from Assessment Report)**

<b>Bariatric surgery compared to conservative treatment for overweight and obesity</b>						
<b>Population:</b> Individuals with overweight or obesity						
<b>Intervention:</b> Bariatric surgery						
<b>Comparison:</b> Conservative treatment						
<b>Outcomes</b>	<b>Illustrative comparative risks* (95% CI)</b>		<b>Relative effect (95% CI)</b>	<b>Number of participants (studies)</b>	<b>Quality of the evidence (GRADE)</b>	<b>Comments</b>
	<b>Assumed risk</b>	<b>Corresponding risk</b>				
	<b>Conservative treatment</b>	<b>Bariatric surgery</b>				
<b>Percent change of body weight from baseline</b>	Mean reduction in body weight with conservative treatment ranged from 1.4% to 7.3%.	Mean reduction in body weight in bariatric surgery groups was <b>17.9%</b> (14.5% to 21.4%).		617 (8 studies)	⊕⊕⊕⊖ <b>moderate</b>	
<b>Quality of life, physical functioning component (SF-36 score)</b>	Mean difference in SF-36 scores for quality of life (physical functioning) in conservative treatment groups was -1.7 and 3.4.	Mean score for quality of life (physical functioning) in bariatric surgery groups was <b>9.4 higher</b> (5.7 to 13.0 higher).		108 (2 studies)	⊕⊕⊖⊖ <b>low</b>	
<b>Quality of life, mental health component (SF-36 score)</b>	Mean difference in SF-36 scores for quality of life (mental health) in conservative treatment groups was -0.8 and 0.8.	Mean score for quality of life (mental health) in bariatric surgery groups was <b>0.1 lower</b> (3.9 lower to 3.8 higher).		108 (2 studies)	⊕⊖⊖⊖ <b>very low</b>	
<b>HbA1c (percent of total hemoglobin)</b>	Mean difference in HbA1c in conservative treatment groups ranged from -1.2 to 0.2%.	Mean HbA1c in bariatric surgery groups was <b>1.40%-points lower</b> (0.25 to 1.92 lower).		549 (7 studies)	⊕⊕⊖⊖ <b>low</b>	
<b>Stroke</b>	<b>10 per 1000</b>	<b>0 per 1000</b>	<b>RR 1.32</b> (0.05 to 31.77)	142 (1 study)	⊕⊖⊖⊖ <b>very low</b>	
<b>Myocardial infarction</b>	-	-	Not estimable	-	-	No RCT reported this outcome.
<b>All-cause mortality</b>	<b>6 per 1000</b>	<b>2 per 1000</b> (0 to 48)	<b>RR 0.33</b> (0.01 to 8.02)	417 (5 studies)	⊕⊖⊖⊖ <b>very low</b>	
<b>Serious adverse events including reoperations</b>	<b>68 per 1000</b>	<b>162 per 1000</b> (41 to 662)	<b>RR 2.4</b> (0.6 to 9.8)	167 (3 studies)	⊕⊖⊖⊖ <b>very low</b>	
<b>Diabetes remission</b>	<b>30 per 1000</b>	<b>309 per 1000</b> (133 to 727)	<b>RR 10.23</b> (4.36 to 24.02)	494 (6 studies)	⊕⊕⊖⊖ <b>low</b>	
<b>Hypertension</b>	<b>541 per 1000</b>	<b>368 per 1000</b> (265 to 514)	<b>RR 0.68</b> (0.49 to 0.95)	168 (2 studies)	⊕⊖⊖⊖ <b>very low</b>	
<b>Dyslipidemia</b>	<b>1467 per 1000</b>	<b>924 per 1000</b> (675 to 1000)	<b>RR 0.63</b> (0.46 to 0.87)	120 (1 study)	⊕⊕⊖⊖ <b>low</b>	
<b>Sleep apnea</b>	<b>42 per 1000</b>	<b>42 per 1000</b> (37 to 47)	<b>RR 1.00</b> (0.88 to 1.13)	46 (1 study)	⊕⊖⊖⊖ <b>very low</b>	
<b>Cancer</b>	<b>18 per 1000</b>	<b>13 per 1000</b> (3 to 54)	<b>RR 0.69</b> (0.16 to 2.95)	270 (2 studies)	⊕⊖⊖⊖ <b>very low</b>	
<b>Revision rates</b>	-	-	Not estimable	-	-	No RCT reported this outcome.

\* The illustrative comparative risks (and their 95% confidence intervals) are based on the mean baseline risks in the studies included in the meta-analyses. **CI:** Confidence interval; **HbA1c:** glycated hemoglobin; **RR:** Risk ratio.

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

### *Evidence from RCTs on long-term follow-up (> 3 years) \*\**

In addition to 3-year outcome data included in the Assessment Report, one study provided data on clinical outcomes from post-trial monitoring after 10 years.<sup>32</sup> Persistence of obstructive sleep apnea was compared between obese trial participants (BMI >35mg/m<sup>2</sup>) who had received either intensive nutritional care or laparoscopic adjustable gastric banding. Data from the 10-year follow-up were available for only 67% (22/33) of the participants initially randomized in the control group and 70% (21/30) in the intervention group. The mean BMI did not differ significantly between both groups at baseline (48.8 kg/m<sup>2</sup> with bariatric surgery vs. 44.4 kg/m<sup>2</sup> with conservative treatment) and after 10 years (43.4 vs. 41.0 kg/m<sup>2</sup>). The authors chose to also report on excess body weight loss (defined as % weight loss above weight corresponding to BMI of 25 kg/m<sup>2</sup>), which can be considered a surrogate outcome. With gastric banding (vs. conservative treatment) excess weight loss was greater after 3 years (27% vs. 8%) and after 10 years (33% vs. 2%).

Since completion of the literature search for the Assessment Report, data on 5-year outcomes have been published from an included RCT in individuals with BMI >35mg/m<sup>2</sup> and type 2 diabetes.<sup>33</sup> The additional analysis showed that the benefit with type 2 diabetes remission was maintained after 5 years but was smaller than after 2 years. The study was not sufficiently powered to show differences in the effectiveness with regard to other clinical outcomes.

One recent Cochrane systematic review reported on other long-term outcomes assessed in RCTs.<sup>11</sup> The studies looking at long-term outcomes were not included in the Assessment Report because they compared Roux-en-Y gastric bypass with adjustable gastric banding but not with conservative treatment.<sup>30,31</sup> At 5-year follow-up, weight loss was maintained in both groups with participants in the group with Roux-en-Y gastric bypass achieving more weight loss than those in the adjustable gastric banding group. However, Roux-en-Y gastric bypass was also associated with more surgical complications.<sup>31</sup>

### *Evidence from observational studies \*\**

The limited data from RCTs, especially on safety and long-term outcomes, warrant considering non-randomized evidence such as prospective cohort studies following persons who underwent bariatric surgery. Long-term data are especially important, given the possible rebound of weight gain or type 2 diabetes and the uncertainty whether benefit in short-term surrogate outcomes translate into benefits in cardiovascular outcomes and all-cause mortality. The evidence from observational studies has been reviewed recently.<sup>2</sup> Large prospective cohort studies shed light on the expected benefits from bariatric surgery.<sup>15-17,34</sup>

The Swedish Obese Subject (SOS) study is a controlled non-randomized intervention study that started in 1987 and is still ongoing. So far, it provided outcome data at 2, 10, 15 and 20 years from 2010 participants who underwent bariatric surgery and were matched on 18 clinical and demographic variables with 2037 participants who received a conservative treatment.<sup>15</sup> Weight loss appeared to be maintained after 20 years of follow-up with reduction of 18% from baseline in the bariatric surgery group compared to 1% in the control group. Diabetes remission has been seen in 72% of participants with surgery after 2 years and in 36% after 10 years. Clinical outcomes have been improved with a lower incidence of myocardial infarction, fatal and non-fatal cancer and 29% reduction of all-cause mortality at 16 years of follow-up. Further, at 10 years generic measures of health-related quality of life appeared to be improved after bariatric surgery, while there was no improvement in measures of anxiety and overall mood.<sup>34</sup>

In a long-term prospective cohort study in Utah/USA, 7,925 participants undergoing bariatric surgery were enrolled between 1984 and 2002 and matched on BMI, age and sex with 7925 participants with BMI  $\geq$  35 kg/m<sup>2</sup> from the general population.<sup>17</sup> After a mean follow-up of 7 years, the overall mortality was 40% lower and the cardiovascular mortality 49% lower with bariatric

surgery. However, the mortality from causes other than disease (e.g. accidents, suicide and poisoning) was increased by 58% in the surgery group. When expressed in natural frequencies, in 10'000 individuals who had bariatric surgery this would prevent 171 deaths from disease but lead to 35 additional deaths not directly related to disease. Consequently, 136 deaths would be prevented in total. Other prospective cohort studies and systematic reviews of observational studies appear to confirm the marked reduction in body weight, type 2 diabetes and disease-related deaths with bariatric surgery in the long-term.<sup>35-39</sup>

Overall, research on bariatric surgery using patient-reported outcome measures is scarce. The generic SF-36 quality of life questionnaire has been used occasionally<sup>40</sup> while disease-specific questionnaires are used only infrequently. Some patient-reported outcome measures have been developed and validated,<sup>41-43</sup> and there are ongoing efforts to better define those and systematically include them in comparative effectiveness research.<sup>44,45</sup> Future studies should use validated patient-reported outcome measures to further examine the effects of bariatric surgery.

The risk of peri-operative mortality up to 30 days after bariatric surgery has been summarized in a large meta-analysis of 361 studies of various designs including data of more than 85'000 individuals.<sup>46</sup> For Roux-en-Y gastric bypass, peri-operative mortality was 1.6 per 1000, for adjustable gastric banding 0.6 per 1000 and for sleeve gastrectomy 2.1 per 1000 interventions. The peri-operative mortality associated with bariatric surgery depends on clinical characteristics, and a risk score has been published to provide estimates according to factors including age, sex, BMI, hypertension and risk factors for pulmonary embolism.<sup>47</sup> Risk prediction scores have been developed to help clinicians predict the peri-operative mortality associated with bariatric surgery.<sup>48,49</sup>

Additional surgical interventions are common with bariatric surgery, especially after adjustable gastric banding. Up to 10 years after initial surgery 13 of 21 patients with gastric banding underwent 16 additional bariatric surgery procedures compared to 6 procedures in 4 of 22 patients with conservative treatment.<sup>32</sup> Another study reported revision rates of up to 41% in the first years of gastric banding surgery (1994 to 2005) followed by a marked decline to 6% (2006 to 2011) as the technique evolved.<sup>50</sup> Some adjustable gastric banding procedures might also be linked to failed weight loss and subsequent scaling up to Roux-en-Y gastric bypass to obtain the desired weight reduction and improvement in clinical outcomes.<sup>2</sup> Bariatric surgery may also entail a need for secondary plastic surgery, although no specific data were reported in the included studies.

Nutritional deficiencies in iron, calcium, vitamin B12, vitamin D and folic acid can occur after bariatric surgery, especially if patients are not compliant with lifelong monitoring of their dietary intake and the recommended supplementation.<sup>51</sup> Although data are scarce with regard to the long-term consequences of nutritional deficiencies, studies have raised concerns about a potential increase in osteoporosis in the long term.<sup>52</sup>

The increase in suicides associated with bariatric surgery in the Utah cohort<sup>17</sup> was confirmed in a systematic review of observational studies summarizing the evidence of 28 studies with a total of 95 suicide events in 190'000 person-years of follow-up.<sup>21</sup> While the risk of suicide appears to be increased overall in individuals with severe obesity, part of this risk might be associated with bariatric surgery in particular.<sup>21,53</sup> In a large population-based cohort in Canada, an increase in self-harm emergencies after bariatric surgery was found.<sup>53</sup> The study enrolled 8815 adults who were followed 3 years before and 3 years after bariatric surgery. Before surgery, the risk of self-harm emergencies was 2.3 per 1000 person-years and after bariatric surgery it was 3.6 per 1000 person-years. 93% of such emergencies were in individuals with a mental health disorder diagnosed within the last 5 years. The study also found that the risk was highest in the second and third years after surgery. A systematic follow-up of patients after bariatric surgery to detect and treat psychiatric co-morbidities appears to be key to limit such adverse outcomes.<sup>54</sup>

Recently, an increase in risk of alcohol misuse disorder has been suggested, especially after Roux-en-Y gastric bypass.<sup>19,20</sup> Gastric bypass patients appear to develop a lower tolerance for alcoholic beverages because their altered digestive tract absorbs alcohol at a faster rate.<sup>55</sup> With an underlying alcohol misuse disorder this might lead to severe alcohol intoxications in some patients.

## 2.2. Health-economic aspects

The assessment included a systematic review of health-economic articles on bariatric surgery. Studies with data applicable to Switzerland were identified and reported incremental cost-utility ratios (ICURs) with bariatric surgery compared to those with conservative treatment. The assessment team then performed budget impact analyses; first, by estimating the costs of treating all eligible individuals in Switzerland with surgery and second, by estimating the potential costs of surgery over a 10-year period from a health system perspective.

Twenty-one individual cost-effectiveness analyses and one systematic review of such studies were included in the Assessment Report. All except one were cost-utility analyses, i.e. cost-effectiveness analyses using quality-adjusted life year (QALY) as their benefit measure. The only exception was the study by Michaud et al., which reported life years and costs per life year gained.<sup>56</sup> Of the individual studies, ten were performed in Europe and eleven in the USA or Australia. Time horizons ranged from 5 years to lifelong. A total of 15 articles fulfilled the criteria for qualitative transferability and underwent numerical adaptation of ICUR values to Switzerland.

### *Cost-utility for individuals with BMI $\geq 35$ kg/m<sup>2</sup> \**

All studies of individuals with BMI  $\geq 35$  kg/m<sup>2</sup> suggested that bariatric surgery is either cost-saving or cost-effective under cost-utility thresholds set by the respective authors. Adaptation to Switzerland resulted in an ICUR below CHF 50'000 per QALY. Most included studies used statistical modeling, some using data from observational studies with up to 20 years of follow-up. Others were limited to effectiveness data from RCTs after 2 years of follow-up and extrapolated for a longer time horizon.

### *Cost-utility for individuals with BMI $< 35$ kg/m<sup>2</sup> \**

Of the 22 retrieved studies, only four specifically estimated the ICUR in individuals with class I obesity (BMI  $\geq 30$  to  $< 35$  kg/m<sup>2</sup>)<sup>57-60</sup> and two in overweight individuals (BMI  $\geq 25$  to  $< 30$  kg/m<sup>2</sup>).<sup>59,60</sup> One study was considered not transferable to Switzerland given insufficient reporting of effectiveness assumptions and type of costs considered.<sup>60</sup> Of the three remaining analyses considering individuals with class I obesity,<sup>57-59</sup> only two included those with type 2 diabetes<sup>57,58</sup> and only one also evaluated individuals without type 2 diabetes.<sup>59</sup> The two studies evaluating the cost-utility of bariatric surgery for individuals with type 2 diabetes used diabetes remission two years after surgery as benefit outcome and, based on this, extrapolated to long-term benefits. However, studies with longer follow-up suggest that a significant proportion experience relapses in diabetes. Consequently, any derived long term incremental cost-utility ratio might overestimate the benefit of bariatric surgery. Thus, only the cost-utility analysis from Sweden by Borg et al.<sup>59</sup> appears to inform reasonably on the economic impact of bariatric surgery among individuals who are overweight or with class I obesity but without type 2 diabetes. The study took BMI as the core predictor of outcomes and costs. Given that survival prospects and costs depend on a patient's BMI, the effect of bariatric surgery on costs and outcomes can be computed by focusing on changes in BMI associated with surgery. Diabetes and other comorbidities were not specifically considered. Extrapolation of the results to individuals with lower BMI should be interpreted

carefully though. The effectiveness data in terms of weight loss associated with bariatric surgery came from the SOS study.<sup>15,16</sup> Data from this study suggest that, in contrast to type 2 diabetes, BMI alone does not explain mortality benefit from bariatric surgery.<sup>15</sup> The investigators of the SOS study specifically called for a change in the guidelines for bariatric surgery to put more importance on metabolic variables and less on BMI.<sup>15</sup> Thus, the results from Borg et al. might be valid to evaluate the benefit of bariatric surgery with BMI >40kg/m<sup>2</sup> but extrapolations to overweight individuals probably require a dedicated modeling approach taking into consideration co-morbidities such as type 2 diabetes.

#### *Budget impact for Switzerland \**

In 2014, a total of 4167 surgeries were performed in Switzerland and the estimated total costs were CHF 61.1 Mio. The budget impact analysis over 10 years was based on the method used previously by Ackroyd et al. to estimate the cost-utility ratio of bariatric surgery among patients with type 2 diabetes.<sup>61</sup> Considering that there were almost 25'000 persons in Switzerland with BMI >40 kg/m<sup>2</sup> in 2012, surgical treatment of all these individuals in a single year would cost about CHF 353 Mio. In addition, if 10-30% of people in Switzerland with BMI of 35 to 40 kg/m<sup>2</sup> were treated with bariatric surgery due to the presence of relevant co-morbidities, the total costs of surgery would reach CHF 496 Mio. to 781 Mio. Given that bariatric surgery leads to diabetes remission in a large proportion of obese individuals with type 2 diabetes, Ackroyd et al. modeled the costs related to this transition. They estimated that individuals undergoing surgery would benefit from 2.8 diabetes-free years compared to 0.2 diabetes-free years in those with conservative treatment. Consequently, in their budget impact analysis the proportion of obese patients with type 2 diabetes determined the overall result. Based on an assumed prevalence of type 2 diabetes of 10% in the population eligible for bariatric surgery in Switzerland, the assessment team calculated that overall costs with surgery would be CHF 41.0 Mio. higher than with conservative treatment in 2016. In turn, with an assumed prevalence of 40%, bariatric surgery would *reduce* costs by CHF 1.2 Mio.

#### *Evidence from observational data \*\**

Given the limitations of the modeling studies that extrapolate from RCT or observational data, claims data from large health insurers might provide some empirical evidence on the impact of bariatric surgery on healthcare costs in individuals with obesity. A recent analysis of data from 29'820 individuals enrolled in a health insurance plan in the USA with more than 18 Mio. members suggested that medical costs were higher with bariatric surgery than with conservative treatment in the second and third year of follow-up and similar afterwards.<sup>62</sup> Other observational studies on healthcare use and expenditures confirm this finding.<sup>63,64</sup> This suggests that, while bariatric surgery might be cost-effective considering the gain in quality of life and life-years per cost unit, actual cost savings in comparison to conservative treatment might not be achieved.<sup>65</sup>

### 2.3. Positions of other health technology assessment agencies

In 1991, the first US consensus guidelines for bariatric surgery recommended that individuals with BMI  $\geq 40$  kg/m<sup>2</sup> or with BMI  $\geq 35$  kg/m<sup>2</sup> and one or more associated diseases should be considered for bariatric surgery.<sup>66</sup> In the meantime most European HTA agencies have issued similar criteria for bariatric surgery.

In 2014, the National Institute for Health and Care Excellence (NICE) in the UK has extended its recommendation for bariatric surgery to individuals with type 2 diabetes of recent onset (defined as a diagnosis within the last 10 years). NICE now recommends that individuals with BMI  $\geq 35$  kg/m<sup>2</sup> have expedited assessment for bariatric surgery and that surgery is considered in the assessment of those with BMI of 30 to 34.9 kg/m<sup>2</sup>.<sup>25</sup> In addition, people of Asian origin who have recent-onset type 2 diabetes should be assessed for surgery already at a lower BMI.

For individuals with type 2 diabetes that was not of recent onset (i.e. diagnosed >10 years ago), NICE recommends bariatric surgery if BMI is  $\geq 40$  kg/m<sup>2</sup> or if it is between 35 and 40 kg/m<sup>2</sup> but associated with other significant diseases such as high blood pressure.<sup>25</sup> NICE recommends that individuals who undergo bariatric surgery have comprehensive follow-up by the bariatric surgery service during a minimum of 2 years including monitoring of nutritional intake, mineral deficiencies and comorbidities, medication review, dietary and nutritional assessment, advice and support for physical activity, tailored psychological support and information about professionally-led or peer-support groups.

In 2009, the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany has recommended bariatric surgery for individuals with BMI  $\geq 35$  kg/m<sup>2</sup> and type 2 diabetes.<sup>67</sup> The recommendation was based on available clinical practice guidelines for the treatment of obesity in individuals with type 2 diabetes and on high-quality systematic reviews.<sup>67</sup> Treatment options under consideration were diet, exercise, behavioral therapy, drug or surgical treatment. Included guidelines recommended bariatric surgery for individuals with BMI  $\geq 35$  kg/m<sup>2</sup> and existing type 2 diabetes if a conservative approach such as dietary intervention, exercise or drug treatment had been unsuccessful in achieving weight loss. Evidence from systematic reviews suggested that diabetes remission was achieved with the surgical procedure in significantly more patients than with a conservative approach.

In the same year the Haute Autorité de Santé (HAS) in France recommended bariatric surgery for individuals with BMI  $\geq 40$  kg/m<sup>2</sup> or with BMI between 35 kg/m<sup>2</sup> and 40 kg/m<sup>2</sup> and another significant disease such as type 2 diabetes, high blood pressure, sleep apnea, other severe respiratory diseases, non-alcoholic steatosis hepatitis (NASH) or invalidating osteoarthritic diseases.<sup>68</sup> To be eligible, individuals should have been unsuccessful with conservative treatment for 6 to 12 months, been well informed about risks and benefits associated with surgery and be at an acceptable risk for surgery.

The Belgian Healthcare Knowledge Center (KCE) issued recommendations for bariatric surgery in 2006 and recommended limiting reimbursement to individuals with BMI of  $\geq 40$  kg/m<sup>2</sup>, or  $>35$  kg/m<sup>2</sup> with severe comorbidity such as diabetes.<sup>69</sup>

## 3. Considerations

### 3.1. Balance between expected benefits and risks

The available randomized evidence from RCTs suggests that obese individuals, in particular those with BMI  $>35$  kg/m<sup>2</sup>, are more likely to achieve a reduction of their body weight in the first two or three years with bariatric surgery than with a conservative approach. However, this evidence is only of moderate quality. For other benefits of bariatric surgery including improvements in quality of life, reduction in type 2 diabetes and hypertension, and in surrogate outcomes such as HbA1c the quality of the evidence is low or even very low. Of note, the probability of diabetes remission at 2 or 3 years appears to be about tenfold higher with surgery than with conservative treatment (RR 10.2, 95% CI 4.4 to 24.0). For relevant long-term clinical outcomes such as

cardiovascular events and mortality the evidence was nearly absent. Evidence of very low quality suggests an increased risk of serious adverse events with surgery. This risk needs to be balanced against the harmful long-term consequences of persistent obesity and its associated co-morbidities such as type 2 diabetes, hypertension and dyslipidemia.

In those with BMI <35 kg/m<sup>2</sup>, existing co-morbidities should be taken into account. There is currently little evidence of increased mortality and risk of cardiovascular events from being overweight or with class I obesity in the absence of co-morbidities.<sup>1,3</sup> Further, there is evidence that type 2 diabetes but not BMI alone is a predictor of long-term outcomes in this group.<sup>15</sup> This underpinned a call for change in bariatric surgery guidelines to give more weight to metabolic co-morbidities and less to classification according to BMI alone.<sup>15</sup> In the UK, bariatric surgery has been recognized as an acceptable therapy in individuals with BMI of 30 to 35 kg/m<sup>2</sup> and recent-onset type 2 diabetes (i.e. diagnosis <10 years ago) after careful review of their eligibility and potential contra-indications.<sup>25</sup> Future assessments should aim to also answer the question whether bariatric surgery is beneficial in individuals with BMI >25 kg/m<sup>2</sup> and type 2 diabetes.

With only limited evidence available from RCTs, observational studies gain in importance for a comprehensive view on the benefit and harm of bariatric surgery. Overall, the considered observational studies showed a substantial long-term benefit of bariatric surgery with regard to all-cause mortality and reduction in cardiovascular events despite an increase in peri-operative mortality and in not directly related deaths such as suicides. While a net benefit in life years and improvements in the physical components of health-related quality of life is likely, there are inherent trade-offs including a limited (if any) benefit in mental health outcomes and the mental components of health-related quality of life. Observational data may also provide a more reliable estimate of the safety of bariatric surgery and the rate of reoperations. Peri-operative mortality estimated from a large systematic review of observational data varied across types of interventions and co-morbidities. Reoperations are common with bariatric surgery, especially after adjustable gastric banding surgery.

Generally, more and better research is needed to identify individuals who are mostly likely to benefit from bariatric surgery in the long term and especially to predict relapses in weight gain and type 2 diabetes.

### 3.2. Balance between expected utility and costs

For individuals with BMI  $\geq$ 35 kg/m<sup>2</sup> with or without co-morbidities such as type 2 diabetes, hypertension and dyslipidemia, the incremental cost-utility ratio (ICUR) of bariatric surgery appears acceptable if commonly accepted cost-utility thresholds are applied. On one hand, there are high upfront costs with bariatric surgery and more medical examinations in the early years following bariatric surgery. On the other hand, the long-term outcomes improve with surgery including a reduction in comorbidities, cardiovascular events and mortality. Consequently, as the postoperative observation period is extended, the ICUR of bariatric surgery becomes more favorable. Evidence from claims data indicates that total costs are higher with bariatric surgery compared to conservative treatment because the cost savings due to reduced prevalence of type 2 diabetes after surgery do not fully compensate the high initial costs of the surgery.<sup>65</sup>

### 3.3. Patient involvement in treatment choice

Bariatric surgery has to be applied according to Swiss professional standards. In this respect, especially the general provisions of medical and healthcare law have to be considered. Rightly, guidelines recommend that individuals should be informed on the potential short- and long-term benefits and risks associated with bariatric surgery.<sup>25,66</sup> Notably patients have to be adequately

informed about the disease pattern, therapeutic options and any consequences with and without bariatric surgery. Given the complex effects of surgery on body weight, quality of life and the risks of type 2 diabetes, hypertension, cardiovascular events and mortality there are considerable uncertainties. Patients should learn about these uncertainties before they give informed consent to bariatric surgery, ideally in an encounter following the principles of shared decision making and based on information provided by healthcare professionals without competing financial and other interests in bariatric surgery.<sup>2,70</sup> Patients' decisions may become complex due to possible pressure from the social environment to reduce weight. Sometimes it is difficult for them to see themselves in the future, e.g. to imagine the change of their dietary and other behavior after bariatric surgery. Therefore, they must be allowed an appropriate delay for reflection before they decide about surgery. Current guidelines of the Swiss Society for the Study of Morbid Obesity and Metabolic Disorders (SMOB) recognize these issues.<sup>7</sup> They support the careful evaluation of patients by a pluri-disciplinary team after at least two years of attempt to reduce weight with conservative treatment and a minimum delay of three months to think about any decision for surgery.

Decision aids have been developed to help patients to decide in the light of current evidence. A video decision aid has been tested in a randomized trial and showed improvements in knowledge, decisional conflict and outcome expectancies compared to an information booklet.<sup>70</sup> Some centers in Switzerland have developed group courses to prepare patients for bariatric surgery and help them understand its benefits, risks and long-term consequences. However, in Switzerland, there is currently no formally endorsed decision aid material detailing the expected short- and long-term outcomes associated with bariatric surgery. This entails the possibility that the information provided to eligible patients varies between the centers offering bariatric surgery in Switzerland.

### 3.4. Further considerations

The long-term consequences of bariatric surgery do not seem to be studied sufficiently. A particular emphasis should be given to psychiatric adverse effects, alcohol misuse and nutritional deficiencies that may lead to bone loss. Few studies have measured patient-reported outcomes specifically, and this underscores the need for better involvement of patients into the design and conduct of clinical research. This corresponds to the general rules concerning "Information and Consent" of the Swiss Human Research Act.<sup>71</sup>

In publicly funded healthcare systems such as the UK or Canada, a patient who, based on an evaluation of individual risks and benefits, has not been deemed eligible for bariatric surgery by a qualified medical team cannot have surgery by another team. In contrast, insurance-based healthcare systems with a fee-for-service reimbursement scheme provide incentives for healthcare providers and opportunities for patients to eventually receive the desired intervention even if a first evaluation was not in favor. Simply, another center might come to a different conclusion and eventually perform surgery. In Switzerland this difficult situation led the SMOB to develop strict guidelines and mandatory follow-up of patients for at least 5 years after surgery. Moreover, its registry has become an important tool to monitor clinical outcomes in patients who underwent bariatric surgery in Switzerland. However, unlike other registries in the USA or Sweden,<sup>9,15</sup> there is no matched comparison group of individuals without surgery that could inform clinicians and decision makers on the comparative effectiveness of bariatric surgery and conservative treatment. In the absence of a population-based registry, individuals who are most likely to benefit from surgery cannot be identified with certainty.

## 4. Recommendations

The Appraisal Committee makes the following recommendations:

1. Individuals with BMI >35 kg/m<sup>2</sup> (obesity of class II or more) should be offered the possibility of bariatric surgery after a careful evaluation of their eligibility for surgery and their individual risk and benefit by an inter-disciplinary team.
2. For individuals with BMI >30 to <35 kg/m<sup>2</sup> (class I obesity) and related co-morbidities such as type 2 diabetes, bariatric surgery can be considered a treatment option after careful evaluation of the severity and duration of the co-morbidities and the risk and benefit of surgery.
3. It is reasonable to delay bariatric surgery for a certain period of time in favor of conservative treatment.
4. Bariatric surgery should be performed in a recognized center.
5. All individuals eligible for surgery should receive balanced and unbiased information on short- and long-term risks and benefits of bariatric surgery including an explanation of the uncertainties around long-term outcomes.
6. All patients undergoing bariatric surgery should be enrolled in a registry such as the current SMOB registry to ensure long-term follow-up for somatic and mental health outcomes.
7. The criteria for reimbursement by the statutory health insurance (i.e. a minimum of 2 years of conservative management before bariatric surgery for individuals with BMI >35 kg/m<sup>2</sup>) should be re-evaluated taking into account the current state of knowledge.
8. Given the limited evidence from RCTs and observational studies, there is a strong case for more research. Patients and health professionals need better evidence to be able to take informed decisions about bariatric surgery.
  - Research should provide data on the life course of obese individuals with or without surgery.
  - Special attention should be given to metabolic co-morbidities as additional prognostic factors and as criteria for bariatric surgery.
  - Risk prediction tools should be developed to better determine participants most likely to benefit from either bariatric surgery or conservative treatment.

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