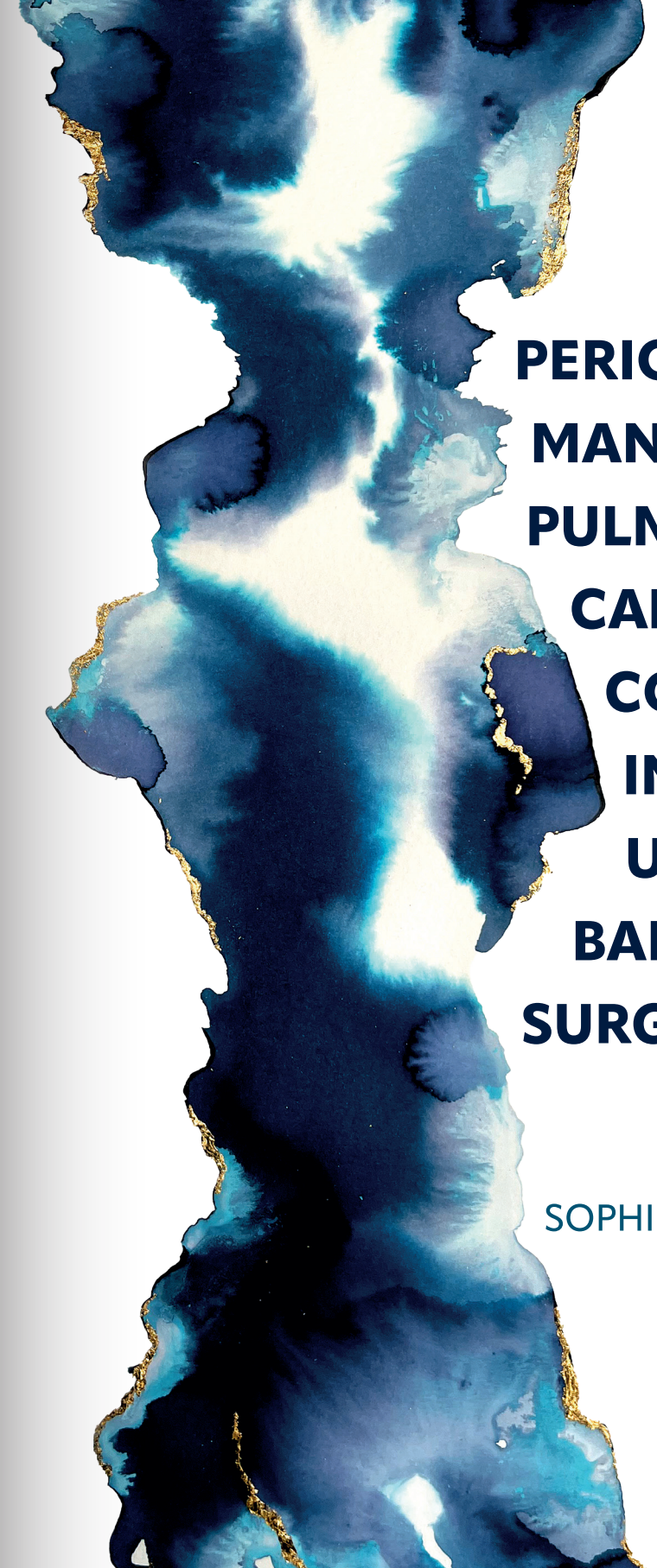

PERIOPERATIVE MANAGEMENT OF PULMONARY AND CARDIOVASCULAR COMORBIDITIES IN PATIENTS UNDERGOING BARIATRIC SURGERY

SOPHIE L. VAN VELDHUISEN

Propositions

1. Postoperative continuous pulse oximetry monitoring is a safe and cost-effective perioperative strategy for bariatric patients with undetected obstructive sleep apnea. (this thesis)

2. Bariatric surgery reduces the incidence of mortality and cardiovascular diseases dramatically compared to best non-surgical care in patients with obesity. (this thesis)

3. People-first language is an essential tool to eradicate weight bias and stigma.

4. The Medicine curriculum should incorporate an Art History course to improve development of diagnostic clinical skills.

5. Playing music in the operating theatre enhances surgical performance.

6. Completing a PhD is much like all major sport achievements: it's all about perseverance and communication, much less about intelligence.

Propositions belonging to the thesis, entitled
Perioperative management of pulmonary and cardiovascular comorbidities in patients undergoing bariatric surgery.

Sophie van Veldhuisen
Wageningen, 30 November
2022

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PERIOPERATIVE MANAGEMENT OF PULMONARY AND CARDIOVASCULAR COMORBIDITIES IN PATIENTS UNDERGOING BARIATRIC SURGERY

Sophie Laura van Veldhuisen

Thesis
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Prof.dr. A.P.J. Mol,
in the presence of the
Thesis Committee appointed by the Academic Board
to be defended in public
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Sophie Laura van Veldhuisen
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Voor mijn ouders

CONTENTS

CHAPTER 1

General introduction and outline of thesis

INTRODUCTION

Obesity, related diseases and treatment

Obesity is a major global health problem, and prevalence continues to rise at an alarming rate. Currently, 650 million people worldwide are affected with obesity, defined as body mass index (BMI) of ≥30 kg/m^2.(1) As obesity is a multifactorial and complex disease, it synchronously increases prevalence of obesity-related comorbidities, placing a heavy burden on global public health, life expectancy and quality of life.(2) Many disorders are related to obesity, including type 2 diabetes (T2DM), hypertension, hypercholesterolemia, heart failure, atrial fibrillation, non-alcohol fatty liver disease, joint disorders, chronic kidney disease and obstructive sleep apnea (OSA). Prevention of obesity should be the cornerstone of the strategy to deal with this global health issue. Unfortunately, no effective programs to prevent overweight and obesity have been developed to date. Treatment has historically focussed on the believed origin of obesity: a disbalance of increased food ingestion and limited energy expenditure. Conservative treatment with diets, combined lifestyle interventions or drug treatment have targeted this imbalance, and seem to achieve mild changes of body weight, but do not generate sustainable results. New drugs developed for treatment of diabetes mellitus, such as glucagon-like peptide 1 agonist (GLP-1) receptor agonist and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, show promising results in weight loss and improvement of T2DM, but do not play a defined role in the treatment for obesity yet.(3) Therefore, bariatric surgery is currently the only treatment option that induces significant and sustainable weight loss. Bariatric surgery was first introduced in 1953, and has undergone various changes ever since.(4) Initially, the term bariatric surgery comes from the Greek words 'baros' meaning weight, and 'iatros' meaning doctor, referring to the significant reduction of body weight. Nowadays, it is increasingly referred to as metabolic surgery due to significant reduction or resolution of most comorbidities. Over the years, techniques have refined and bariatric procedures now have an acceptable rate of complications, with a 30-day mortality rate <0.2%.(5) Annually, almost 700,000 procedures are performed worldwide, and the most commonly used procedures are currently the Sleeve Gastrectomy and the Roux-en-Y gastric bypass. Both procedures limit food intake and alter gut hormone regulation, and the gastric bypass additionally induces nutrient malabsorption. All effects of bariatric surgery improve long-term survival of obese persons compared to controlled matched obese patients who do not undergo bariatric surgery, but also increases general quality of life. (6) Bariatric surgery can be considered in adults with a BMI of ≥40 kg/m^2, or for patients with a BMI ≥35 kg/m^2 who additionally have an obesity-related comorbidity that is expected to improve after surgically induced weight loss.(7)

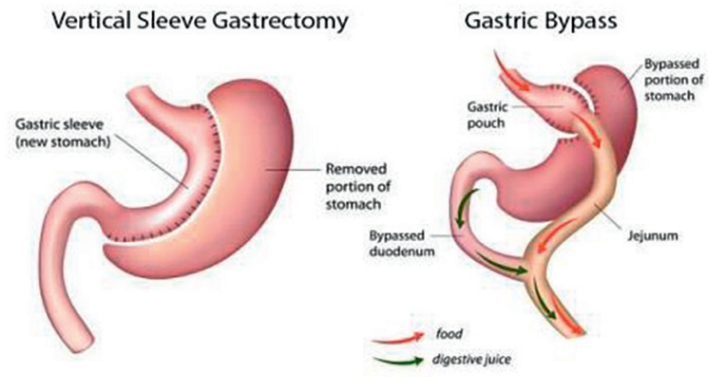


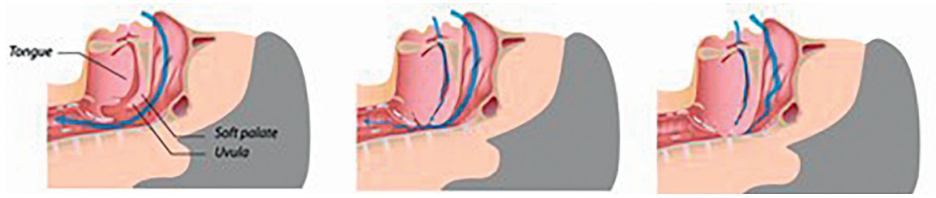
Figure 1: The most commonly performed bariatric procedures: sleeve gastrectomy and Roux-en-Y gastric bypass

Obstructive sleep apnea

Of all obesity-related comorbidities, OSA is perhaps the most common; with prevalence of approximately 60-70% in literature.(8-10) This high prevalence can be explained by the close relationship between obesity and OSA. This sleep-breathing disorder is characterized by recurrent collapses of the upper airway during sleep, resulting in complete or partial cessations of breathing, respectively called apneas or hypopneas. These breathing cessations lead to hypoxia, causing frequent arousals from sleep and henceforth result in excessive daytime sleepiness.(11) No curative treatment options for OSA exists, but treatment with continuous positive airway pressure (CPAP) is considered the golden standard, and is recommended once moderate or severe OSA is detected. Other options such as mandibular advancement devices, tongue stimulators, or surgical procedures that enlarge the upper airway by partial resection of the palate and pharynx are applied too, but cannot be considered as curative treatment options. However, following weight loss, OSA can completely resolve, or be reduced in severity. Due to the close-knit relation between obesity and OSA, it may come as no surprise that remission and even resolution of OSA occurs in a high percentage of patients following surgically induced weight loss, in 60-75% of OSA patients.(12, 13)

Studies in bariatric populations all note the same phenomenon: the prevalence of OSA is extremely high, but the majority of patients is unaware of this diagnosis until preoperative sleep studies is performed.(14) This creates a clinical challenge, as untreated OSA increases the risk of peri- and postoperative desaturations and subsequent complications. Currently, the best perioperative management of patients without known OSA remains unclear. Although mandatory OSA screening using poly(somno)graphy of bariatric surgical patients has been

advocated, sleep studies are costly and time consuming. An alternative strategy is using a screening questionnaire that select patients with high risk of undetected OSA. These questionnaires are easy to use, limit the utilization of hospital resources, but are unfortunately unable to render both high specificity and sensitivity rates in the general population, let alone patients with severe obesity. Patient evaluated to bariatric surgery score high in many criteria in these questionnaires due to high bodyweight and frequent obesity-related comorbidities, thus making distinction between high-risk patients unreliable.(15) An alternative is continuous postoperative pulse oximetry without preoperative screening for OSA. Using this strategy, patients do not undergo preoperative screening diagnostics, but receive supplemental oxygen via nasal cannula after surgery, and are monitored during the first postoperative night for the incidence of desaturations. The hypothesis is that hypoxemic periods can be stopped in an early phase, thus preventing postoperative complications. No literature comparing perioperative strategies for OSA is available. A consensus-based guidelines are currently highest level of evidence, which is an strong indicator that much research can be done in this research area.(16)



Normal breathing | Hypopnea: partial obstruction of the airway | Apnea: complete obstruction of the airway

Figure 2: Pathogenesis / functional aetiology of obstructive sleep apnea

Cardiovascular disease in obesity

Cardiovascular (CV) risk factors such as diabetes, hypertension, dyslipidaemia and systemic inflammation are common in obese persons. As a result, CV diseases and related mortality are also related to obesity.(17) Among these CV diseases, coronary artery disease, atrial fibrillation (AF), heart failure (HF), myocardial infarction and stroke are frequently present in obese subjects, especially compared to their peers with a healthy BMI.(18) However, many studies on prevalence of specific CV disease in bariatric patients are mostly retrospectively conducted. Most bariatric clinics do not thoroughly assess each patient for CV disease, because bariatric patients are generally relatively young compared to average patients that are affected by CV disease. Current prevalence data on CV disease in the bariatric population usually stems from large nation-wide registries, and therefore might be incomplete. This is probably the reason why current guidelines give hardly any direction to clinicians which patients need to be preoperatively screened, and what the true effect of bariatric surgery is on

(development of risk factors for) CV disease.(19) As weight reduction can resolve or reduce a substantial amount of CV risk factors and thus potentially prevent development of CV diseases, bariatric surgery poses an opportunity to conduct research to the reversibility of various CV diseases.

AIM AND OUTLINE OF THIS THESIS

The purpose of this thesis is to gain further insight into both pulmonary and cardiovascular comorbidities in bariatric patients and to optimize perioperative care. In particular, Part A will focus on obstructive sleep apnea; whether preoperative assessment is needed in order to safely undergo bariatric surgery, and if so, what type of assessment is necessary and cost-efficient. In Part B, preoperative assessment of the presence of a CV disease is evaluated, and additionally the effect of weight loss on the incidence of CV disease in obese patients in reported.

Part A - Obstructive sleep apnea in patients undergoing bariatric surgery

To answer the question what the best type of perioperative care is for undiagnosed OSA in patients undergoing bariatric surgery, we looked into the different strategies that are currently used. Outcomes that we were particularly interested in were optimal patient care with an optimal safety profile regarding postoperative complications, optimize quality of life, and efficient use of available healthcare resources. In **Chapter 2** we retrospectively evaluate perioperative care of potential OSA patients undergoing bariatric surgery without preoperative OSA screening. Instead, patients were postoperatively monitored using continuous pulse oximetry. In **Chapter 3** we compare two different types of preoperative screening. We analysed whether less-invasive, home-based testing with polygraphy is also suited for preoperative OSA screening in the bariatric population, and we did so by comparing the results following polygraphy testing with the results from the golden standard, the in-hospital test polysomnography. In **Chapter 4** we retrospectively analyse the patients that have already undergone formal sleep studies, and aimed to identify risk factor for prevalence of OSA and predict postoperative complications.

With the growing obesity epidemic, utilization of resources should be accounted for, and the balance between too little and too much diagnostic efforts should be assessed. Therefore, in the POPCORN study, we compared continuous pulse oximetry monitoring with routine preoperative OSA assessment with sleep studies in terms of complications and quality of life, we analysed cost-effectiveness. In this way, justification of expenses can be made based on actual data instead of assumption-based calculations. In **Chapter 5** we describe the research protocol of the POPCORN study, and in **Chapter 7** we report the primary outcomes; cost-effectiveness expressed in costs vs. quality-adjusted life years (QALYs), and surgical outcomes such as postoperative complications, intensive care admissions and quality of life. In **Chapter 6** we report on secondary outcomes of the patient group that underwent polygraphy and consequent CPAP treatment, and see the impact of routine screening on actual implications

in daily life. We analysed the adherence to CPAP of patients newly diagnosed with OSA, and compare these outcomes to patients who have been CPAP users for years, and express this in hours per night of CPAP use, but also to (sleep related) quality of life.

Part B - Cardiovascular diseases and risk factors in bariatric patients

The majority of patients that suffer from CV disease are older than the average bariatric patients, with an mean age of 40-45 years. Even so, patients that undergo bariatric surgery usually have many risk factors for development of CV disease and together with high BMI, one could argue these patients are biologically older than their non-obese peers. Therefore, in **Chapter 8** we screened the 'elderly' bariatric population for the prevalence of CV disease using NT-proBNP assessment in all in consecutive patients 50 year and older, to evaluate actual CV disease prevalence and related echocardiographic features. In **Chapter 9** we used a different approach to evaluate the influence of abundant body weight on the risk of development of CV disease, by performing a systematic review and meta-analysis that assessed the incidence of mortality and CV disease following bariatric surgery and compare this to obese controls.

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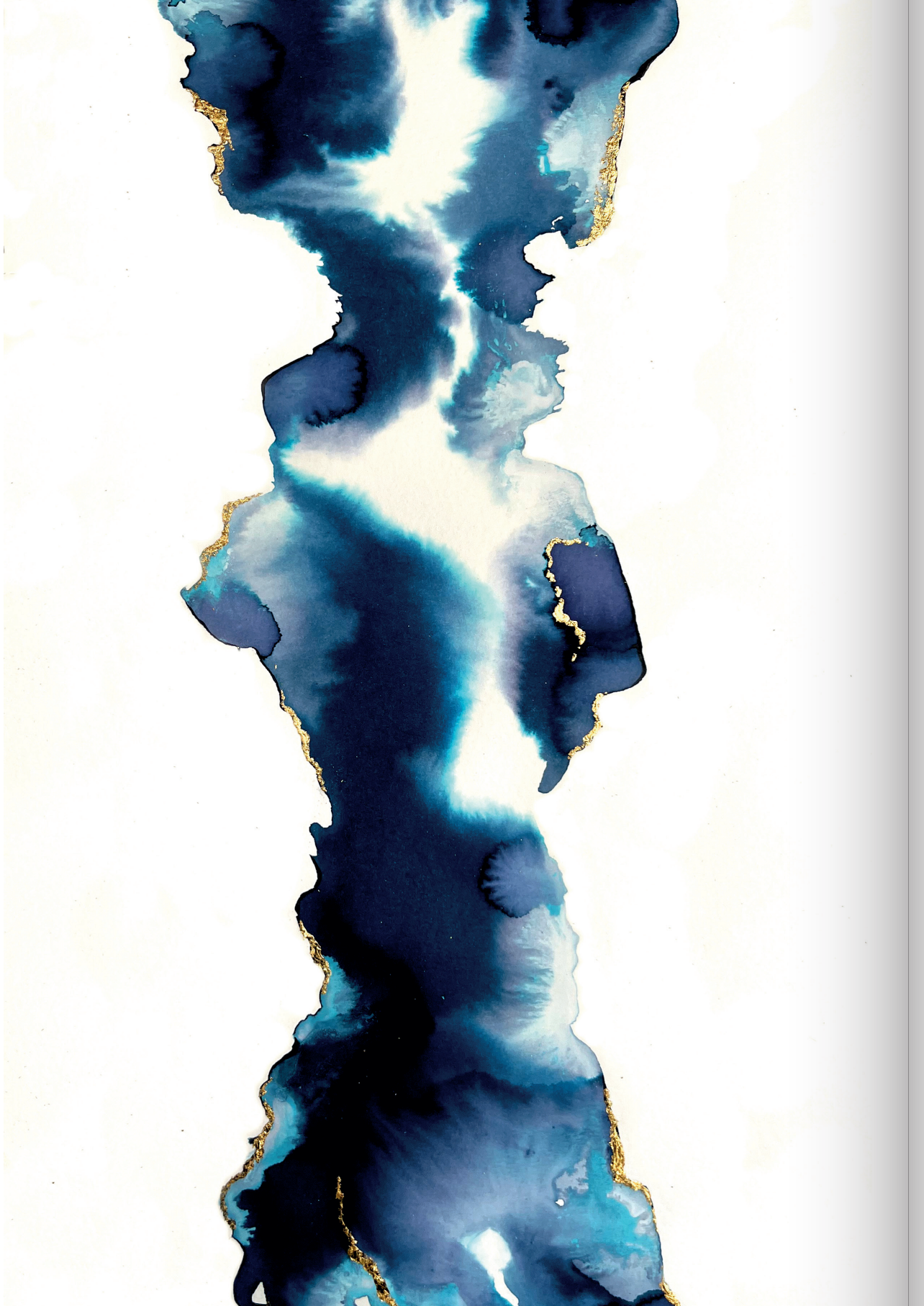

PART A

OBSTRUCTIVE SLEEP APNEA IN PATIENTS UNDERGOING BARIATRIC SURGERY

CHAPTER 2

Safety of continuous postoperative pulse oximetry monitoring without obstructive sleep apnea screening in > 5000 patients undergoing bariatric surgery

Van Veldhuisen SL, Arslan I, Deden LN, Aarts EO, Hazebroek EJ

Obesity Surgery, 2020.

ABSTRACT

Introduction
Obstructive sleep apnea (OSA) is common but often undiagnosed in obese patients undergoing bariatric surgery, and is associated with increased risk of cardiopulmonary complications. The aim of this study is to evaluate the safety of continuous postoperative pulse oximetry (CPOX) without preoperative OSA screening in bariatric patients.

Methods
Retrospective, single-center cohort study of all consecutive patients who underwent bariatric surgery between 2011 and 2017. All patients were postoperatively monitored with CPOX and received oxygen supplementation. Patients with no history of OSA (the "CPOX" only group) were compared to patients with adequately treated OSA as a reference group. The primary outcome was the incidence of cardiopulmonary complications within 30 days after surgery. Secondary outcomes included overall 30-day complications, mortality, intensive care unit (ICU) admissions, readmissions and length of stay.

Results
In total, 5682 patients were included, 89.6% (n=5089) had no history of OSA, 10.4% (n=593) had adequately treated OSA. Cardiopulmonary complications occurred in the CPOX group and OSA group in 0.6% (n=31) and 0.8% (n=5), respectively (p=0.171). No mortality occurred due to cardiopulmonary complications. In both groups, one patient required ICU admission for respiratory failure (p=0.198). Non-cardiopulmonary complications occurred in 6.4% in the CPOX group and 7.8% in the OSA group (p=0.792). Mortality, ICU admissions, readmissions and length of stay were not significantly different between groups.

Conclusions
These data suggest that CPOX monitoring without preoperative OSA-screening is a safe and effective strategy in perioperative care of bariatric patients. Future studies are needed to assess whether this strategy is also cost-effective.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep-breathing disorder in obese patients undergoing bariatric surgery, with a reported prevalence of 35-94%(1-6). OSA is characterized by recurrent complete or partial collapses of the upper airway during sleep, resulting in cessations of breathing, hypoxia, hypercapnia and arousals from sleep(7). The presence of (untreated) OSA is associated with postoperative desaturations, cardiopulmonary complications and the need for reintubation, subsequent morbidity and mortality(8, 9). This can be the result of several anesthetic agents, difficult intubation and postoperative obstruction of the upper airway(8, 10).

Considering that the majority of patients with OSA are undiagnosed and thus untreated at the time of bariatric surgery, and more than 700,000 bariatric procedures are performed yearly worldwide(11), it is surprising that optimal perioperative care of these patients remains unclear. As data is scarce, a consensus-based guideline is currently the highest form of evidence and advocates mandatory preoperative OSA screening with polysomnography before bariatric surgery. Patients with OSA are subsequently treated with continuous positive airway pressure (CPAP)(12). However, sleep studies used in this approach are costly and time consuming. Alternatively, questionnaires have been proposed for risk stratification of OSA, in order to apply extensive diagnostics only in high-risk patients. However, these questionnaires are inconsistently reliable in terms of specificity and sensitivity(13). In addition, no data is available on the effectiveness of these preoperative interventions in long-term outcomes of OSA.

Our protocol for perioperative management of bariatric patients is based on the assumption that every patient potentially has OSA. Consequently, diagnostic measures to assess OSA (e.g. sleep questionnaires and polysomnography) are not employed in the preoperative work-up of patients undergoing bariatric surgery. This perioperative management strategy focuses on maintaining adequate saturation rates during the first night after surgery using continuous postoperative pulse oximetry (CPOX) monitoring and non-invasive supplemental oxygen via a nasal cannula.

Therefore, the aim of this study is to assess the safety of postoperative CPOX monitoring, without performing extensive preoperative OSA screening in a large cohort of morbidly obese patients undergoing bariatric surgery. These results will be compared to those of patients with known and adequately treated OSA.

METHODS

Patient selection

All consecutive patients who underwent bariatric surgery between November 2011 and September 2017 in Rijnstate Hospital were reviewed for this single-center, retrospective cohort study. Patients were divided into two groups, based on whether or not they had a prior OSA diagnosis. Patients with no history of OSA were included in the "CPOX" group, and did not undergo preoperative OSA screening for OSA. Patients with known and adequately treated OSA served as the reference group; adequate treatment was defined as CPAP or treatment with a similar treatment modality with positive airway pressure (PAP). Patients were excluded if they were known to have OSA, but did not receive adequate treatment for OSA. Patients were also excluded if relevant data regarding follow-up of the first 30 days after surgery were missing. The protocol of this retrospective study was reviewed and approved by the Medical Ethics Committee of Rijnstate Hospital Arnhem.

Standard perioperative protocol

Rijnstate Hospital (in the Netherlands) comprises a high-volume bariatric center, performing 1000-1300 bariatric procedures per year. All patients are treated according to the local protocol for peri- and postoperative care, which was implemented in November 2011 and is based on the principles of enhanced recovery after bariatric surgery (ERABS), also referred to as 'fast-track' surgery(14). Additionally, our local protocol includes routine postoperative CPOX monitoring, starting directly after a patient's arrival on the surgical ward and is continued during the first postoperative night. CPOX monitoring is performed using a Draeger Infinity Delta monitor (Draeger Medical Systems Incorporated, USA). In addition to monitoring, all patients receive 2L/min of supplemental oxygen via a nasal cannula. Heart frequency and saturation rates are displayed at the patient's bedside and in the nurses' office, where audible alarms go off when a desaturation occurs of <92% Sp02, lasting >10 seconds. In case of a desaturation, the attending nurse performs a clinical evaluation and consults the attending physician when clinically relevant desaturations occur. Patients with adequately treated OSA are also postoperatively monitored by CPOX, and supplemental oxygen is added to the ventilation of the CPAP machine. Patients are generally discharged on the first day after surgery.

Outcomes

The primary outcome was the incidence of cardiopulmonary complications within 30 days after bariatric surgery. These complications included the following: acute respiratory failure, aspiration, the need for tracheal reintubation, atelectasis, pneumonia, arrhythmias such as atrial fibrillation (AF), myocardial infarct, heart

failure, tachycardia/bradycardia combined with clinical deterioration, malignant hypertension defined as systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg with or without secondary organ damage.

The secondary outcomes were overall 30-day complications, mortality, transfers to intensive care unit (ICU) or medium care unit (MCU), reoperations, readmissions and length of stay. Complications were prospectively registered in a database by a specialized bariatric nurse. These data were reviewed anew for this study by SvV and IA. In addition, the ICT team conducted searches in patient files for deaths, ICU and MCU admissions, readmissions and reoperations. All patients had standard follow-up appointments, at ten days and six weeks after surgery, during which potential complications were also evaluated. The severity of all complications was assessed using the Clavien-Dindo Classification(15). Minor complications were defined as class 1 or 2, for which required interventions did not exceed antibiotic treatment or intravenous fluids. Major complications were defined as all complications of class 3A and higher, defined as complications requiring at least an intervention under local anesthesia. In case of multiple, consecutive complications, the initial complication was listed.

Statistical analysis

Normally distributed data are described using means with standard deviation, and non-normally distributed data are described in median and interquartile range (IQR). Unpaired t-tests were used for comparison of continuous data with normal distribution between the CPOX group and the OSA group. Non-normally distributed data were compared using a Mann Whitley U test and discrete data using Chi Square tests or Fisher's exact tests. All tests were two-tailed and p-values <0.05 were considered statistically significant. Univariate logistic regression analysis was used to determine associations between potential confounders and the primary outcome. Data was analyzed using IBM SPSS Statistics, version 25.0 for Windows (SPSS, Chicago, IL).

RESULTS

During the study period, a total of 5918 patients underwent laparoscopic bariatric surgery at our institution. Of these, 178 patients were excluded due to a pre-existent OSA diagnosis with inadequate treatment and 58 patients due to missing follow-up data (Supplementary Table 1). In total, 5682 patients were included; 5089 patients (89.6%) had no pre-existent OSA diagnosis and 593 patients (10.4%) were already diagnosed with OSA and received adequate treatment. The groups were significantly different regarding gender, age, preoperative BMI, prevalence of DM and surgical procedure (Table 1). The majority of patients (72%) underwent laparoscopic Roux-en-Y gastric bypass

(LRYGB), while 13.3% underwent laparoscopic sleeve gastrectomy (LSG). The remaining patients (14.7%) underwent revisional surgery; either conversion of a laparoscopic adjustable band to a LRYGB, or a single anastomosis duodeno-ileal bypass following LSG.

Table 1. Baseline patient characteristics

	Total (n=5682)	CPOX (n=5089, 89.6%)	OSA (n=593, 10.4%)	*p*-value
Female (n,%)	4531 (79.7)	4239 (83.3)	292 (49.2)	<0.001
Age, years (mean, SD)	44.8 ±10.8	44.1 ±10.8	51.1 ±8.6	<0.001
BMI, kg/m2 (mean, SD)	43.9 ±6.4	43.8 ±6.3	45.1 ±6.8	<0.001
Waist circumference, cm (mean, SD)	129.1 ±14.4	128.2 ±14.2	136.8 ±14	<0.001
Diabetes Mellitus (n,%)	1400 (24.6)	1142 (22.4)	258 (43.5)	<0.001
Type of surgery				
LRYGB (n,%)	4089 (72)	3615 (71)	474 (79.9)	<0.001
LGS (n,%)	755 (13.3)	684 (13.5)	71 (12)	
Revision surgery (n,%)	838 (14.7)	790 (15.5)	48 (8.1)	

BMI body mass index, LRYGB laparoscopic Roux-en-Y gastric bypass, LSG laparoscopic sleeve gastrectomy, ± standard deviation

Primary outcomes

Cardiopulmonary complications within 30 days after surgery occurred in 0.6% (n=31) of the CPOX group and in 0.8% (n=5) of the OSA group (p=0.171), though none of these were fatal (Table 2). Although the incidence of major complications was low in both groups and no significant difference was detected, there was a trend towards a higher incidence of major complications in patients with OSA (CPOX 0.04% (n=2) vs. OSA 0.33% (n=2), p=0.057). The incidence of minor cardiopulmonary complications was similar between the two groups, 0.57% vs. 0.51%, respectively (p=0.844). In both groups, one major complication led to an ICU admission (Table 3). In the CPOX group, ICU admission was necessary in a patient who developed respiratory failure immediately after surgery. This patient developed hypoxemia, hypercapnia and decreased awareness, and required reintubation. The patient was extubated and discharged to the clinical ward the next day. In the OSA group, ICU admission with reintubation was necessary for respiratory failure due to an acute episode of severe asthma immediately after surgery. The patient was extubated the next day and was discharged to the clinical ward on the third postoperative day. The remaining major complications (n=2) resulted in MCU admissions; one patient in the CPOX group suffered from new onset AF, unresponsive to medication, and therefore required cardioversion. New

onset AF was also the reason for medication and cardioversion in one patient in the OSA group.

Table 2. Cardiopulmonary complications

	CPOX (n,%)	OSA (n,%)	*p*-value
All cardiopulmonary complications	**31 (0.61)**	**5 (0.84)**	**0.171**
Major CDC	2 (0.04)	2 (0.33)	0.057
Minor CDC	29 (0.57)	3 (0.51)	0.844
Pulmonary complications	**18 (0.36)**	**1 (0.17)**	**0.714**
Respiratory failure	1 (0.02)	1 (0.17)	
Bronchial spasms	1 (0.02)	0 (0)	
Pneumonia	14 (0.28)	0 (0)	
Acute bronchitis	1 (0.02)	0 (0)	
Upper airway infection	1 (0.02)	0 (0)	
Cardiologic complications	**13 (0.26)**	**4 (0.67)**	**0.093**
Atrial fibrillation	7 (0.14)	2 (0.34)	
Atrial flutter	1 (0.02)	0 (0)	
Supraventricular tachycardia	2 (0.04)	0 (0)	
Malignant hypertension	1 (0.02)	1 (0.17)	
Bradycardia	1 (0.02)	1 (0.17)	
Intraoperative ST-segment elevation	1 (0.02)	0 (0)	
Requiring readmission	**9 (0.18)**	**1 (0.17)**	**0.947**
Requiring ICU admission	**1 (0.02)**	**1 (0.17)**	**0.198**
Requiring MCU admission	**5 (0.10)**	**2 (0.34)**	**0.161**

CDC complication severity according to Clavien Dindo Classification. Minor CDC: class 1-2. Major CDC ≥ class 3A, ICU intensive care unit, MCU medium care unit.

Table 3. Predictors of cardiopulmonary complications

	OR	95% CI	*p*-value
Gender	1.126	0.512-2.476	0.769
Age	1.038	1.005-1.072	0.023
BMI	1.043	0.999-1.088	0.055
Waist circumference	1.018	0.996-1.040	0.105
OSA	0.721	0.279-1.861	0.499
Diabetes Mellitus	0.742	0.364-1.511	0.410
Type of surgery	1.073	0.416-2.767	0.884

OR odds ratio, CI confidence interval, BMI body mass index, OSA obstructive sleep apnea

Ten patients with cardiopulmonary complications were readmitted, nine in the CPOX group and one in the OSA group (p=0.947). Reasons for readmission were dyspnea due to pneumonia (n=6) or severe upper airway infection (n=1) and new onset AF (n=3, of which two were CPOX patients, and one was an OSA patient). In univariate logistics regression analysis, age proved to be the only parameter that was associated with an increased risk for cardiopulmonary complications (odds ratio (OR) 1.038, 95% CI 1.005-1.072, p=0.023). For each year gained in age, the odds of developing a cardiopulmonary complication increased 1.038-fold (Table 3). Outcomes of other variables were not significantly associated with complications, which included: prior diagnosis of OSA (p=0.499), BMI (p=0.055), gender (p=0.769), waist circumference (p=0.105), DM (p=0.410) and type of surgery (p=0.884).

Secondary outcomes

Complications within 30 days of surgery, other than cardiopulmonary complications, occurred in the CPOX and OSA group in 6.4% (n=326) and 8.6% (n=51), respectively (p=0.219). No significant differences were found in the incidence of major and minor complications (p=0.288 and p=0.530, respectively), as shown in Table 4. Of all the complications, four had a fatal outcome. Three patients (0.05%) in the CPOX group died of abdominal sepsis, due to leakage of the gastrojejunostomy (n=2) and following bowel obstruction with consecutive cecum perforation (n=1). One patient in the OSA group (0.17%) died due to postoperative hemorrhage of the spleen. Admissions to the ICU or MCU were not significantly different (p=0.098 and p=0.582, respectively), neither were the rates of readmissions, despite being slightly higher in the OSA group 4.6% vs. 3.4% in the CPOX group (p=0.161). Reoperations rates were 3.4% in the OSA group vs. 2.1% in the CPOX group (p=0.078). Median length of stay was similar in both groups; patients were generally admitted for one day, with an interquartile range between 1 and 2 days, p=0.597.

Table 4. Complications, other than cardiopulmonary

	CPOX (n,%)	OSA (n,%)	*p*-value
Mortality	**3 (0.06)**	**1 (0.17)**	**0.357**
Complications	**326 (6.4)**	**46 (7.8)**	**0.792**
Major complications	173 (3.4)	25 (4.2)	0.288
Minor complications	153 (3.0)	21 (3.5)	0.530
Requiring reoperation	**109 (2.1)**	**20 (3.4)**	**0.078**
Requiring readmission	**174 (3.4)**	**27 (4.6)**	**0.161**
Length of stay, days*	**1 (1-2)**	**1 (1-2)**	**0.597**
Nature of complication			
Bleeding	141 (2.7)	21 (3.5)	
Dysphagia / stenosis of GJ-anastomosis	65 (1.3)	6 (1.0)	
Postoperative abdominal pain	34(0.6)	0 (0)	
Staple line / anastomotic leakage	32 (0.6)	7 (1.2)	
Superficial SSI	15 (0.3)	5 (0.8)	
Deep SSI	6 (0.12)	0 (0)	
Gastrointestinal ulcer	7 (0.14)	0 (0)	
Constipation	6 (0.12)	3 (0.5)	
Perforation of small bowel	4 (0.08)	1 (0.2)	
Acute kidney injury	3 (0.06)	0 (0)	
Pancreatitis	3 (0.06)	1 (0.2)	
Thromboembolic events	3 (0.06)	0 (0)	
Bowel herniation	2 (0.04)	1 (0.2)	
Acute cholecystitis	2 (0.04)	0 (0)	
Nephrolithiasis	1 (0.02)	0 (0)	
Delirium	1 (0.02)	0 (0)	
Epileptic insult	1 (0.02)	0 (0)	
UTI	0 (0)	1 (0.2)	

CDC complication severity according to Clavien Dindo Classification, Minor CDC class 1-2, Major CDC ≥ class 3A, GJ Gastrojejunal anastomosis, SSI surgical site infection. *median (interquartile range)

DISCUSSION

In this study, we evaluated the safety of CPOX monitoring without preoperative OSA screening as perioperative care in >5000 morbidly obese patients without a pre-existing OSA diagnosis by examining outcomes and comparing them to those of bariatric patients with known, and adequately treated, OSA. The main finding of this study is that the incidence of cardiopulmonary complications in this group of patients was low (0.6% of CPOX patients) and not different from the observed 0.8% in the OSA group (p=0.171). Furthermore, there was no mortality related to cardiopulmonary complications in either of the groups. In both groups, one ICU admission was necessary for respiratory failure. To our knowledge, the present study is one of the largest studies on the use of CPOX without extensive preoperative OSA screening as perioperative care in patients undergoing bariatric surgery.

Previous studies that described cardiopulmonary complication rates following bariatric surgery reported incidences ranging from 0.0-10.2% (16-23). There are several potential explanations for this wide range in the literature and the favorable outcomes of this retrospective study. First, in two cited articles only cases of open abdominal procedures were described. Open surgery is known to have a higher overall complication rate, as well as increased cardiopulmonary complication rates(17, 18). Second, ERABS protocols, promoting non-opioid pain relief and early mobilization, had not been implanted when these studies were conducted(14, 24). Thus, peri- and postoperative desaturations and pulmonary complications are potentially reduced, as opioids and other anesthetics deteriorate postoperative ventilation by decreasing muscular pharyngeal tone and impair ventilatory response to hypoxemia and hypercapnia(8, 10).

The incidence of unscheduled ICU admissions in our cohort was 0.37%, which compares favorably to previous studies of bariatric surgery, with reported incidences of 0.0-2.4%(22, 25, 26). This is further supported by a recent meta-analysis of CPOX application in general surgery. In this study, CPOX resulted in reduced incidences of hypoxemia and showed a trend towards less ICU transfers when compared to regular care(27).

Readmission rates in this study were 3.6% in the CPOX group and 4.8% in the OSA group, which is lower than reported in a recent meta-analysis by Malczak et al., who reported a readmission rate of 6.5% in hospitals using ERABS protocols(23). These low readmission rates suggest that CPOX protocols can be safely administered to patients that do not live the proximity of a bariatric center. Therefore, implementation of CPOX would also be feasible in countries geographically different from the Netherlands. Only a few studies have described

CPOX monitoring in bariatric surgical patients. Mostly, CPOX was used in addition to thorough preoperative OSA screening(28-30). One study by Jensen et al.(21) replaced CPAP treatment with CPOX and supplemental oxygen in bariatric patients with OSA. The outcomes were compared to those of bariatric patients with no history of OSA. In these patients neither preoperative OSA screening was performed nor preventive measures were applied to prevent adverse events. No significant difference was observed in pulmonary complications. The authors therefore stated that bariatric patients, regardless of OSA diagnosis, can be safely monitored with CPOX and additional oxygen supply. In our opinion, bariatric patients with no history of OSA should always receive care (e.g. CPOX monitoring) to prevent potential adverse outcomes related to undetected OSA.

We acknowledge that our study also has some limitations. First, patients with OSA, even when adequately treated, have a higher risk of developing postoperative complications than patients without OSA(31). This must be taken into account when comparing the control group (only patients with OSA) to the CPOX group (patients with and without OSA). Second, continuous saturation measurements were not routinely logged in patient files and were therefore unavailable for retrospective analysis. Clinical parameters such as frequency, duration and severity of desaturations are relevant outcomes, especially in future decision making to determine which patients do not require supplement oxygen in addition to CPOX monitoring. This needs to be further evaluated in prospective studies.

In addition to the safety of perioperative care strategies, cost-efficiency should also be considered. Despite the well-known health benefits associated with bariatric surgery, obesity treatment and perioperative care have become a large burden on health care costs and use of hospital resources. Currently, there is inconclusive evidence that supports routine screening for OSA in asymptomatic bariatric patients. This creates a dilemma, as the incidence of postoperative adverse events potentially improves when thorough OSA screening and treatment are applied, while healthcare resource utilization will increase. Therefore, more cost-effective ways to manage these patients are needed. In theory, CPOX monitoring without preoperative OSA screening may lead to a substantial reduction in hospital resources because indications for polysomnography or postoperative admission to medium or high-care facilities will be tempered. The associated cost savings can be used to cover the investments needed to facilitate CPOX monitoring, oxygen supplementation and education of the clinical nursing staff. To address the aforementioned cost and safety issues, we are now conducting a large prospective multicenter cohort study that will assess the cost-effectiveness of routine preoperative OSA screening vs. postoperative CPOX monitoring with oxygen supplementation

in morbidly obese patients undergoing bariatric surgery (the Netherlands Trial register, https://www.trialregister.nl, identification no. NTR6991).

In conclusion, this study demonstrated a low incidence of cardiopulmonary and overall complications in a cohort of 5089 bariatric surgery patients who were monitored with CPOX without preoperative OSA screening, and this incidence was not higher than in patients with adequately managed OSA. These findings suggest that CPOX is a safe strategy for the perioperative management of bariatric patients without a pre-existing OSA diagnosis. Prospective clinical studies are needed to assess if this strategy is not only safe, but more also cost-effective compared to routine OSA screening.

Conflict of interest

SLVV, IA, LD, EOA and EJH declare to have no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Baseline characteristics and main outcomes of all excluded patients

	Excluded patients (n=238)
Reason for exclusion	
OSA without treatment (n,%)	178 (75.4)
Incomplete follow-up data (n,%)	58 (24.6)
Baseline characteristics (n=236)	
Gender, female (n,%)	150 (63.6)
Age (mean, SD)	47.7 ±13.3
BMI, kg/m2 (mean, SD)	44.6 ±7.6
30 day outcomes (n=178)*	
Mortality (n,%)	0 (0)
ICU admissions (n,%)	3 (1.7)
Cardiopulmonary complications (n,%)	1 (0.6)
Other complications (n,%)	2 (1.1)
No-ICU complications (n,%)	15 (8.4)
Cardiopulmonary complications (n,%)	1 (0.6)
Bleeding (n,%)	9 (5.1)
Staple line / anastomosis leakage (n,%)	2 (1.1)
Dysphagia / stenosis of GJ-anastomosis (n,%)	2 (1.1)
Abdominal pain (n,%)	1 (0.6)
Outcomes of primary admission (n=58)**	
Mortality (n,%)	0 (0)
Cardiopulmonary complication (n,%)	0 (0)
Other complications (n,%)	0 (0)

OSA obstructive sleep apnea, BMI body mass index, ICU intensive care unit, GJ gastrojejunostomy
*Patients with a prior OSA diagnosis without adequate treatment
**Patients with incomplete data regarding 30 day follow-up

CHAPTER 3

Preoperative assessment of obstructive sleep apnea in bariatric patients using polysomnography or polygraphy

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ABSTRACT

Introduction
Preoperative assessment of obstructive sleep apnea (OSA) in patients scheduled for bariatric surgery can be performed by in-laboratory polysomnography (PSG) or by portable polygraphy (PP) at home. We aimed to evaluate the association between PSG/PP, OSA diagnosis, and implementation of continuous positive airway pressure (CPAP) therapy.

Methods
All patients who underwent bariatric surgery from 2015 through 2017 were retrospectively reviewed. Patients underwent preoperative PSG or PP, based on prevailing protocols or at the physician's discretion. Logistic regression analyses were performed to determine predictors of CPAP implementation. OSA-related postoperative complications were analyzed in both groups.

Results
During the study period, 1464 patients were included. OSA was diagnosed in 79% of 271 patients undergoing PSG, compared to 64% of 1193 patients undergoing PP ($p<0.001$), with median apnea-hypopnea index (AHI) of 15.8 and 7.7, respectively. CPAP treatment was initiated in 52% and 27% of patients, respectively, $p<0.001$. Predictors (with adjusted odds ratio) in multivariate regression analysis for CPAP implementation were: male gender (5.15), BMI≥50 (3.85), PSG test (2.74), hypertension (2.38), and age≥50 (1.87). OSA-related complications did not differ between groups ($p=0.277$).

Conclusion
Both PSG and PP are feasible options for preoperative OSA assessment in bariatric patients. When PP is performed, some underdiagnosis may occur as cases of mild OSA may be missed. However, clinically relevant OSA is detected by both diagnostic tools. No difference in OSA-related complications was found. PP is a safe, less invasive option and can be considered as a suitable measure for OSA assessment in this population.

INTRODUCTION

Obstructive sleep apnea (OSA) is the most prevalent sleep-related breathing disorder in obese patients scheduled for bariatric surgery with an estimated prevalence of 60-70% (1, 2). OSA is characterized by recurrent collapses of the upper airway during sleep, resulting in partial (hypopnea) or complete (apnea) cessations of breathing. In the general population, OSA is treated in order to minimize symptoms and reduce long-term morbidity and complications. In surgical patients, detecting and treating OSA is also performed to prevent complications. Undiagnosed or untreated OSA increases perioperative risk, as opioids and sedatives administered during general anesthesia can induce respiratory depressant effects during the first night after surgery (3-5). These effects can result in severe hypoxemia and long-lasting apneas and can consecutively cause serious cardiopulmonary or thromboembolic complications and even death (5).

Strategies that aim to prevent these rare but serious complications mostly consist of preoperative OSA-screening and subsequent treatment with continuous positive airway pressure (CPAP) for patients with moderate or severe OSA (6). The preoperative screening for OSA in the bariatric population varies from the use of questionnaires, e.g., STOP-BANG, alternative non-invasive screening devices such as wearables, portable polygraphy up to the gold standard in-laboratory polysomnography (PSG) (7-9). Despite the effectiveness and thorough approach of a preoperative PSG, it is a time-consuming measurement, costly, and often limited in availability. A less comprehensive alternative to diagnose OSA is portable polygraphy (PP), a portable monitoring device that is less invasive and less expensive. Both forms of sleep study establish the apnea-hypopnea index (AHI), which is most accepted as indicative of disease severity.

The crucial difference between these sleep studies is that PSG does not only focus on respiratory efforts but simultaneously conducts an electroencephalography. Hence, PSG has the ability to distinguish between an awake state and sleep and can measure accurate sleeping time to calculate the AHI. PP denominates the AHI through total recording time (e.g. self-reported sleeping time) instead of objective sleeping time, which generally reduces the AHI. Still, PP identifies moderate or severe OSA and is recommended in patients with a high pre-test probability for OSA, such as the bariatric population (9, 10).

Both PSG and PP testing are widely applied in bariatric clinics, but it is unclear whether this has a substantial impact on diagnosing clinically relevant OSA, without compromising the prevention of major cardiopulmonary and thromboembolic complications in bariatric patients. We hypothesize that clinically relevant OSA

that could induce postoperative complications, will be detected by both PSG and PP. The aim of this study was to evaluate the prevalence of OSA (AHI≥5 events/hour) detected by PSG (the gold standard), compared to PP in patients scheduled for bariatric surgery. In addition, we analyzed the implementation of CPAP treatment and OSA-related adverse postoperative outcomes.

METHODS

Study design and patient population

This is a retrospective review of a prospectively maintained database that contains all consecutive patients who underwent bariatric surgery and preoperative OSA assessment between January 2015 and January 2018 in a high-volume bariatric center: OLVG, Amsterdam, the Netherlands. This database contained general patient characteristics, OSA-specific data, and surgical outcomes such as complications. Patients were excluded if they had undergone PSG or PP before surgical consultation, or because they did not undergo PSG or PP before revisional surgery. During the study period, a transition in preoperative OSA assessment using PSG to PP was made (temporal changes from PSG to PP will be reported in table 1). Patients were referred for either PSG or PP based on the availability of resources, the prevailing protocol, waiting lists for PSG tests, and at the discretion of the treating physician as no formal protocols for the referral selection were used. Patients were divided into two groups based on the type of sleep study used for OSA assessment. The local ethical committee gave permission to perform this retrospective study, without the need for formal informed consent as data was used anonymously.

Sleep studies performed

Patients undergoing polysomnography were admitted for a full-night sleep study using the Embla recorder (Flaga Medical devices, Reykjavik, Iceland). PSGs were performed either attended or unattended and comprised measurements of respiratory efforts (thoracic and abdominal sensors), sleep architecture (electroencephalogram, electrooculogram, and submental electromyogram), leg and body position (motion sensor), oxygen saturation, and heart rate (pulse oximetry), airflow and snoring (pressure sensor).

Portable polygraphy was performed at home using the Vivisol recorder (Dolby Vivisol, Stirling, United Kingdom) / Embla. The same parameters were measured, except for sleep architecture.

In case of incomplete results, sleep studies were repeated and the results of the complete measurement were used for the analyses.

Prevalence and severity of OSA were based on AHI: an AHI<5 excluded OSA prevalence, while 5≥AHI<15 defined mild, 15≥AHI<30 moderate, and AHI≥30 severe OSA. Patients diagnosed with moderate or severe OSA were treated with CPAP. Patients with mild OSA were treated with CPAP in case of clinically significant deviant PSG or PP metrics, other than AHI, such as time during sleep study that saturation levels were <90% SpO_2, or in case of reported excessive daytime sleepiness.

Outcomes

The primary outcome is the prevalence of OSA detected by PSG compared to the OSA prevalence detected by PP, expressed as odds ratio (OR) and adjusted odds ratio (aOR). Secondary outcomes were exact outcomes of sleep studies, i.e., AHI and oxygen desaturation index (ODI), the prevalence of consequent initiation of CPAP treatment, and postoperative clinical outcomes within 30 days of surgery, such as general complications and readmissions. Finally, an analysis of specific complications that could be OSA-related i.e., pulmonary, cardiac or, thromboembolic complications was performed.

Statistical analysis

Baseline characteristics were displayed using the number of cases (n) and percentages (%). Normally and non-normally distributed data were described using means with standard deviation (SD) and medians with interquartile range (IQR), respectively. Continuous data were analyzed using independent t-tests, Mann Whitney U test, or Kruskal-Wallis test, depending on distribution normality. Binary data were analyzed with Chi-Square analysis or Fishers' exact test, depending on the expected value. Univariable logistic regression was performed to analyze the odds ratio (OR) for the association of OSA diagnosis and CPAP therapy following PSG or PP tests. To correct for confounders and formulate an adjusted odds ratio (aOR), multivariable logistic regression analysis was performed. All associated factors with a p-value of <0.1 in univariable analysis were used for multivariable analysis. A p-value of ≤0.05 was considered statistically significant. Statistical analyses were performed by using IBM SPSS Statistics, version 25.0 for Windows (SPSS. Chicago, IL).

RESULTS

A total of 1598 patients underwent bariatric surgery during the study period, of which 1464 patients were included in this analysis. Patients were excluded due to previously conducted PSG or PP in other centers (n=114), or because they did not undergo PSG or PP before revisional surgery (n=20). Analysis of these 1464 patients revealed that 271 patients (18.5%) underwent PSG and 1193 patients (81.5%) underwent PP. Patients who underwent PSG were more often male, were older on average and presented with a higher prevalence of hypertension. These and other baseline characteristics are shown in Table 1.

Table 1. Baseline Characteristics

	PSG n=271 (18.5%)	PP n= 1193 (81.5%)	*p*-value
Gender, female (n,%)	206 (76.0)	1015 (85.1)	0.001
Age, years (mean, SD)	47.2 ±11.8	43.5 ±12.0	<0.001
BMI, kg/m^2 (mean, SD)	42.8 ±5.8	43.3 ±6.4	0.169
Waist circumference, cm (mean, SD)	126.9 ±12.5	125.9 ±14.5	0.289
Comorbidities (n,%)			
Hypertension	103 (38)	344 (28.8)	0.003
Dyslipidemia	53 (19.6)	175 (14.7)	0.051
Type 2 Diabetes	56 (20.7)	229 (19.2)	0.581
GERD	68 (25.1)	320 (26.8)	0.594
COPD	7 (2.6)	26 (2.2)	0.652
History of CVD	26 (9.6)	76 (6.4)	0.065
Alcohol consumption (n,%)	67 (24.7)	333 (27.9)	0.326
Smoking (n,%)			
Current	44 (16.2)	254 (21.3)	0.078
Former	114 (42.1)	364 (30.5)	<0.001
Year of sleep study			
2015	59 (13.5)	378 (86.5)	<0.001
2016	127 (27.0)	343 (73.0)	<0.001
2017	85 (15.7)	472 (84.7)	<0.001
Type of procedure (n,%)*			**<0.001**
LRYGB	196 (72.3)	813 (68.1)	0.191
LSG	51 (18.8)	232 (19.5)	0.865
One-Anastomosis bypass	2 (0.7)	2 (0.2)	0.158
Revisional surgery			
Conversion LAGB to LRYGB	12 (4.5)	103 (8.6)	0.018
Conversion LAGB to LSG	2 (0.7)	25 (2.1)	0.207
Other*	8 (3.0)	18 (1.5)	0.123

*All procedures were performed laparoscopically

**Other: placement of minimizer-ring, single-anastomosis duodenal ileal bypass, pouch revision, conversion of vertical band gastroplasty to LRYGB, band removal, LSG to LRYGB, elongation of alimentary limb.

BMI Body mass index, *COPD* Chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *GERD* gastroesophageal reflux disease, *LAGB* laparoscopic adjustable gastric band, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *LSG* Laparoscopic sleeve gastrectomy, *PP* portable polygraphy, *PSG* polysomnography

Outcomes of sleep studies

Results of sleep studies showed significantly higher median AHI of 15.8 and ODI of 17.2 events/hour in the PSG group, compared to median AHI of 7.7 and median ODI of 11.3 events/hour in the PP group, respectively (P<0.001). [Table 2] Overall, OSA (AHI≥5) was diagnosed in 79% of patients who underwent PSG compared to 64% of patients undergoing PP (p<0.001). Mild OSA was diagnosed in 26% of patients undergoing PSG compared to 37% of PP patients, p<0.001. Moderate and severe OSA was diagnosed in 26% and 27% of PSG patients, compared to 14% and 13% of PP patients, both p<0.001, respectively.

In univariable regression analysis, several significant predictors for OSA prevalence following PSG testing were identified: male gender, age ≥50 years, and hypertension. After multivariate analysis, male gender (aOR 13.9) and age≥50 years (aOR 4.0) remained significant.

For OSA prevalence following PP, in univariable analysis male gender, age ≥50 years, BMI ≥50 kg/m^2, hypertension, dyslipidemia, type 2 diabetes, gastroesophageal reflux disease (GERD), alcohol consumption, and history of cardiovascular disease (CVD) were significant. [Table 3] After multivariable logistic regression, the following predictors remained significant: male gender (adjusted odds ratio (aOR) 5.7), age ≥50 years (aOR 3.5), BMI ≥50 kg/m^2 (aOR 3.1), and hypertension (aOR 2.3).

Table 2. Outcomes of sleep studies and surgery

	PSG n=271	PP n=1193	*p*-value
P(S)G parameters			
AHI (median, IQR)	15.8 (6.3-32.6)	7.7 (3.2-16.6)	<0.001
ODI (median, IQR)	17.2 (8.9-29.2)	11.3 (5.4-21.2)	<0.001
No OSA (AHI <5) n,%	57 (21.0)	429 (36.0)	<0.001
Overall OSA (AHI≥5) n,%	214 (79.0)	764 (64.0)	<0.001
Mild (AHI 5-15)	71 (26.2)	440 (36.9)	<0.001
Moderate (AHI 15-30)	70 (25.8)	170 (14.2)	<0.001
Severe (AHI ≥ 30)	73 (27.0)	154 (12.9)	<0.001
CPAP implementation (n,%)	140 (51.7)	325 (27.2)	<0.001
Surgical outcomes (n,%)			
Complications <30days	27 (10.0)	121 (10.1)	0.930
OSA-related complications*	4 (1.5)	9 (0.8)	0.277
Pulmonary	3 (1.1)	6 (0.5)	
Cardiac	1 (0.4)	1 (0.1)	
Thromboembolic	0	2 (0.2)	
Bleeding	8 (3.0)	42 (3.5)	0.853
Anastomotic leakage	6 (2.2)	15 (1.3)	0.254
GJS stenosis	1 (0.4)	11 (0.9)	0.707
Wound infection	0	6 (0.5)	-
Intra-abdominal abscess	0	5 (0.4)	-
Perforation	0	6 (0.5)	-
Other**	8 (3.0)	27 (2.3)	0.066
Severity of complications			
Minor (CDC ≤2)	14 (5.2)	59 (5.0)	0.968
Major (CDC ≥3A)	13 (4.8)	61 (5.1)	0.487
Readmission	17 (6.3)	83 (7.0)	0.790

* OSA-related complications include e.g., pneumonia, acute respiratory insufficiency, atrial fibrillation, deep venous thrombosis, pulmonary embolism.
** Other complications include e.g., gastrointestinal ulcer, internal herniation, postoperative pain, gallstones, gastroesophageal reflux, acute kidney failure, urinary tract infection.
AHI apnea hypopnea index, CDC Clavien Dindo Classification, CPAP continuous positive airway pressure, ODI oxygen desaturation index, OSA obstructive sleep apnea, PP portable polygraphy, PSG polysomnography

CPAP implementation

The disparities of OSA severity between the PSG and PP group were consequently found in CPAP implementation, as 51.7% of PSG patients started CPAP treatment before surgery, compared to 27.2% of PP patients, p<0.001. Patients undergoing PSG had an odds ratio of CPAP implementation of 1.9, compared to patients undergoing PP.

Predictors for CPAP implementation that were significant in the univariable analysis were male gender, age ≥50 years, BMI ≥50 kg/m^2, PSG as a diagnostic tool (compared to PP), hypertension, dyslipidemia, type 2 diabetes, GERD, alcohol consumption, and history of CVD. [Table 3] Predictors for CPAP implementation that remained significant in the multivariable analysis were male gender (aOR 5.15), BMI ≥50 (aOR 3.58), PSG as preoperative assessment (aOR 2.74), hypertension (aOR 2.38), age ≥50 years (aOR 1.87).

Surgical outcomes

Complications within 30 days of surgery occurred in 27 patients who underwent PSG (10.0%) and 121 patients who underwent PP (10.1%), p=.930. [Table 2] No differences in the type of complications that occurred between groups were found (e.g., anastomotic leakage or bleeding) and no differences in severity of complications, defined as minor or major based on Clavien Dindo classification, were found. The incidence of readmissions did not differ between groups (p=0.790). OSA-related complications occurred in 11 patients (0.8%), but with no difference between patients who underwent PSG or PP, p=0.277 [Table 2]. In the PSG group, these complications were pneumonia (n=3) and cardiac arrhythmias (n=1). In the PP group, the complications were pneumonia (n=4), respiratory failure (n=1), bronchospasm with consequent failed detubation (n=1), atrial fibrillation (n=1), deep venous embolism (n=1), and pulmonary embolism (n=1).

Table 3. Uni- and multivariable logistics regression analysis for predictors of AHI ≥5 for PSG patients, AHI ≥5 for PG patients, and CPAP initiation combined

Factors	n (%)	Univariable OR (95% CI)	*p*-value	Multivariable aOR (95% CI)	*p*-value
AHI≥5 for PSG (n=271)					
Gender (male=1, female=0)	65 (24.0)	11.47 [2.72-48.48]	0.001	13.93 [3.24-59.79]	<0.001
Age (≥50=1 vs. <50 years)	130 (48.0)	3.64 [1.88-7.04]	<0.001	4.00 [1.90-3.38]	<0.001
BMI (≥50=1 vs. <50 kg/m2)	27 (10.0)	1.19 [0.43-3.30]	0.736		
Hypertension (yes=1, no=0)	103 (38)	2.19 [1.13-4.24]	0.020	1.24 [0.58-2.67]	0.574
Dyslipidemia (yes=1, no=0)	53 (19.6)	1.380 [0.63-3.03]	0.421		
Type 2 Diabetes (yes=1, no=0)	56 (20.7)	1.29 [0.60-2.74]	0.513		
GERD (yes=1, no=0)	68 (25.1)	1.30 [0.641-2.64]	0.468		
COPD (yes=1, no=0)	7 (2.6)	1.62 [0.19-13.70]	0.660		
Alcohol consumption (yes=1, no=0)	67 (24.7)	1.68 [0.80-3.55]	0.174		
History of CVD (yes=1, no=0)	26 (9.6)	1.52 [0.50-4.60]	0.460		
Current smoking (yes=1, no=0)	44 (16.2)	1.027 [0.46-2.29]	0.948		
AHI≥5 for PP (n=1193)					
Gender (male=1, female=0)	178 (14.9)	6.05 [3.66-10.00]	<0.001	5.66 [3.31-9.66]	<0.001
Age (≥50=1 vs. <50 years)	419 (35.1)	4.5 [3.36-6.07]	<0.001	3.50 [2.52-4.87]	<0.001
BMI (≥50=1 vs. <50 kg/m2)	159 (12.5)	2.47 [1.65-3.72]	<0.001	3.10 [2.00-4.80]	<0.001
Hypertension (yes=1, no=0)	344 (28.8)	3.83 [2.80-5.24]	<0.001	2.27 [1.58-3.28]	<0.001
Dyslipidemia (yes=1, no=0)	175 (14.7)	2.86 [1.91-4.28]	<0.001	1.13 [0.68-1.89]	0.640
Type 2 Diabetes (yes=1, no=0)	229 (19.2)	2.19 [1.56-3.06]	<0.001	0.97 [0.64-1.49]	0.899
GERD (yes=1, no=0)	320 (26.8)	1.27 [0.97-1.67]	0.083	1.23 [0.91-1.66]	0.170
COPD (yes=1, no=0)	26 (2.1)	1.27 [0.55-2.95]	0.578		
Alcohol consumption (yes=1, no=0)	333 (27.9)	1.31 [1.00-1.72]	0.047	1.24 [0.92-1.67]	0.164
History of CVD (yes=1, no=0)	76 (6.3)	2.62 [1.45-4.74]	0.001	1.15 [0.59-2.25]	0.686
Current smoking (yes=1, no=0)	254 (21.3)	0.83 [0.63-1.11]	0.203		

Table 3. Uni- and multivariable logistics regression analysis for predictors of AHI ≥5 for PSG patients, AHI ≥5 for PG patients, and CPAP initiation combined *(continued)*

Factors	n (%)	Univariable OR (95% CI)	*p*-value	Multivariable aOR (95% CI)	*p*-value
CPAP implementation (n=1464)					
Gender (male=1, female=0)	243 (16.6)	5.41 (4.04-7.25)	<0.001	5.15 (3.72-7.11)	<0.001
Age (≥50=1 vs. <50 years)	549 (37.5)	2.69 (2.14-3.37)	<0.001	1.87 (1.41-2.48)	<0.001
BMI (≥50=1 vs. <50 kg/m2)	186 (12.7)	2.50 (1.83-3.41)	<0.001	3.58 (2.52-5.10)	<0.001
OSA diagnostic tool (PSG=1, PP=0)	271 (18.5)	2.86 (2.18-3.74)	<0.001	2.74 (2.02-3.72)	<0.001
Hypertension (yes=1, no=0)	447 (30.5)	3.28 (2.59-4.15)	<0.001	2.38 (1.77-3.21)	<0.001
Dyslipidemia (yes=1, no=0)	228 (15.6)	2.52 (1.89-3.36)	<0.001	1.13 (0.76-1.69)	0.534
Type 2 Diabetes (yes=1, no=0)	285 (17.3)	1.96 (1.51-2.56)	<0.001	0.98 (0.68-1.41)	0.914
GERD (yes=1, no=0)	388 (26.5)	1.30 (1.12-1.66)	0.036	1.32 (1.00-1.75)	0.053
COPD (yes=1, no=0)	33 (2.3)	1.41 (0.69-2.86)	0.343		
Alcohol consumption (yes=1, no=0)	400 (27.3)	1.39 (1.09-1.77)	0.008	1.30 (0.98-1.72)	0.068
History of CVD (yes=1, no=0)	102 (7.0)	2.61 (1.74-3.92)	<0.001	1.34 (0.83-2.17	0.225
Current smoking (yes=1, no=0)	298 (20.4)	1.05 (0.80-1.38)	0.734		

AHI apnea hypopnea index, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, CPAP continuous positive airway pressure, *CVD* cardiovascular disease, *GERD* gastroesophageal reflux disease, *OSA* obstructive sleep apnea, *PP* portable polygraphy, *PSG* polysomnography

DISCUSSION

The present study found that patients who undergo preoperative PSG prior to bariatric surgery are diagnosed with OSA more frequently than those who underwent preoperative PP. Clinically significant OSA, i.e. moderate or severe OSA, was diagnosed more frequently in patients who underwent PSG than PP. This led to a significant difference in CPAP implementation, and patients who underwent PSG had a 1.9-fold higher odds ratio to receive CPAP treatment before surgery than those that underwent PP. However, OSA-related complications did not differ between both groups.

To our knowledge, this is the first study that compares a large cohort of patients undergoing either PSG or PP testing before bariatric surgery. Oliveira et al. (11) described the diagnostic accuracy of PP monitoring at home for OSA diagnosis and compared it to PSG by performing both sleep studies during preoperative work-up in the same bariatric patient with OSA symptoms. They found a higher diagnostic accuracy when higher AHI cut-off values were used. For AHI ≥30 the sensitivity and specificity were 67% and 100%, while for an AHI between 5-30 these outcomes were much lower: 40% and 81%, respectively. Due to the small sample size, high drop-out rate (26 of 58 patients, 45%), and a preselected study population with a high pre-test probability for OSA, no definitive conclusions could be drawn from their study. Malbois et al. (12) compared nocturnal oximetry to portable OSA monitoring in 68 bariatric patients and found a positive and negative predictive value of 100% and 95%, but they did not conduct PSG for comparison.

Despite a significant difference in perioperative use of CPAP between patients who underwent PSG and PP tests, postoperative complications did not differ between groups. A possible explanation why postoperative outcomes were similar despite a discrepancy in OSA diagnosis and CPAP initiation could be that patients with severe and clinically relevant OSA are identified both by PSG and PP. This is also suggested by the data of the previously mentioned trial by Oliveira et al. (11). To strengthen this hypothesis, a relationship between OSA severity and OSA-related complications in untreated patients has to be assumed. However, several studies attempted to analyze this relationship, but the outcomes are conflicting. In the largest cohort study, Mutter et al. compared 2640 surgical patients with OSA to 16,220 controls and found a 2.3 odds ratio for patients with severe OSA (AHI ≥30) to develop respiratory complications compared to controls (13). However, in two smaller studies comparing surgical patients with no OSA to known OSA patients, no correlation between OSA severity and AHI was found (14, 15). It should be noted that these three studies comprised patients who underwent surgical interventions other than bariatric procedures, and thus

are not optimally suited to be compared to bariatric patients. This is because patients undergoing bariatric surgery have a higher probability of undiagnosed OSA, compared with the patient population undergoing general surgery who have a low or intermediate risk of undiagnosed OSA.

The present findings should be interpreted in light of the following limitations. First, the retrospective study design precludes comparing PP and PSG outcomes within the same patient. Second, we did not perform a sample size calculation for the secondary outcome: occurrence of OSA-related complications. Therefore, any interpretation of the prevention of these complications warrants some caution, as cardiopulmonary and thromboembolic complications can result in significant morbidity, or even in fatalities, but are very rare following bariatric surgery. In addition, the percentage of patients using CPAP was different between PSG and PP groups, and this might influence the outcomes as well. Third, extensive preoperative OSA screening has been standard care in many bariatric centers. Historically, like in our hospital, PSG was initially always used as OSA screening due to its status as golden standard diagnostic, but in recent years, a shift towards more ambulatory tests has occurred. This partially explains the uneven distribution of patients in the study groups, as patients who underwent PSG testing only comprised 18.5% of the total cohort. In addition, we observed that patients with a high probability for OSA (e.g., male, older patients with higher prevalence of hypertension) were more likely to undergo PSG than PP, which was most likely a result of selection bias, as patients were referred for PSG or PP at the physician's discretion. Although we attempted to correct for these confounding factors in logistic regression analyses, other factors (such as implicit bias by physicians) may have also played a part in decision making for either PSG or PP, that were not identified as confounders.

A prospective trial that randomized bariatric patients to either PSG or PP prior to surgery would have been ideal. However, by performing univariable and multivariable analysis, we were able to correct for potential confounders, and thus feel able to draw some conclusions from data of this large cohort.

The benefits of extensive preoperative OSA evaluation attempting to prevent postoperative complications should be carefully weighed against the overuse of diagnostic tools and hospital resources. The need to detect undiagnosed severe OSA to avoid preventable complications is paramount, but the results of this study suggest that complications can also be prevented by less invasive diagnostics, despite a lower sensitivity for OSA diagnosis. On the other hand, one could question whether preoperative screening is necessary or not, when alternatives to OSA screening and CPAP treatment would also lead to comparable outcomes. Such an alternative is continuous monitoring of saturation levels

in all patients after bariatric surgery to prevent apneas or hypopneas. One argument for this strategy is that up to 93.5% of patient completely resolves their OSA within a year of surgery (16). A currently active study, the POPCORN study, compares routine preoperative assessment of OSA by performing PP and CPAP initiation to postoperative monitoring with continuous pulse oximetry and supplemental oxygen without preoperative OSA assessment in bariatric patients, with outcome parameters of cost-effectiveness, complications, and quality of life (17). Future studies should focus on elucidating the balance between safety and invasiveness to optimally manage undiagnosed OSA in bariatric patients in the perioperative period.

Conclusion

Both PSG and PP are feasible options for preoperative diagnosis of OSA in bariatric patients. When PP is performed, some underdiagnosis may occur. Cases of mild OSA might be missed but this seems to be acceptable. However, clinically relevant OSA is detected by both diagnostic tools, and no difference in OSA-related complications was found, taking into consideration that patients were treated with CPAP when OSA was diagnosed. PP is a safe, but less invasive option and can thus be considered as a suitable measure for preoperative assessment of OSA in this population.

Conflict of interest

All authors declare that they have no conflict of interest.

Statement of informed consent

Given the retrospective design of this study, informed consent was not required.

Ethics Approval

This study was approved by the Institutional Review Board of the OLVG.

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CHAPTER 4

Complications and predictors associated with moderate and severe obstructive sleep apnea in bariatric surgery: evaluation of routine obstructive sleep apnea screening

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Submitted

ABSTRACT

Purpose
Obstructive sleep apnoea (OSA) is a breathing disorder resulting in blockage of airflow and hypo-oxygenation. The incidence of OSA in patients with class 2 or 3 obesity (BMI >35) is 60-70%. Unfortunately, most bariatric patients are unaware they suffer from OSA. Untreated OSA can lead to perioperative cardiopulmonary complications and most clinics perform routine preoperative OSA screening.

The aim of this study was to identify predictors associated with moderate to severe OSA in bariatric patients and asses the incidence of OSA-related complications in patients who underwent OSA screening and CPAP therapy if indicated.

Methods
All consecutive patients who underwent primary bariatric surgery between September 2013 and September 2019 were included. Univariable and multivariable logistic regression analysis was performed to identify potential predictors for moderate to severe OSA, defined as an Apnoea Hypopnea Index (AHI) ≥15 using sleep studies.

Results
A total of 2872 patients who underwent bariatric surgery were included for analysis. Overall, OSA was identified in 62.5% of all patients and moderate to severe OSA (AHI ≥15) in 28.6%. Independent predictors for moderate to severe OSA were male gender (p<0.001), age (p<0.001), preoperative BMI (Body Mass index) (p<0.001), preoperative waist circumference (p<0.001), hypertension (p<0.001), and dyslipidaemia (p=0.046). The incidence of OSA-related complications was low (0.8%) and not significantly different among the different OSA severity classes.

Conclusion
Male gender, age, preoperative BMI, waist circumference, hypertension and dyslipidaemia were independent predictors for moderate to severe OSA. The incidence of OSA-related complications was low (0.8%) in the present OSA screened population.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a breathing disorder resulting in blockage of airflow to the lungs and subsequent reduced blood oxygenation. Around 2-4% of the general adult population and 60-70% of the patients with class 2 or 3 obesity (Body Mass Index above 35) suffer from OSA [1, 2]. This high prevalence in is explained by obesity which is the most significant risk factor for OSA [3, 4]. Many patients with obesity are unaware they suffer from OSA and untreated OSA can lead to daytime fatigue, weight gain and perioperative cardiopulmonary complications [5].

Many clinics perform preoperative OSA screening and initiate treatment before bariatric surgery as recommended in an international consensus guideline to decrease perioperative risks caused by untreated OSA [6]. The recommended golden standard sleep study for OSA screening is a polysomnography (PSG). The first choice treatment is Continuous Positive Airway Pressure (CPAP) in case of diagnosed moderate or severe OSA, which is defined as an Apnoea Hypopnea Index (AHI) above 15 [7]. However, the PSG is often replaced by the less costly polygraphy (PG) whereas clinics without the sufficient resources for sleep studies use OSA screening questionnaires i.e. the STOP-BANG in patients undergoing bariatric surgery [2, 8]. However, none of these questionnaires have reached an acceptable high accuracy of > 90% to be used as a stand-alone diagnostic tool [9, 10]. At the same time, some experts question the value of preoperative OSA screening and CPAP therapy in the bariatric population if patients are continuously monitored after bariatric surgery.

In the last years the approach towards OSA screening in the bariatric population has been influenced by different factors including the high costs of sleep studies, available resources and expertise, availability of continuous postoperative monitoring and more important evidence of a high OSA resolution rate of almost 75% within the first year after bariatric surgery [7].

The aim of this study was to identify preoperative predictors for moderate to severe OSA in a large cohort of patients who underwent bariatric surgery and to analyze the incidence of OSA-related complications after surgery in patients who underwent OSA screening and CPAP therapy if indicated.

METHODS

A retrospective study was performed using data from all consecutive patients who underwent primary bariatric surgery including laparoscopic Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) and omega loop bypass (OAGB-MGB)

and adjustable gastric band (ABG) between September 2013 and September 2019 in a single high-volume bariatric center in the Netherlands. The data used for this retrospective analysis was obtained from a large prospectively entered database of all patients undergoing bariatric surgery. Permission to perform the study with registration number WO 20.068 was obtained from the local ethical committee called ACWO, without the need of formal patient informed consent as data was used anonymously.

All patients underwent preoperative OSA screening by either PSG or PG following the national guidelines [6]. The incidence of OSA in patients was assessed using data from medical records and results of the PSG and PG prior to surgery. OSA was diagnosed according to the international guidelines by the average number of apnoeas and hypopneas which occur during the hours of sleep. This forms the AHI and provides an indication of the severity of OSA with the following categories; no OSA (AHI <5), mild OSA (AHI 5-14.9), moderate (AHI 15-29.9), and severe OSA (AHI ≥30). All patients with an AHI of 15 or higher were referred to a pulmonologist to start CPAP therapy. The patient's toleration of CPAP therapy before surgery was evaluated by a pulmonologist with the criteria that the CPAP device had to be used for minimal 4 hours per night for at least 2 consecutive weeks with lowering of the AHI index under 15 as a result. A small number of patients with mild OSA were also referred for CPAP therapy in case of severe sleep related clinical symptoms or prolonged desaturations SaO2 < 90% monitored by PSG or PG.

Patients who received CPAP therapy after the sleep study were documented and recorded in the database. The CPAP therapy compliance during hospital admission was obtained from patient records. In case the CPAP device was taken to the hospital by the patient, the device was brought to the operating room to be applied directly after surgery when oxygen supply was discontinued. Patients were scored CPAP complaint during admission if the CPAP device was used at least during the first consecutive night after surgery as the length of the hospital stay was variable with most patients only staying for one night. The CPAP compliance was scored as missing in case of unclear reporting.

Patients were screened for eligibility for bariatric surgery by a multidisciplinary team. All patients underwent assessments and were consulted by a medical doctor, physical therapist, dietician and psychologist. All patients attended a 6-week lifestyle program before surgery and follow up was performed during an intensive 18-month lifestyle program after surgery and thereafter yearly medical check-up until 5 years after surgery. Work-up before surgery included blood tests, Helicobacter Pylori test and screening for OSA using PSG or PG, followed

by an appointment at the pulmonologist for CPAP therapy if indicated. From 2015 the PSG was replaced by remote PG. No other OSA screening tools were used.

All patients were consulted by the anaesthesiologist for preoperative assessment. Preoperative factors such as comorbidities, medication, AHI, alcohol consumption and smoking were documented. Bariatric procedures were performed by four bariatric surgeons using standardized techniques for the laparoscopic RYGB, SG, OAGB-MGB and ABG [11].

All data was analysed using SPSS 22.0 for Windows (SPSS Inc. Chicago Illinois, USA). Patient characteristics are described as the mean with standard deviation (SD) for normally or medians (min- max. range) for non-normally distributed variables. Categorical data are presented in number of patients with percentages (%). Differences in complications were assessed using Chi-square test. A p value of ≤ 0.05 was considered significant. Univariable and multivariable logistic regression according to the TRIPOD statement was used to identify predictors for moderate to severe OSA (binary outcome), using the stepwise backward method (17). Based on the best discriminatory cut-off value, each continuous variable was converted into a dichotomous variable. Variables in the univariable analysis with a P value under ≤ 0.1 were added to the multivariable model. Associated factors are presented including the odds ratio (OR) and independent predictors including the adjusted odds ratio (aOR) with 95% confidence intervals (CI).

RESULTS

Study population

Overall, 3356 patients were operated during the study period. Three hundred forty-five patients (10.8%) who underwent revisional surgery and 138 patients (4.1%) without a documented AHI or CPAP status were excluded leaving 2872 patients eligible for analysis. Patients underwent various bariatric procedures as showed in table 1.

Table 1. Baseline characteristics

Variable	Total patients (n = 2872)
Gender (%):	
Female	2318 (80.7)
Male	554 (19.3)
Age (SD); year	43.8 (±12.0)
Preoperative BMI (SD); kg/m^2	43.4 (±5.9)
Preoperative waist (SD); cm	123.3 (±21.0)
Hypertension (%)	969 (33.7)
NIDDM (%)	316 (11.0)
IDDM	236 (8.2)
Dyslipidaemia (%)	504 (17.5)
GERD (%)	669 (23.3)
COPD (%)	71 (2.5)
Vascular disease (%)	74 (2.6)
Cardiac diseases (%)	220 (7.7)
Smoking (%)	503 (17.5)
Yes	937 (32.6)
Former	1431 (49.9)
No	
Alcohol consumption (%)	864 (30.1)
Procedure (%)	
RYGB	2248 (78.3)
SG	618 (21.5)
AGB	3(0.1)
OAGB-MGB	3 (0.1)

% = the corresponding percentages; SD = standard deviation
BMI = Body Mass Index; NIDDM =Non-Insulin Dependent Diabetes Mellitus; IDDM = Insulin Dependent Diabetes Mellitus; GERD = Gastro Esophageal Reflux Disease; COPD = Chronic obstructive Pulmonary Disease; RYGB = Roux-en-Y Gastric bypass; SG= Sleeve Gastrectomy; AGB= Laparoscopic adjustable gastric band; OAGB-MGB = Omega Loop Gastric bypass

Prevalence OSA

Overall OSA (AHI ≥ 5) was present in 1795 patients (62.5%) and moderate to severe OSA (AHI ≥15) in 823 patients (28.6%) (Table 2). Eight hundred and two out of 2872 patients (27.9%) received CPAP therapy before surgery including 66 patients (8.2%) with mild OSA (AHI < 15) who also received CPAP therapy because of severe sleep-related symptoms or prolonged desaturations. A total of 823

patients (28.6%) were diagnosed with moderate to severe OSA (AHI ≥15). In 736 patients (89.4%) with moderate to severe OSA CPAP therapy was initiated and implemented after evaluation of the tolerance of CPAP. Overall, 722 out of 802 patients (90.0%) were CPAP therapy compliant during hospital admission. Ten patients (1.2%) with moderate to severe OSA used a mandibular advancement device (MAD). The remaining 77 patients with moderate to severe OSA (9.6%) did not tolerate CPAP therapy before surgery. These patients were monitored on the Intensive Care Unit postoperatively. Subgroup analysis of CPAP therapy compliance in the moderate to severe group showed no significant difference between age groups (p=0.295), OSA severity (p=0.394) or AHI score (p=0.409).

Table 2. OSA classification, CPAP therapy implementation and compliance

OSA severity	Patients (n=2872)	CPAP therapy implementation (n=802)	CPAP therapy compliance (n=722)
No OSA (AHI < 5) (%)	1077 (37.5)	0 (0)	n.a.
Mild OSA (AHI 5 – 15) (%)	972 (33.8)	66 (8.2)	58 (87.9)
Moderate OSA (AHI 15 – 30) (%)	394 (13.7)	327 (40.8)	289 (88.4)
Severe OSA (AHI ≥ 30) (%)	429 (14.9)	409 (50.0)	375 (91.7)

% = the corresponding percentages; n = number; n.a.= not applicable.
OSA = Obstructive Sleep Apnoea; AHI = Apnoea-Hypopnoea Index; CPAP = Continuous Positive Airway Pressure

Predictors for moderate to severe OSA

Univariable and multivariable analysis was performed to assess predictors for moderate to severe OSA. All 823 patients with moderate to severe OSA were analysed and compared to 2049 patients without moderate to severe OSA. In the univariable analysis, several significant predictors associated with moderate to severe OSA were found (table 3). Significant independent predictors in the multivariable analysis include including male gender (p<0.001), age > 495 year (p<0.001), preoperative BMI (Body Mass Index) > 45 (p<0.001), preoperative waist circumference >130 cm (p<0.001), hypertension (p<0.001) and dyslipidaemia (p=0.046). Gender had the highest aOR of 3.7 (table 4).

Table 3. Univariable logistic regression; factors associated with moderate to severe OSA. (n= 2872)

Variable	AHI <15	AHI ≥ 15	OR	95% CI	*p*-value
Gender (%):			4.74	[3.90-5.76]	*<0.001*
Female	1811 (88.4)	507 (61.6)			
Male	276 (11.6)	316 (38.4)			
Age (SD); year	41.5 (±11.8)	49.2 (±10.8)	1.06	[1.05-1.07]	*<0.001*
Age ≥ 49(%); year	631 (30.8)	490 (59.5)	3.31	[2.80-3.91]	*<0.001*
Preoperative BMI (SD); kg/m^2	42.9 (±5.3)	44.7 (±7.1)	1.05	[1.04-1.07]	*<0.001*
Preoperative BMI ≥ 45(%); kg/m^2	600 (29.3)	337 (40.9)	1.68	[1.42-1.99]	*<0.001*
Preoperative waist (SD); cm	123.9 (12.6)	133.5 (14.3)	1.05	[1.05-1.06]	*<0.001*
Preoperative waist ≥130 (%); cm	489 (23.9)	393 (47.8)	2.92	[2.46-3.46]	*<0.001*
Hypertension (%)	562 (27.4)	407 (49.5)	2.59	[2.19-3.06]	*<0.001*
NIDDM (%)	198 (9.7)	118 (14.3)	1.56	[1.23-2.00]	*<0.001*
IDDM (%)	136 (6.6)	100 (12.2)	1.95	[1.48-2.55]	*<0.001*
Dyslipidaemia (%)	280 (13.7)	234 (27.2)	2.36	[1.94-2.88]	*<0.001*
GERD (%)	472 (23.0)	197 (23.9)	1.05	[0.87-1.27]	0.605
COPD (%)	46 (2.2)	25 (3.0)	1.36	[0.83-2.54]	0.218
Vascular disease (%)	44 (2.1)	30 (3.6)	1.73	[1.08-2.76]	*0.024*
Cardiac diseases (%)	125 (6.1)	95 (11.5)	2.01	[1.52-2.66]	*<0.001*
Smoking (%)			1.13	[1.03-1.24]	*<0.001*
Yes	366 (17.9)	137 (16.6)			
Former	636 (31.0)	301 (36.6)			
No	1047 (51.1)	385 (46.8)			
Alcohol consumption (%)	578 (28.2)	286 (34.8)	1.36	[1.14-1.61]	*<0.001*

95% CI = 95% confidence interval, p value ≤0.05 is significant.
% = the corresponding percentages; n = number; AHI= Apnoea–Hypopnoea-Index; OSA = Obstructive Sleep Apnoea; BMI = Body Mass Index; NIDDM =Non Insulin Dependent Diabetes Mellitus; IDDM = Insulin Dependent Diabetes Mellitus; GERD = Gastro Oesophageal Reflux Disease; COPD = Chronic Obstructive Pulmonary Disease.

Table 4. Multivariable logistic regression analysis; Predictors for moderate to severe OSA (AHI ≥15)

Variable	B	aOR	95% CI	*p*-value
Male gender	1.28	3.60	[2.90-4.47]	*<.001*
Age ≥ 49 years	1.07	2.92	[2.40-3.57]	*<.001*
Preoperative BMI ≥ 45 kg/m2	0.45	1.57	[1.28-1.92]	*<.001*
Preoperative waist ≥ 129 cm	0.68	1.98	[1.61-2.44]	*0.004*
Hypertension	0.45	1.40	[1.11-1.76]	*<.001*
Dyslipidaemia	0.24	1.27	[1.00-1.60]	*0.046*

All variables with a p ≤ 0.1 were added to the multivariable analysis. A p value of p ≤0.05 was considered significant.
Regression coefficient= B, aOR= adjusted odds, 95% CI = 95% confidence interval;
OSA = Obstructive Sleep Apnoea; AHI = Apnoea-Hypopnoea Index; BMI = Body Mass Index

Postoperative complications

Overall 237 patients (8.3%) had a (30-day)postoperative complication including 22 patients (0.8%) with OSA-related complication as presented in table 5. We found no significant difference in overall complications (p= 0.076) and OSA-related complications (p=0.100) among OSA severity groups. Two patients died after a non-OSA related complication resulting in a mortality rate of 0.1%. Both patients died due to uncontrollable sepsis after anastomotic leakage.

Table 5. Postoperative complications within 30 days

OSA severity classes	No OSA (AHI < 5)	Mild OSA (AHI 5 – 15)	Moderate OSA (AHI 15 – 30)	Severe OSA (AHI ≥ 30)
Overall complications (%)	74 (6.9)	79 (8.1)	40 (10.2)	44 (10.3)
CDC >2 (%)	43 (4.0)	40 (4.1)	26 (6.6)	25 (5.8)
Cardiovascular & respiratory complications (%)	8 (0.7)	3 (0.3)	5 (1.3)	6 (1.4)
Pneumonia (%)	5 (0.5)	3 (0.3)	2 (0.5)	3 (0.7)
Acute respiratory insufficiency	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.5)
Acute cardiac arrest (%)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Atrial fibrillation (%)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Deep venous thrombosis (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pulmonary embolism (%)	1 (0.1)	0 (0.0)	2 (0.5)	0 (0.0)

OSA = Obstructive Sleep Apnoea; AHI = Apnoea-Hypopnoea Index; CDC= Clavien-Dindo classification

DISCUSSION

This is the largest study to date to analyze predictors for moderate to severe OSA in patients who underwent bariatric surgery. Obstructive Sleep Apnoea (defined as AHI ≥5) was present in 62.5% of patients, and 28.6% of patients was diagnosed with moderate to severe OSA (AHI≥15). Independent predictors for OSA were male gender, age, preoperative BMI, hypertension, waist circumference and dyslipidaemia. OSA-related complications after screening and treatment (CPAP initiation) were low with a range of 0.3 to 1.4% and comparable to patients without OSA. The OSA-related complications did not differ among the OSA classes after screening and CPAP therapy if necessary.

Many previous studies have identified obesity as a predominant risk factor [3, 4]. The moderate to severe OSA rates in previous studies vary between 31.8% and 40.4% and are comparable to the present study [1, 7, 12]. Previous studies have also identified male gender, age, preoperative BMI, hypertension and waist circumference as independent predictors for moderate to severe OSA [9, 13-16]. The present study found dyslipidaemia as a new independent predictor for moderate to severe OSA in patients undergoing bariatric surgery (p=0.046). Evidence supporting the existence of the possible relationship between OSA and dyslipidaemia, and potential underlying mechanisms have been evaluated in a recent systematic review [17]. The conclusion of the review was that data so far suggests OSA affects the lipid metabolism by intermittent hypoxia based on animal studies but that

clinical evidence supporting the link between OSA and dyslipidaemia so far is limited. They also describe that the lipid profile may be improved by CPAP therapy but that the exact mechanism has not been clarified [18, 19]. The present study now shows that dyslipidaemia is a predictor in general practice since the patients first undergo routine laboratory test and then subsequent OSA screening. A study discussed by Karkinski et al. also showed that the effect of OSA on the lipid metabolism is more intense in obese patients than non-obese patients [20]. Two other studies found that an elevated level of free fatty acids was independently associated with increased AHI levels. However, the precise pathways for altered lipid metabolism in patients with moderate to severe OSA severity remains unclear.

Many studies have attempted to create OSA prediction models in order to exclude low risk patients for OSA and avoid unnecessary testing [9, 13-16]. A study testing the discriminatory ability of the commonly used STOP-BANG score for identifying moderate to severe OSA showed that a STOP-BANG score of 4 has the highest sensitivity of 86% with a low specificity of 28 % in patients with morbid obesity[10]. Duarte et al. compared the predictive value of three different models: the STOP-BANG (snoring, tiredness, observed apnoeas, hypertension, BMI>35, age>50, neck circumference, male gender), the two-item No-Apnoea (neck circumference and age), and the NoOSAS model (neck circumference, obesity, observed apnoea, snoring, age, and male sex) in patients eligible for bariatric surgery. The discriminatory accuracy of the three models, which was assessed by the Area Under the Curve (AUC), were 0.74 (0.691-0.788), 0.79 (0.740-0.829) and 0.76 (0.711-0.805), respectively [9]. A fourth model created by Dixon et al. consisted of six variables: BMI≥45, age, observed apnoeas, HbA_{1c} ≥6%, fasting plasma insulin ≥28 µmol/L, and male sex reached the highest accuracy with an AUC of 0.91 in bariatric patients with OSA symptoms compared to polysomnography [13]. However, Kolotkin et al. were unable to confirm this high diagnostic accuracy in an external validation study and found an AUC of 0.73 (95% CI 0.675–0.786). Overall, most of the studies developing or validating OSA prediction models have moderate accuracy and therefore it is unlikely that these prediction models can substitute routine sleep studies i.e. PG or PSG in these patients. The use of routine OSA screening questionnaires as a stand-alone diagnostic tool should be discouraged due to the low accuracy but may be used to exclude low risk patients before PSG or PG.

Overall, OSA-related complications after screening and CPAP initiation were low and not significantly different among different OSA severity classes. These results are in line with the previously published study of Weingarten et al. which showed no association between pulmonary complications and OSA severity in a OSA screened and treated population [21]. The question arises what the complications

rate is if no screening is performed but only intense postoperative continuous monitoring.

Clearly, the present study has several limitation. It was not possible to asses all previously described associated factors of OSA due to the retrospective nature. This made it impossible to validate other screening models such as the STOP-BANG questionnaire, since neck circumference, snoring, observed nocturnal apnoeas and some necessary blood values were not recorded. In addition, this study might be underpowered to analyse the effect of OSA screening on complications since the OSA-related complications occur seldom and causality between OSA and these complications cannot always be proven. Another limitation is the use of the AHI, a commonly reported measurement to describe OSA severity. Despite its general clinical acceptance to use for defining the severity of OSA, it is questionable if the AHI is the best clinical measurement to describe the severity of OSA. Recent findings indicate that other OSA-related parameters such as length of apnoeas and degree of oxygen desaturation index (ODI) play a more important role in classifying OSA severity [6]. At last, in this study we were unable to assess the effect of screening and CPAP therapy in avoiding potential OSA-related complications compared to non-treated patients or patients who are instead continuously monitored after surgery.

It is questionable if future studies should focus on the refinement or development of tool to predict OSA since all previous questionnaires have not been able to achieve high predictive accuracy. Alternatively, the focus could be shifted towards strategies where OSA screening is omitted such as perioperative continuous monitoring. In this approach all patients are treated as potential OSA patients and provided intense postoperative monitoring with pulse oximetry and additional oxygen supplementation if necessary during the first postoperative night(s) [22]. This strategy may be more pragmatic and cost-efficient in patients undergoing bariatric surgery considering the high OSA prevalence, low chance of severe complications and the high OSA resolution after weight loss [7]. This is currently being investigated in the POPCORN trial were this novel approach is compared with standard care that includes preoperative OSA screening using sleep studies and CPAP therapy in case of moderate or severe OSA [23].

In conclusion, gender, age, preoperative BMI, waist circumference, hypertension and dyslipidemia are independent factors associated with moderate to severe OSA. The incidence of OSA-related complications in patients who underwent OSA screening and CPAP therapy if indicated was low (0.8%). The routine use of OSA screening questionnaires as an substitute for sleep studies should be discouraged as none have reached high accuracy in the bariatric population.

Alternatively, future studies should focus on the safety and cost-effectiveness of novel perioperative OSA strategies in which OSA screening in omitted.

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None.

Conflict of Interest
All authors contributed to the original manuscript. The authors declare that there is no conflict of interest.

Availability of data and material
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical approval
This study has been approved by the local and institutional research ethics committee called ACWO and all procedures have been performed in accordance with the Declaration of Helsinki originally adopted in 1964 and its later amendments or comparable ethical standards. For this type of study formal consent was not required.

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CHAPTER 5

Protocol of a multicenter, prospective cohort study that evaluates cost-effectiveness of two perioperative care strategies for potential obstructive sleep apnea in morbidly obese patients undergoing bariatric surgery

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ABSTRACT

Introduction

Despite the high prevalence of obstructive sleep apnea (OSA) in obese patients undergoing bariatric surgery, OSA is undiagnosed in the majority of patients and thus untreated. While untreated OSA is associated with an increased risk of per- and postoperative complications, no evidence-based guidelines on perioperative care for these patients are available. The aim of the POPCORN study (*P*ost-*O*perative *P*ulse oximetry without OSA s*C*reening vs. perioperative continuous positive airway pressure (CPAP) treatment following *O*SA sc*R*ee*N*ing by polygraphy (PG)) is to evaluate which perioperative strategy is most cost-effective for obese patients undergoing bariatric surgery without a history of OSA.

Methods and analysis

In this multicentre observational cohort study, data from 1380 patients who will undergo bariatric surgery will be collected. Patients will either receive postoperative care with pulse oximetry monitoring and supplemental oxygen during the first postoperative night, or they receive care that includes preoperative PG and CPAP treatment in case of moderate or severe OSA. Local protocols for perioperative care in each participating hospital will determine into which cohort a patient is placed. The primary outcome is cost-effectiveness, which will be calculated by comparing all health care costs to the quality-adjusted-life-years (QALYs, calculated using EQ-5D questionnaires). Secondary outcomes are mortality, complications within 30 days after surgery, readmissions, reoperations, length of stay, weight loss, generic quality of life (QOL), OSA-specific QOL, OSA symptoms and CPAP adherence. Patients will receive questionnaires before surgery and 1, 3, 6, and 12 months after surgery to report QALYs and other patient reported outcomes.

Ethics and dissemination

Approval from the Medical research Ethics Committees United was granted in accordance with the Dutch law for Medical Research Involving Human Subjects Act (WMO) (reference number W17.050). Results will be submitted for publication in peer-reviewed journals and presented at (inter)national conferences.

Trial registration number

NTR6991, registered at the Netherlands Trial register, https://www.trialregister.nl.

INTRODUCTION

Obesity is a health care issue of epidemic proportions that is rapidly increasing. Worldwide, more than 650 million people are affected by obesity, defined as body mass index (BMI) ≥ 30 kg/m^2, with subsequent morbidity and mortality(1). Many conservative and life-style interventions that are aimed at reducing weight are available but most lack effectiveness and durable results. To date, bariatric surgery is the only effective treatment for obesity that achieves sustainable, long-term weight loss(2, 3).

Obesity is the main risk factor for obstructive sleep apnea (OSA), a sleep-breathing disorder with recurrent breathing cessations that occur when the pharyngeal airway collapses completely or partially. These collapses are respectively called apneas and hypopneas. The number of breathing cessations per hour of sleep, the apnea hypopnea index (AHI), indicates the severity of OSA (4, 5). Intermittent hypoxemia, hypercapnia and arousals from sleep are a result of breathing cessations, which lead to excessive daytime sleepiness, cognitive impairment and increased risk of cardiovascular disease. The golden standard for OSA diagnosis is an in-laboratory polysomnography (PSG), but in recent years home-based polygraphy (PG) has also been validated as a diagnostic tool(6). Currently, the best treatment for OSA is positive airway pressure (PAP), most commonly provided as continuous PAP (CPAP), and aims to maintain an open airway during sleep. Hereby, arousals from sleep will be reduced, which improves daytime functioning with less excessive sleepiness, as well as quality of life and cognitive functioning(7).

OSA is highly prevalent in patients who are eligible for bariatric surgery, affecting approximately 60-70%, compared to OSA prevalence of 3-17% in the general adult population(8-10). Due to the strong correlation of OSA and obesity, weight loss should be recommended to all obese patients with moderate or severe OSA(11, 12). Bariatric surgery is highly effective for this disease, as 60-85% patients achieve complete remission of OSA or significant reduction of their disease severity(2, 13-16).

Perioperative care for bariatric patients with OSA pose a clinical challenge, given that the majority is asymptomatic or experiences unrecognized symptoms, and is consequently untreated(17). Opioids administered during general anesthesia can induce long-lasting apneas in patients with untreated OSA. As a result, (untreated) OSA is associated with a higher risk of cardiopulmonary and neurovascular complications, as well as higher overall mortality and morbidity in general surgery populations(18, 19). Evidence that this phenomenon of increased perioperative risk also exists in bariatric patients is thin, and most studies do not mention

whether precautions were taken to prevent OSA-related adverse events(20). More recent prospective studies and reviews demonstrate a consistently low incidence of cardiopulmonary and neurovascular complications following bariatric surgery, and statistical analyses fail to indicate a direct causative link to OSA(21-23).

Evidence-based guidelines for perioperative care of potential OSA in bariatric patients are lacking(24). Therefore, a wide variety of perioperative modalities has emerged, that all aim to minimize the risk of serious adverse events related to untreated OSA. One of the options is routine preoperative assessment of OSA in every bariatric patient by performing PSG or PG. Newly diagnosed moderate or severe OSA patients will consequently be treated with CPAP. Another option relies on questionnaires to identify patients at high risk of OSA who subsequently undergo PG. These questionnaires, such as the STOP-BANG or Berlin questionnaire, are frequently used, but none of these screening tools has been able to render both high sensitivity and specificity. Therefore, its applicability remains controversial(25-27). Another alternative is routine, postoperative continuous monitoring with pulse oximetry with supplemental non-invasive oxygen administration but without preoperative OSA assessment. In this approach, all patients receive the same intervention to achieve adequate saturation levels in the early post-operative phase(21).

Obesity and obesity-related disorders increasingly demand utilization of available health care resources. Justification of high screening expenses for OSA is debatable given the low incidence of OSA-related complications, despite the high prevalence of OSA. In addition, CPAP adherence rates are poor even in patients with symptomatic OSA, ranging between 29-83%(28). While specific data are lacking, adherence rates are putatively even lower in asymptomatic bariatric patients, which questions the actual protective effect that is added by preoperative initiation of CPAP. In contrast, adequate treatment with CPAP in symptomatic OSA patients positively influences societal costs, as symptomatic patients without treatment use more health care resources, suffer more unemployment and are more prone to work-related or traffic accidents(29-31). However, routine screening and treatment of asymptomatic patients is not likewise supported by conclusive evidence(27, 32). Deliberate consideration is needed when comparing outcomes such as safety, costs and patients' satisfaction between different perioperative strategies for OSA care in bariatric patients.

RATIONALE

The primary aim of the POPCORN study (*P*ost-*O*perative *P*ulse oximetry without OSA s*C*reening vs. *O*SA sc*R*ee*N*ing) is to evaluate the most cost-effective

perioperative strategy for bariatric patients who have no history of OSA. We will compare postoperative continuous pulse oximetry without OSA screening with routine OSA screening by PG and subsequent application of CPAP. This study will provide evidence that will enable clinicians to make an evidence-based decision on perioperative care of patients with no known OSA undergoing bariatric surgery. This paper describes the design and protocol of the POPCORN study.

METHODS AND ANALYSIS

Study design

The POPCORN study is a prospective, multicentre, observational cohort study that evaluates two cohorts of bariatric patients who have no history of OSA. The first cohort consists of patients who are postoperatively monitored with continuous pulse oximetry (CPOX cohort) who do not undergo a PG or PSG. In the second cohort, all bariatric patients undergo a preoperative PG and in case of moderate or severe OSA receive consequent treatment with CPAP before and after surgery (PPG cohort) (Figure 1).

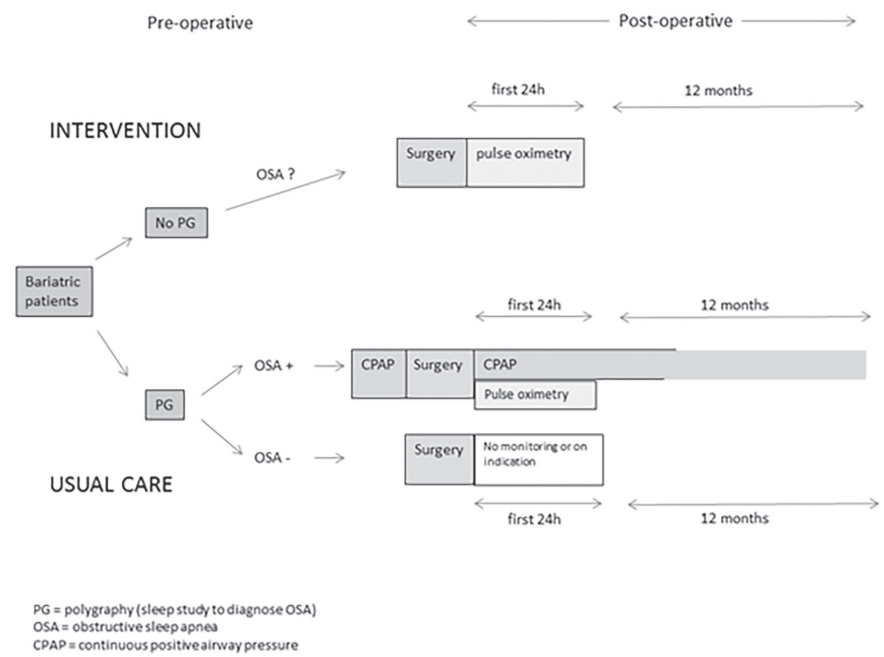

Figure 1: Flowchart of the POPCORN study
PG Polygraphy, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure

Recruitment procedures and consent

In total, 1380 obese patients scheduled to undergo bariatric surgery will be included for participation in the POPCORN study. For study participation, a subject must meet the following inclusion criteria: (A) preoperative BMI ≥ 35 kg/m^2 combined with an obesity-related comorbidity or preoperative BMI ≥40 kg/m^2(33), (B) Age ≥18 years, (C) undergo a primary bariatric procedure. Potential subjects will be excluded from participating in the following situations: (A) previous bariatric surgery, such as laparoscopic adjustable gastric banding; (B) inability to speak or read the Dutch language; (C) concomitantly performed procedures during bariatric surgery that increase the risk of postoperative complications and costs, such as cholecystectomy or paraesophageal hernia repair; (D) Use of treatment options for OSA other than PAP modalities, such as a mandibular advancement device or positional therapy.

In both cohorts, 690 patients will be included. Local protocols of participating hospitals will determine which strategy of perioperative care is used and this will consequently determine the allocation of patients into one of the two cohorts. Seven hospitals in the Netherlands will collaborate to recruit all study-patients. Of the participating hospitals, the only hospital that applies CPOX without preoperative OSA screening is Rijnstate Hospital, Arnhem, who will recruit patients for the CPOX arm. For the PG cohort, patients are recruited from the other participating hospitals (St. Antonius Hospital, Nieuwegein; Onze Lieve Vrouwe Hospital, Amsterdam; Dutch Obesity Clinic, the Hague; Zuyderland Hospital, Heerlen; Rode Kruis Hospital, Beverwijk and Máxima Medical Centre, Veldhoven). Written or digitally signed informed consent will be obtained from all participants enrolled in this study. Recruitment has started in April 2018 and is expected to be completed in March 2020.

Continuous pulse oximetry (CPOX) - cohort

Bariatric patients in the CPOX cohort receive no preoperative screening for OSA: no PG, polysomnography or questionnaires for risk stratification are conducted. Postoperatively, bariatric patients return to the surgical ward where continuous surveillance with pulse oximetry is immediately started, with supplemental oxygen provided via a nasal cannula (2 L/min SpO_2). Pulse oximetry is performed using a Draeger Infinity Delta monitor (Draeger Medical Systems Incorporated, USA). Clinical desaturations are defined as <92% SpO_2, lasting at least 10 seconds. A desaturation sets off an alarm that alerts the attending nurse who will perform a clinical evaluation. Long-lasting apneas can either be terminated by awaking the respective patient, or by providing additional supplemental oxygen via the non-invasive nasal cannula. In case of a serious desaturation that cannot be managed appropriately by these minor interventions, patients can be admitted

to the intensive care unit for potential reintubation at discretion of the treating physician.

Preoperative polygraphy (PPG) - cohort

The PPG cohort will consist of bariatric patients that are preoperatively screened for OSA with a polygraphy or polysomnography. Patients with moderate or severe disease, defined as AHI≥15 and AHI ≥30 events/hour, CPAP treatment is initiated. In patients with mild disease, defined as AHI 5-14 events/hour, CPAP is only advised in presence of clinically significant symptoms such as excessive sleepiness and unrefreshing sleep(34). In patients where an AHI of <5 events/hour is observed, OSA is excluded and no additional perioperative precautions are needed. [Figure 1] In mild, moderate and severe disease, automatic or bi-level continuous airway pressure (APAP and BiPAP) are considered qualitatively equal, compared to CPAP. Therefore, if CPAP treatment is unsuccessful, APAP and BiPAP are also defined as optimal treatment in the perioperative phase.

Enhanced Recovery After Bariatric Surgery Protocols

All participating hospitals will use per- and postoperative protocols during the study period that are based on the principles of Enhanced Recovery After Bariatric Surgery (ERABS)(35). These principles underline aspects of care that enable quick recovery after surgery to minimize per- and postoperative opioid administration and to stimulate early postoperative mobilization. To prepare patients for the bariatric procedure and the associated lifestyle changes, all centres have comparable pre-and postoperative programs for bariatric care. This enlarges a patients' knowledge and expectations on the procedure, the admission and alarm signs for adverse events.

Surgical procedures

Laparoscopic Roux-en-Y gastric bypass (LRYGB) is the most performed procedure in all participating hospitals, followed by laparoscopic sleeve gastrectomy (LSG). LRYGB and LSG are both stomach-reducing procedures, and thus induce significant restriction on food intake. Both procedures influence metabolic and hormonal responses that additionally contribute to weight loss. Furthermore, LRYGB has an additional malabsorptive element as food bypasses the duodenum and a part of the ileum. Both procedures are performed in a protocolled fashion and will be very similar in all participating hospitals.

Primary outcomes

Cost-effectiveness of CPOX compared with standard care with PPG is the primary outcome and will be evaluated during the period from baseline to 12 months after surgery from a societal perspective. Effectiveness of perioperative care (e.g. CPOX and PPG) will be expressed in quality-adjusted-life-years (QALYs).

The QALYs will be calculated using the EuroQol 5 Dimensions – 3 level (EQ-5D-3L) questionnaire, which rates a person's autonomy and well-being on 5 scales; mobility, self-care, usual activities, pain/discomfort and anxiety/depression(36). All scores will be calculated using the subset that was validated for the Dutch population of the EQ-5d-3L(37) . Additionally, patients indicate their general health of that day on a Visual Analog Scale (VAS). The EQ-5D score creates a so called utility between 0-1, indicating 1 as the highest form of well-being, and 0 as the lowest form of well-being, i.e. death.

Direct and indirect costs during the entire study period will be assessed for each individual study subject. Direct costs will be extracted from hospital files and electronic patient records. These costs will be carefully evaluated with regard to the relationship with obesity or OSA. Any unrelated costs will not be considered for the cost-effectiveness analysis. Uncertainty regarding the involvement of OSA or obesity on certain health care costs will be resolved by discussion between authors SvV, EJH and KK.

In addition, we aim to collect health care costs outside the hospital and so called indirect costs which refer to lost resources and opportunities (for instance inability to work) resulting from OSA. These costs will be evaluated using two questionnaires: the Productivity Costs Questionnaire (PCQ) and the Medical Costs Questionnaire (MCQ). The PCQ is a validated questionnaire that assesses the relationship of general income and productivity to physical and mental well-being (38). The MCQ is used to measure extramural medical costs, e.g. visits to a general practitioner or dietician, or medical care in another hospital than the bariatric centre. The PCQ and MCQ questionnaires are conducted at 3 and 12 months postoperatively.

Secondary outcomes

Mortality, morbidity, complications, intensive care unit (ICU) admissions, length of hospital stay, OSA-related symptoms, adherence to CPAP and quality of life (QOL) are all secondary outcomes.

Baseline morbidity will be documented and remission of OSA evaluated after 12 months in the patient files, e.g. comorbidities resolution and weight loss progression during the first postoperative year. Weight loss will be expressed as percentage excessive weight loss (%EWL), percentage total weight loss (%TWL) and change in BMI.

Complications

All complications that occur within 30 days of the bariatric procedure will be analysed.

Distinction will be made in each complication whether it could be caused by (untreated) OSA; this will mainly entail pulmonary, cardiac, thromboembolic and neurovascular complications. Uncertainty regarding these decisions will be solved by discussion between authors SvV, EJH en KK. If the authors conclude that a pulmonary, cardiac, thromboembolic or neurovascular complication is not a result of OSA, this will be described in the manuscript. Severity of complications will be registered according to the Clavien-Dindo Classification (39).

Quality of life (QOL)

Generic QOL will be measured using the EQ-5D-3L, and the Rand-Short Form 36-items questionnaire, which assesses general health in nine different aspects, including physical activity and bodily pain(40). Sleep-related QOL will be assessed with the Functional Outcome Sleep Questionnaire-10(41). This 10-item questionnaire measures the effect of tiredness and sleepiness on QOL and scores are obtained through a 4-point Likert scale. The outcome score ranges from 5 to 20: low scores indicate poor QOL that is greatly influenced by daytime sleepiness, while high scores inversely indicate good QOL uninfluenced by daytime sleepiness(42).

OSA-related outcomes

The main symptom of OSA, daytime sleepiness, will be assessed by the Epworth Sleepiness Scale questionnaire(43). Patients report the likelihood of falling asleep during eight daytime activities on a Likert scale of 0-3, indicating results that range from normal daytime sleepiness (score 0-5) to severe excessive daytime sleepiness (score 16-24).

Pre- and postoperative PGs (or PSGs) during the study period will be analysed for AHI, AHI in supine position, oxygen desaturation index, total sleeping time in supine position, mean oxygen saturation, lowest oxygen saturation, time of saturation <90% SpO_2, number of episodes of saturation <90% SpO_2 and number of episodes with >4% saturation drop below mean saturation. Additional factors that could contribute to disease-load or probability are also monitored; previous ENT surgery that provides a wider pharyngeal girth (i.e. uvulopalatopharyngoplasty), smoking status, alcohol consumption and daily use of opioids and benzodiazepines will also be registered.

CPAP adherence

Due to known discrepancies between patient reported adherence to treatment and objective treatment adherence data, we will obtain both objective and subjective data on CPAP adherence. Adherence will be expressed in days per week of CPAP treatment and hours per night. To obtain objective data, we will consult online databanks for collection of day-to-day adherence rates. CPAP

devices automatically send adherence data and corresponding AHIs to an online databank, which health care providers in the Netherlands use to monitor their patients. In addition, electronic patient records will be evaluated for physicians' recommendation regarding (dis)continuation of CPAP during follow-up.

Subjective data on CPAP adherence will be collected through patient reported outcomes measurements. By using questionnaires, insight can be obtained regarding patients' motives for treatment discontinuation.

Data management

Handling of data was prospectively addressed in a data management plan with the aim of generating data in accordance with the FAIR criteria: Findable, Accessible, Intra-operable and Reusable.

Sample size calculation

A non-inferiority design was chosen to evaluate whether CPOX with no preoperative PG is non-inferior to preoperative PG in bariatric patients. In patients with moderate or severe OSA, CPAP treatment is part of standard care. The primary outcome is QALY difference compared to costs, where QALYs are measured by the EQ-5D. Therefore, the sample size calculation is based on a predefined non-inferiority margin of 0.03 on the EQ-5D score. Based on an EQ-5D score of 0.68 in the usual care group, QALYs of OSA patients before and after one year of CPAP treatment, and calculating with 80% power to detect the predefined non-inferiority margin at a one-sided a level of 0.05, there are 621 patients needed in each study group(44). Assuming a loss to follow up of 10%, the total study population will be set at 1380 patients, resulting in 690 patients per arm.

Analysis of primary outcome measures

An extensive cost-effectiveness analysis (CEA) and budget impact analysis (BIA) will be performed. The cost-effectiveness analysis adheres to the Dutch guideline (45) and reporting will adhere to the CHEERS checklist(46). The BIA will adhere to current Dutch guidelines and also guidelines as published by Sullivan et al. (47). We aim to perform a trial based economic evaluation in which we do not extrapolate costs and effect outside the study period. The effect of the CEA will be expressed in change of QALYs during the study period, and this outcome will be compared to the total costs of each individual patient. Outcomes will be average cost per patient, differences between groups and incremental costs per QALY. An incremental cost-effectiveness ratio analysis will be performed to compare the outcomes (in QALY) rendered by the CPOX and the PPG strategy to the costs related to each perioperative strategy.

Sensitivity analysis will be carried out to correct all potential confounders, such as gender, age, preoperative BMI, comorbidities, choice of bariatric centre, intraoperative and postoperative administered opioids, smoking status, previous ENT surgery. One-way sensitivity analyses will be illustrated graphically using tornado diagrams; probabilistic sensitivity analyses (PSA) will be illustrated in cost-effectiveness planes and so called cost-effectiveness acceptability curves. Bootstrapping will be used if deemed necessary.

Cost assessment

This analysis will be performed using a societal perspective.

- Identification: we aim to identify all health care utilization for every included patient within the study period. All consumption potentially related to obesity, bariatric surgery, and obstructive sleep apnea will be identified in this total set of health care consumption. The latter comprised a fast amount of health care resources that are potentially related to OSA: costs resources related to sleep medicine, cardiovascular disease, pulmonary disease, ear-, nose and throat disease, and work- or traffic related accidents.
- Measurement: utilization of health care resources within the hospital were gathered by using each hospital billing system (detailed health care consumption data send to insurance companies). Additional medical costs that were made in a different hospital or outside of hospitals (i.e. visits to the general practitioner, dietician, physical therapist) were scored based on patients' answers in the Medical Cost Questionnaire. The outcomes were scored in a numerical manner, for example 0, 1, 2 visits to the GP, etc. These results were analysed and valued based on a fixed national cost as documented in the Dutch Health Care Institute guideline.
- Evaluation of costs: Unit costs used are derived from the guidelines commissioned by the Dutch Health Care Institute (Zorginstituut Nederland). Moreover, additional unit costs are gathered from the Dutch Health Care Authority (Nederlandse Zorg Autoriteit; https://www.nza.nl/)

Analysis of secondary outcome measures

Baseline characteristics of patients will be documented with mean/standard deviation or median/range, depending on normality. The number of desaturations, both cardiopulmonary and general complications, interventions, total hospital stay and total costs between both groups will be analysed with the independent t-test/Mann-Whitney U test. Compliance of CPAP and opioids use will be evaluated with chi-square testing. Mixed model analysis will be performed to evaluate the weight loss, severity of OSA symptoms and CPAP adherence at different time points. Predictive values for cardiopulmonary complications will be evaluated with logistic regression analysis, starting with a univariate analysis.

All variables with a significance level p < 0.2 will be included in a multivariate analysis. Within this analysis, only seven independent variables may be included as ten event cases are allowed per dependent predictor. Statistical significance is defined as $p < 0.05$.

To correct for potential confounder between these (non-randomized) cohorts, all outcomes will be analysed by propensity score matching or multivariate analysis, depending on the secondary outcome of interest (48).

Loss to follow-up or replacement of participants

Study participants will be replaced with new participants in case of A) cancellation of the surgery, B) uncompleted preoperative questionnaire, or C) when positive airway pressure treatment is switched to a different modality such as a mandibular advancement device. Patients who do not complete the postoperative questionnaire at 12 months after surgery due to other reasons, will be considered lost-to-follow-up.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, of our research. However, a non-profit organization for OSA patients was consulted in the final phase of designing this study. The organization underlined the need for this research and requested no significant changes to the protocol. In addition, OSA patients who previously underwent bariatric surgery in the hospital that initiated this study were invited to share their opinion on the questionnaires and OSA outcomes.

Ethics and dissemination

The Medical Ethics Committee United (MEC-U) approved this study, in accordance with the Dutch law Medical Research Involving Human Subjects Act (WMO), Medical Research in Humans (MEC-U, W17.050). In addition, local Medical Ethics Committees of each participating hospital also reviewed and approved the study protocol.

Findings of the POPCORN study will be disseminated to all disciplines that are involved in care for bariatric surgery, through articles in peer-reviewed journals, national and international congresses, and revising the national guidelines of the Netherlands.

DISCUSSION

The POPCORN study is a prospective observational cohort study that evaluates the cost-effectiveness of two strategies of perioperative care in bariatric patients

without a pre-existent OSA diagnosis: CPOX without extensive preoperative OSA screening vs. mandatory PG, potentially followed by CPAP treatment. The outcomes will enable the development of new, evidence-based guidelines on perioperative care for bariatric patients with no known OSA. The secondary outcomes, such as (cardiopulmonary) complications, OSA-related symptoms and quality of life, will provide an overview of the correlation between cost-effectiveness and clinical outcomes that are highly relevant in the decision making for perioperative care in bariatric patients.

Best practice regarding perioperative care in bariatric patient has been an ongoing debate for many years, with high prevalence and potential detrimental effects of undetected OSA on one side and substantial costs of related perioperative care and CPAP treatment on the other(27, 49, 50). No comparative studies between different perioperative strategies have been conducted to evaluate outcomes of postoperative complications or cost-effectiveness. In a recent review, conducted by the US preventative task force, no effectiveness of OSA screening in patients who are asymptomatic or who experience unrecognized symptoms was found(27). Despite improvements in intermediate outcomes such as AHI or sleepiness symptoms, no improvement in final health outcomes have been demonstrated, such as mortality or serious adverse events. The paucity in evidence regarding beneficial outcomes is especially relevant when cost-effectiveness is regarded. The obesity epidemic and its related costs are continuously expanding, and this underlines the need for optimal use of available health care resources. With no confirmative data on positive influence of OSA screening in bariatric patients with no known OSA, and approximately 700.000 bariatric procedures annually worldwide, clarification on this topic is needed.

The perioperative strategies evaluated in the POPCORN study are both widely used in general practice and it is expected that results of this study will lead to evidence-based recommendations and guidelines.

The strength of this study is that a general, bariatric population is evaluated. In both cohorts, large groups of bariatric patients are prospectively observed, while little exclusion criteria are applied. In addition, the follow-up period in this study that investigates a perioperative intervention is relatively long. Previous studies that describe preoperative assessment and treatment of OSA mainly reported prevalence of newly detected OSA and related adverse outcomes restricted to the direct perioperative period (51). The follow-up duration of one year after surgery enables us to investigate long-term clinical outcomes of a perioperative regime. Interesting comparisons are to be made between the preoperatively diagnosed OSA patients and the unscreened bariatric patients in terms of

sleepiness symptoms, daytime productivity, general quality of life and health care resource utilization.

Ideally, a randomized controlled trial would have been conducted, in which all patients would undergo a preoperative PG. Consecutive randomization would have determined the type of perioperative care: CPOX monitoring or treatment based on the PG outcome. However, this was considered unethical, as randomization into the CPOX cohort would result in withholding appropriate treatment from patients with confirmed OSA diagnosis, which is associated with many health care hazards (30, 31, 52). Despite the non-randomized design of the POPCORN trial, the large sample size will provide sufficient data to render a balanced statement that will be representable for the general bariatric population in the Netherlands. Furthermore, it is expected that implementation of these perioperative strategies is also feasible in countries other than the Netherlands.

In addition to the non-randomized design of the POPCORN study, another limitation is that preoperative weight loss programs can result in changes in comorbidities. This can be particularly true for OSA, a comorbidity that is greatly influenced by weight loss. Each participating hospital applied local protocols which advocates weight loss before surgery, but in absence of a strict program we do not expect major changes in weight between preoperative (OSA) assessment and the surgical procedure. In conclusion, the POPCORN study will conclude which perioperative strategy is most cost-effective for obese patients scheduled for bariatric surgery and who have an unknown OSA status. These data will contribute to evidence-based guidelines which are urgently needed in this particular field of bariatric care.

Contributors
EJH conceived and designed the study, with support of RJW, SMMDC, RNVV, DJS, AD, EGB, JWMG and FMHVD, who all contributed significantly to the study design. CALDR, KK and GWJF reviewed and refined the research questions and search strategy. SVV wrote the first draft of this manuscript. EJH is the principal investigator and SVV is the main investigator. All authors critically reviewed the content and approved the final manuscript.

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Competing interests
Not applicable for any of the authors

Data sharing statement
After completion of the project, the research data will be stored and shared via EASY, a certified sustainable data archive of Data Archiving and Networked Services (DANS). In EASY each dataset will receive a Digital Object Identifier (DOI). The preferred formats of DANS (e.g. PDF/A, Unicode text, DB tables, SPSS Portable) and the Dublin Core Metadata standard will be used.

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CHAPTER 6

Evaluation of CPAP adherence in bariatric patients diagnosed with obstructive sleep apnea: outcomes of a multicenter cohort study

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ABSTRACT

Purpose
Obstructive sleep apnea (OSA) is highly prevalent but mostly undiagnosed in obese patients scheduled for bariatric surgery. To prevent cardiopulmonary complications, many clinics perform pre-operative OSA-screening. Consequently, adequate adherence to continuous positive airway pressure (CPAP) therapy is essential, but challenging. We aimed to evaluate CPAP adherence and its influence on postoperative outcomes.

Methods
In a prospective multi-center cohort study we compared different perioperative strategies for handling undiagnosed OSA in bariatric patients. In this subgroup analysis patients newly diagnosed with OSA were compared to those with pre-existing OSA. We assessed inadequate CPAP adherence, defined as <4 hours/night, between the preoperative period and 6 months postoperative. Cardiopulmonary complications and (un)scheduled ICU admissions were also evaluated.

Results
In total, 272 patients with newly diagnosed OSA (67.4%) and 132 patients with pre-existing OSA (32.6%) were included. Before surgery, 41 newly diagnosed patients used CPAP inadequately, compared to 5 patients with pre-existing OSA (15% vs. 4%,p=0.049). Six months after surgery inadequate CPAP use increased to 73% for newly diagnosed patients and 39% for patients with pre-existing OSA, respectively(p<0.001). Incidences of cardiopulmonary complications, scheduled and unscheduled ICU admissions were similar in the two study groups (p=0.600,p=0.972, and p=0.980, respectively).

Conclusion
Inadequate CPAP adherence is higher in bariatric patients newly diagnosed with OSA when compared to patients with pre-existing OSA. Strategies to increase CPAP adherence may be valuable when considering routine OSA-screening and CPAP therapy in patients undergoing bariatric surgery. Further studies are needed to improve current guidelines on peri-operative OSA management of obese patients.

INTRODUCTION

Obesity has become a health issue of pandemic proportions, with currently 650 million people that are obese worldwide (1). Treatment of obesity is difficult, and initially starts with conservative strategies such as life-style interventions, diet and occasionally drugs. However, as these interventions lack sustainable effectiveness, bariatric surgery can be considered in patients with morbid obesity (2). Bariatric procedures, such as Roux-en-Y gastric bypass and sleeve gastrectomy, are currently the only treatment options that result in significant weight loss that is sustained during long-term follow-up (3). In addition, many obesity-related comorbidities are positively affected by weight reduction or even completely resolved.

Obstructive sleep apnea (OSA) is associated with obesity (4). Obese patients scheduled for bariatric surgery have an excessively high prevalence of OSA compared to the general population (60-83% vs. 1-9%) of which the majority is undiagnosed (5, 6). Unrecognized and untreated OSA is associated with an increased risk of perioperative cardiopulmonary and thromboembolic complications in patients undergoing surgery (7). These complications are relatively rare, and occur in 1.3% of patients following bariatric surgery. However, these complications can lead to potentially fatal outcomes, which is especially true for major cardiac adverse events, and occur approximately in 0.1% of all bariatric patients (8, 9). The exact attributable risk for developing these complications due to OSA is unclear, as no randomized studies have been conducted to evaluate this causative link, but observational data show increased odds ratios for these complications in OSA patients compared to those without OSA (10).

To prevent OSA-related complications, guidelines advise to perform preoperative screening in bariatric patients who report symptoms of OSA using questionnaires, polysomnography or home sleep apnea testing (HSAT) (11, 12). Patients with a high apnea-hypopnea index (AHI), or in case of HSAT respiratory event index (REI), indicating moderate or severe disease, should be treated with continuous positive airway pressure (CPAP) (12). Some studies describing patients undergoing general surgery have shown that adequate CPAP therapy decreases the risk of perioperative complications (13). Additionally, CPAP therapy may reduce excessive daytime sleepiness, cognitive impairment and cardiovascular risk profile during the pre-and postoperative months (14). Although the benefits of CPAP seem apparent, studies describing CPAP adherence and subsequent influence on perioperative outcomes in bariatric patients are scarce.

Data on non-surgical, general OSA patients shows that adherence to CPAP is often poor, with reported adherence rates between 15-71% (15, 16). CPAP is often

rejected by patients due to side effects such as nasal congestion, claustrophobia, or mucosal dryness. Although it is unclear if adherence rates differ between the bariatric surgery population and patients with symptomatic OSA, it can be postulated that the latter group is more compliant. Bariatric patients often do not experience symptoms related to OSA, or do not recognize these symptoms as a result of OSA, and therefore may subjectively benefit less from CPAP therapy (14). Therefore, they could be at risk for poor adherence to CPAP. In addition, many bariatric patients are aware of the effectiveness of bariatric surgery on OSA prevalence, as reduction or complete remission of OSA occurs in 68.4 – 92.2% (17). This may also encourage patients to stop CPAP prematurely, before OSA remission is proven by a polysomnography or HSAT. Currently, there is only a consensus-based guideline, that recommends postoperative polysomnography to evaluate whether CPAP can be safely discontinued (11). In this guideline, the timing of postoperative reevaluation is left up to the discretion of the treating physician, based on weight loss and reported symptoms.

The aim of this study was to evaluate CPAP adherence in bariatric patients with newly diagnosed OSA before and after surgery, and to compare these results to patients who have been diagnosed with OSA in the past. We hypothesized that newly diagnosed patients might have lower adherence to CPAP, and this could lead to and increased rate of postoperative complications.

MATERIAL AND METHODS

Study Design and Subjects

In this multicenter, observational, prospective cohort study, consecutive patients referred for bariatric surgery were recruited from seven centers in the Netherlands between April 2018 and December 2019. Patients with no prior history of OSA were eligible for participating in the POPCORN study, a study that evaluates cost-effectiveness of two different strategies of perioperative management of OSA in patients undergoing bariatric surgery. This study is registered at the Netherlands Trial Register, https://www.trialregister.nl/trial/6805, and was approved by the Medical research Ethics Committees United, reference number W17.050 (18). The primary outcome of the POPCORN study is cost-effectiveness, and these results are not yet complete. In this current paper, we present secondary outcomes in all patients that were diagnosed with OSA. The secondary outcomes are CPAP adherence, reasons to discontinue CPAP, postoperative complications, ICU admissions, outcomes of questionnaires on sleep-scores and sleep-related quality of life. Data on weight loss are presented as percentage total body weight loss (%TBWL), and as percentage excess weight loss (%EWL). Patients undergoing preoperative HSAT were diagnosed with OSA, and CPAP was initiated, if they had REI ≥15. Some patients with REI

5-15, who reported excessive daytime sleepiness, CPAP treatment was offered too. These patients will be referred to as Group A. Four of seven participating hospitals performed HSAT in patients that were pre-selected by STOPBANG-questionnaires, while the higher volume centers screened all consecutive patients eligible for bariatric surgery, regardless of STOPBANG scores. During the same time period, consecutive patients who presented with pre-existing OSA and current CPAP therapy were recruited as controls (Group B). Inclusion criteria were A) eligibility for primary bariatric surgery according to the current IFSO guidelines, B) age ≥18 years, C) Dutch language proficiency. Exclusion criteria were D) absence of OSA on HSAT, E) OSA treatment other than CPAP, or variable / bilevel positive airway pressure, F) revisional bariatric procedure, H) concomitant procedures that could enhance risk of (cardiopulmonary) complications, such as repositioning of an intrathoracic stomach. All patients provided either written or digitally-signed informed consent.

Outcomes and Data Collection

In this current analysis, we aimed to evaluate the prevalence of patients with inadequate adherence to CPAP (defined as < 4 hours per night) during the preoperative phase, and during the first six months after surgery. We also analyzed the incidence of cardiopulmonary complications, scheduled/unscheduled admissions to the ICU or medium care unit (MCU), and perioperative measures to prevent complications in patients with inadequate CPAP use. Furthermore, reasons to stop CPAP therapy within six months after surgery were documented. Predictors to stop CPAP therapy were also analyzed. Data were extracted from hospital files, and telemonitoring of CPAP usage was used to determine adherence to CPAP in terms of hours/night and date of potential discontinuation, if available. Patient reported outcomes were retrieved from questionnaires: the Epworth sleepiness scale (ESS) and the functional outcomes of sleep questionnaire (FOSQ), 10-items edition, and patients were asked whether they still used CPAP treatment, and if not; which data CPAAP was ceased, reasons for discontinuation, and whether they had undergone a new HSAT (19, 20). Questionnaires were sent to patients pre-operatively, and after surgery at 1, 3 and 6 months. Weight at baseline and all other timepoints was documented, and weight loss was represented as %TBWL, defined as weight loss divided by weight before surgery, and also as %EWL. This percentage was calculated as loss of excess weight (defined as weight above the ideal weight, i.e. =BMI 25 kg/m^2) divided by excess weight before surgery.

Statistical Analysis

Data are presented as means ± standard deviations (SD) or medians and interquartile ranges (IQR). Comparison of continuous data were performed using independent t-tests or Mann Whitney U test. Binary data were analyzed with chi-

square test or a Fishers' exact test. To identify predicting factors for inadequate use of CPAP, we performed univariable and multivariable logistic regression. Variables in the univariable analysis with a *p* value under <0.10 were added to the multivariable model. Risk factors are presented including the odds ratio (OR) and adjusted odds ratio (aOR) with 95% confidence intervals (CI). A *p* value of < 0.05 was considered as statistically significant. Statistical analyses were performed by using IBM SPSS Statistics, version 25.0 for Windows (SPSS. Chicago, IL).

RESULTS

Of 542 patients that underwent a preoperative HSAT prior to bariatric surgery, 272 patients (50.2%) were diagnosed with OSA and consequently treated with CPAP (group A). In this group, median time from preoperative HSAT to bariatric surgery was 125 days. During the study period, 132 patients with pre-existing OSA and CPAP therapy were recruited (group B). In this group, median time between HSAT and bariatric surgery was 1013 days. Patients in group B were more often male, with higher mean REI and lower mean preoperative BMI and higher prevalence of asthma. [Table 1]

Inadequate CPAP use

Before surgery, 41 patients in group A (15%) used their CPAP device insufficiently, compared to 5 patients (4%) in group B (p=0.049) [Table 2]. Time between the start of CPAP therapy until surgery did not affect CPAP adherence in newly diagnosed patients. One month postoperatively, 43% patients in group A were inadequate users, compared to 20.5% in group B (p<0.001). At 3 months after surgery, results similarly differed between group A and B: 57.7% vs. 37.9% (p<0.001). At 6 months after surgery, 199 Patients in group A (73%) were inadequate CPAP users, compared to 51 (39%) patients in group B (p<0.001). At that time, six patients were lost to follow-up, and one patient in group A died 156 days after surgery due to a stroke.

Postoperative outcomes

Total postoperative complications were similar in patients with newly diagnosed OSA and patients with pre-existing OSA (9.6% vs. 8.3%, p=0.689) [Table 1]. Cardiopulmonary complications were also similar between study groups (n=2, 0.7% vs. n=2, 1.5%, p=0.600). To analyze the influence of CPAP use on cardiopulmonary complications, we also combined group A and B, and made comparisons between adequate and inadequate CPAP users. Complications between these two groups (3/357 vs. 1/47, p=. 212) showed no significant difference.

Distribution of minor and major complications based on the Clavien-Dindo Classification (21) did not differ between group A and B. Scheduled ICU admissions of group A (n=4) were due to severe chronic obstructive pulmonary disease, non-adherence to CPAP (n=2), and severe OSA (REI>100), and in group B (n=2) due to severe OSA (REI>80) and congestive heart failure. Unscheduled ICU admissions in group A (n=2) were anastomotic leakage and diabetic ketoacidosis, and in group B one patient was admitted to the ICU due to severe postoperative desaturations, despite adequate CPAP therapy. Admission to the MCU was required in one patient in group A for postoperative CPAP intolerance, despite adequate preoperative adherence.

Other interventions to prevent OSA-related complications in inadequate CPAP users before surgery mostly consisted of mandatory use of CPAP during hospital admission as a prerequisite to undergo surgery, despite the patients' inability to adhere to CPAP at home (group A; n=23, group B; n=4). The remaining patients that were inadequate CPAP users were all postoperatively monitored with continuous pulse oximetry and received supplemental oxygen as needed (group A, n=18, group B, n=1).

Table 1. Baseline characteristics and surgical outcomes

	Total (n=404)	Group A (newly diagnosed OSA, n=272, 67.4%)	Group B (Pre-existing OSA, n=132, 32.6%)	*p*-value
Age (median, IQR)	51 (45-57)	51 (45-57)	51 (46-58)	0.605
Gender, female (n,%)	239 (59.2)	182 (66.9)	57 (43.2)	<0.001
BMI in kg/m² (mean, SD)	43.1 ±6.4	43.6 ±6.3	42.3 ±6.3	0.049
Abdominal circumference, in cm (mean, SD)	132 ±14.7	132 ±15.0	132 ±13.9	0.868
Medical history (n,%)				
Type 2 Diabetes	111 (27.5)	70 (25.7)	41 (31.1)	0.465
Hypertension	202 (50)	139 (51.1)	63 (47.7)	0.596
Hypercholesterolemia	132 (32.7)	86 (31.6)	46 (34.8)	0.572
GERD	109 (27)	78 (28.7)	31 (23.5)	0.285
Asthma	60 (14.9)	28 (10.3)	32 (24.2)	0.001
Chronic Obstructive Pulmonary Disease	17 (4.2)	9 (3.3)	8 (6.1)	0.198
Obesity Hypoventilation Syndrome	2 (0.5)	2 (0.7)	0	0.280
Chronic Kidney Disease	17 (4.2)	12 (4.4)	5 (3.8)	0.977
History of Psychiatric Disorder	131 (32.4)	89 (32.7)	42 (31.8)	0.910
HSAT outcomes				
REI (median, IQR)	25.0 (17.6-40.3)	23.4 (16.5-36.8)	34 (20.0-52.4)	0.001
REI in supine position (median, IQR)	31.3 (19,0-53.1)	28.1 (17.9-46.8)	45.0 (27.0-71.7)	0.001
ODI (median, IQR)	25.7 (17.5-43.5)	24.5 (17.2-39.5)	34.6 (19.4-52.4)	0.045
Baseline saturation (median, IQR)	93.0 (91.3-94.1)	92.9 (91.2-94.1)	93.0 (92.0-94.7)	0.162
Lowest saturation (median, IQR)	79.0 (73.3-84.0)	79.0 (73.0-84.2)	81.5 (74.0-85.8)	0.400
Smoking (n,%)				
Current smoking	19 (4.7)	14 (5.1)	5 (3.8)	0.550
History of smoking	158 (39.1)	103 (37.9)	55 (41.7)	0.444
Type of Surgery (n,%)				
LRYGB	302 (74.8)	202 (74.3)	100 (75.8)	0.746
LSG	102 (25.2)	70 (25.7)	32 (24.2)	0.747
Complications <30 days (n,%)	37 (9.2)	26 (9.6)	11 (8.3)	0.689
Minor*	21 (5.2)	14 (5.1)	7 (5.3)	0.947
Major *	15 (3.7)	12 (4.4)	3 (2.3)	0.403
Cardiopulmonary complications	4 (1)	2 (0.7)	2 (1.5)	0.600
ICU admission (n,%)	9 (2.2)	6 (2.2)	3 (2.3)	0.788
Scheduled	6 (1.5)	4 (1.5)	2 (1.5)	0.972
Unscheduled	3 (0.7)	2 (0.7)	1 (0.8)	0.980
MCU admission (n,%)	1 (0.2)	1 (0.4)	0	0.673
Readmission (n,%)	15 (3.7)	12 (4.4)	3 (2.3)	0.568
Reoperation (n,%)	6 (1.5)	6 (2.2)	0	0.186

*Based on Clavien Dindo Classification (CDC); minor and major complications were defined as CDC 1-2 and CDC ≥3A.

BMI Body Mass Index, *GERD* gastroesophageal reflux disease, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *LSG* laparoscopic sleeve gastrectomy, *ICU* Intensive Care Unit, *IQR* interquartile range, *MCU* medium care unit, *ODI* Oxygen Desaturation Index, *OSA* obstructive sleep apnea, *REI* Respiratory event index, *SD* standard deviation.

Table 2. Inadequate use of CPAP before and after surgery

	Group A (n= 272)	Group B (n=132)	*p*-value
Before surgery **(n,%)**			
Inadequate CPAP use	42 (15.4)	5 (3.8)	0.049
CPAP discontinued	23 (8.4)	0	
CPAP use <4h/night	19 (7.0)	5 (3.8)	
Adequate CPAP use	230 (84.6)	127 (96.2)	
1 month postoperative **(n,%)**			<0.001
Inadequate CPAP use	117 (43.0)	27 (20.5)	
CPAP discontinued*	81 (29.8)	12 (9.1)	
CPAP use <4h/night	36 (13.2)	15 (11.4)	
Adequate CPAP use	155 (56.9)	105 (79.5)	
3 months postoperative **(n,%)**			<0.001
Inadequate CPAP use	157 (57.7)	50 (37.9)	
CPAP discontinued*	130 (47.8)	22 (16.7)	
CPAP use <4h/night	27 (9.9)	28 (21.2)	
Adequate CPAP use	115 (42.3)	82 (62.1)	
6 months postoperative **(n,%)**			<0.001
Inadequate CPAP use	199 (73.2)	51 (38.6)	
CPAP discontinued*	180 (66.2)	45 (34.0)	
CPAP use <4h/night	20 (7.4)	6 (4.6)	
Adequate CPAP use	71 (26.1)	76 (57.6)	
Missing**	2 (0.7)	5 (3.8)	

Group A: newly diagnosed OSA patients, group B: patients with a pre-existent OSA diagnosis.
* cumulative number of patients who discontinued CPAP therapy
** Missing data: 6 lost to FU, 1 fatality (156 days after surgery)
CPAP continuous positive airway pressure, OSA obstructive sleep apnea

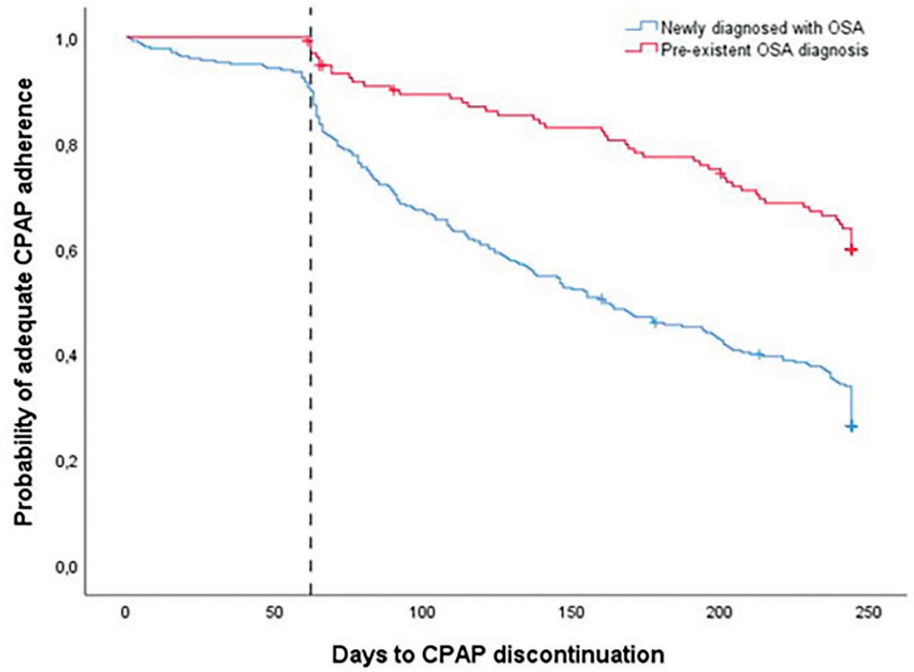

Figure 1: Kaplan Meier Curve illustrating the time-to-event, i.e., CPAP discontinuation between 2 months before surgery and at six months after surgery (p<0.001).
Patients newly diagnosed with OSA are indicated in blue. Patients with a pre-existent OSA diagnosis are indicated in
red. The day of surgery is indicated by the intermittent line. *CPAP* Continuous Positive Airway Pressure, *OSA* Obstructive Sleep Apnea

CPAP use

During the pre-operative phase, rates of patients who stopped using CPAP differed between the two groups; 8.4% of group A stopped CPAP therapy, while all patients in group B used their CPAP device [Table 2]. Six months after surgery, the percentage of patients who stopped CPAP therapy increased to 66.2% and 34.0% in group A and B, respectively (p<0.001) [Figure 1].

Reasons to stop CPAP therapy also differed between the two study groups [Figure 2]. The majority of patients stopped CPAP therapy without consultation of a physician (group A=39% vs. group B=55%, *p*=0.004). None of these patients attended a postoperative appointment in an outpatient clinic, either because there were no scheduled appointments or because patients cancelled on their own initiative. Another reason to stop CPAP was intolerance to CPAP, which occurred in 23% in group A vs. 9.4% in group B (*p*=0.002). In total, 30.5% (n=83)

of group A and 24.2% (n=32) of group B underwent a postoperative HSAT. All patients underwent HSAT between 3 and 6 months, and an additional 10.3% and 8.3% indicated they had an HSAT scheduled for >6 months postoperative, respectively. Following these HSATs, remission of OSA proven in 12.5% of group A and 10.6% of group B, and they could cease therapy (p=0.351). A few patients stopped CPAP therapy despite contrary advise of their physician. In these specific cases, moderate to severe OSA was diagnosed on a postoperative HSAT although patients did not experience any OSA related symptoms (group A=4.9% vs. group B=3.1%, p=0.737). Based on symptom reduction after significant weight loss, 21.9% of group A and 10.9% of group B were advised by their physician to stop therapy without a HSAT was performed (p=0.497).

A univariable logistic regression was performed to identify predictors to stop CPAP and correct for potential confounders [Table 3]. The strongest predictor in multivariable analysis was preoperative diagnosis of OSA: aOR 2.9 (p<0.001). In contrast, patients with preoperative BMI ≥45 kg/m^2 were less likely to cease CPAP therapy (aOR 0.43, p=0.003), just like patients with baseline REI≥30 (aOR 0.56, p=0.029) and type 2 diabetes (aOR 0.55, p=0.021).

Table 3. Univariable and multivariate logistic regression analysis of predictors for CPAP discontinuation (n=397*)

	N (%)	Univariable		Multivariable	
		OR [95% CI]	p value	aOR [95% CI]	p value
Gender **(female)**	239 (59.2)	0.74 [0.48-1.13]	0.160		
Age ≥ 50 years	238 (58.9)	0.78 [0.51-1.21]	0.271		
Preoperative BMI ≥ 45 kg/m2	127 (31.4)	0.53 [0.34-0.83]	0.006	0.43 [0.25-0.75]	0.003
Preoperative waist**, in cm (mean, SD)**	132 ±14.7	0.99 [0.98-1.00]	0.165		
Pre-existing diagnosis of OSA	272 (67.4)	3.10 [1.99-4.85]	<0.001	2.93 [1.74-4.92]	<0.001
Baseline REI ≥30	161 (42.2)	0.45 [0.29-0.70]	<0.001	0.59 [0.37-0.95]	0.029
Asymptomatic before CPAP therapy	93 (23)	2.39 [1.28-4.46]	0.006	1.39 [0.74-2.63]	0.310
ESS ≥11**	111 (27.5)	1.022 [0.64-1.64]	0.927		
Hypertension	202 (50)	0.99 [0.65-1.51]	0.972		
Type 2 Diabetes	111 (27.5)	0.58 [0.36-0.91]	0.018	0.55 [0.33-0.91]	0.021
Hyperlipidemia	132 (32.7)	1.30 [0.84-2.03]	0.245		
Asthma	60 (14.9)	1.60 [0.90-2.82]	0.109		
COPD	17 (4.2)	1.92 [0.73-5.11]	0.188		
History of psychiatric disease	131 (32.4)	0.96 [0.61-1.51]	0.867		
Current smoking	19 (4.7)	0.80 [0.31-2.09]	0.654		
EWL ≥60%***	215 (53.0)	1.85 [1.20-2.84]	0.005	1.28 [0.66-2.47]	0.467
TWL ≥25%***	198 (49.0)	1.64 [1.07-2.52]	0.024	1.45 [0.79-2.63]	0.230

* 7 patients have missing data: 6 lost to follow-up and 1 fatality
** Indicating mild excessive daytime sleepiness
*** measured at six months postoperative
BMI Body Mass Index, *CI* Confidence Interval, *COPD* Chronic Obstructive Pulmonary Disease, *ESS* Epworth Sleepiness Score, *%EWL* Percentage Excess Weight Loss, (a)*OR* (adjusted) Odds Ratio, *OSA* Obstructive Sleep Apnea, *REI* Respiratory Event Index, *%TWL* Percentage Total Weight Loss.

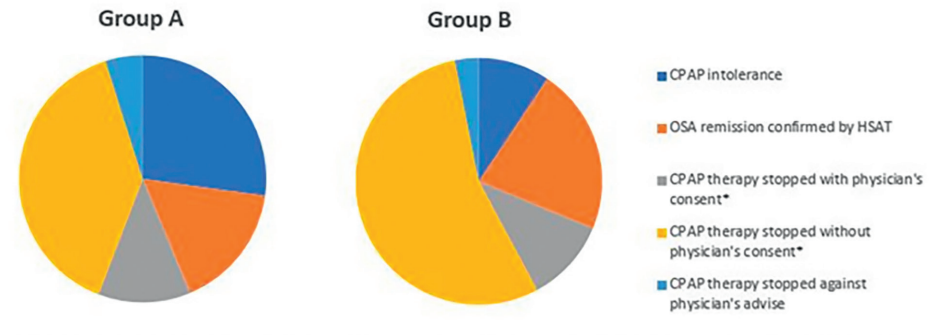

Figure 2: Motivation to stop CPAP therapy of group A (newly diagnosed OSA patients) and group B (patients with a pre-existent OSA diagnosis). * No postoperative HSAT performed
CPAP Continuous Positive Airway Pressure, *HSAT* Home Sleep Apnea Testing, *OSA* Obstructive Sleep Apnea

Outcomes of questionnaires and weight

All outcomes of questionnaires were evaluated for both groups, with further subdivision based on whether they still used CPAP at time of the questionnaire (Table 4). There were no significant changes in outcomes of ESS, FOSQ, weight or BMI between group A and B, that were consistently observed at all timepoints. FOSQ scores were significantly lower for group A at baseline and after surgery at 1 and 3 months, while this difference disappeared at 6 months postoperative. Initial BMI of patients newly diagnosed with OSA who used CPAP before surgery was lower compared to patients who did not use their CPAP device, this difference was not seen during all follow-up visits. In patients with pre-existent OSA, no significant distinction could be made between CPAP users and non-user regarding the self-reported outcomes retrieved from questionnaires.

As sensitivity analyses, we performed subgroups analyses of newly diagnosed patients. We compared patients based on whether preselection for HSAT was performed with STOPBANG-questionnaires or not. We found no difference in CPAP adherence at any time-point, neither were any postoperative outcomes different (i.e. all complications, cardiopulmonary complications, or weight loss).

DISCUSSION

Preoperative OSA assessment and subsequent CPAP therapy is perceived to prevent OSA-related complications in obese patients undergoing bariatric surgery, while not conclusively proven. Although 15% of newly diagnosed bariatric patients in this large cohort study did not adequately adhere to CPAP before surgery, this did not lead to an increased number of postoperative complications when compared to patients with pre-existing OSA and CPAP therapy. Six months after surgery, the percentage of patients with inadequate adherence to CPAP increased to 73% in newly diagnosed patients, which was significantly higher than the 39% of patients with pre-existent OSA.

In absence of robust literature on CPAP adherence in bariatric patients who are diagnosed with OSA in the preoperative phase, the true efficacy of routine OSA screening and consequent CPAP therapy remains to be elucidated. In recent years, OSA prevalence in bariatric patients has been extensively reported in studies that performed routine preoperative polysomnography or HSAT (6, 22). However, limited data is available on consequent perioperative outcomes related to preoperative OSA screening, such as cardiopulmonary complications and related morbidity and mortality (23, 24). In addition, without accurate data on CPAP adherence and well-designed prospective studies, it seems unjust to assume that CPAP therapy should be applied routinely to prevent postoperative complications. In a study by Guralnick et al., low adherence to CPAP was reported in 104 preoperatively diagnosed patients, as 33% was adherent after 30 days of CPAP therapy (25). However, it is unclear how many patients in their study failed to adjust to CPAP before hospital admission, as CPAP was initiated only 4 days prior to surgery. In our cohort, we observed that 15% of patients had no or inadequate use of CPAP at time of surgery. It is important to note that some studies, like ours, perform polygraphy on all patients, instead of pre-selecting patients with a high pre-test probability for OSA, by first applying a screening questionnaire. This means that patients in our cohort are overall less likely to have OSA, and this might negatively influence the adherence rate. To optimize treatment of OSA and CPAP therapy in bariatric care additional educational, behavioral or troubleshooting interventions should be considered (16, 26). In addition, postoperative adherence to CPAP might be enhanced by regularly adjusting CPAP pressures, as surgically induced weight loss changes the pressure demand (27). However, all patients in our cohort used CPAP, while other modalities that also provide positive airway pressure (PAP) may be more suitable for patients with changing pressure demands, such as automated PAP. This potentially increases the ease of continuing CPAP during weight loss. Although these strategies may improve CPAP adherence, they will also require additional time from hospital staff and an increase in costs.

Table 4. Outcomes of questionnaires and weight loss

	Group A (n=272)				Group B (n=132)				p value*
	Total	CPAP use	No CPAP use	p-value**	Total	CPAP use	No CPAP use	p-value**	
Before surgery (n,%)									
ESS score	7.6 ±5.2	7.6 ±5.1	7.3 ±6.1	0.723	8.4 ±5.3	8.4 ±5.3	NA	NA	0.483
FOSQ score	20 (19-20)	20 (19-20)	20 (19-20)	0.476	19.7 18.3-20)	19.7 (18.2-20)	NA	NA	0.013
Weight	128.7 ±23.0	128.2 ±22.1	136.5 ±30.5	0.009	128.8 ±23.9	128.5 ±23.5	NA	NA	0.912
BMI	43.8 ±5.8	43.6 ±5.6	45.1 ±7.5	0.006	41.2 ±6.6	42.3 ±6.3	NA	NA	0.337
1 month postoperative (n,%)									
ESS score	5.9 ±4.9	6.5 ±5.4	5.0 ±3.5	0.029	6.7 ±4.6	6.7 ±4.5	6.7 ±5.4	0.532	0.778
FOSQ score	20 (19.3-20)	20 (19.5-20)	20 (19.3-20)	0.788	20 (18.7-20)	20 (18.7-20)	20 (17.4-20)	0.827	0.012
Weight	116.8 ±21.9	117.4 ±19.8	116,45 ±23.9	0.067	116.6 ±21.9	117.6 ±21.9	104.6 ±18.3	0.573	0.889
BMI	39.5 ±5.9	39.8 ±5.7	38.9 ±6.1	0.682	37.9 ±6.3	38.2 ±6.3	33.7 ±4.2	0.442	0.513
%TWL	9.8 ±5.6	23.3 ±15.6	26.5 ±11.4	0.831	10.2 ±3.6	10.1 ±3.2	12.5 ±6.0	0.015	0.263
%EWL	24.3 ±14.4	20.2 ±9.5	23.5 ±10.6	0.903	27.4 ±12.2	26.5 ±10.7	37.8 ±19.0	0.085	0.418
3 months postoperative (n,%)									
ESS score	4.7 ±4.7	4.7 ±4.9	4.7 ±4.5	0.686	6.4 ±5.0	6.0 ±4.5	8.4 ±6.5	0.066	0.402
FOSQ score	20 (20-20)	20 (20-20)	20 (19.7-20)	0.172	20 (19-20)	20 (19.4-20)	20 (18.7-20)	0.334	0.009
Weight	105.6 ±19.7	105.7 ±18.1	105.5 ±23.2	0.245	105.1 ±20.7	106.7 ±20.9	97.0 ±17.9	0.557	0.816
BMI	35.9 ±5.5	36.1±5.2	35.3 ±6.2	0.996	34.2 ±6.0	34.8 ±6.2	31.3 ±4.1	0.342	0.499
%TWL	18.3 ±4.4	17.8 ±3.9	18.6 ±4.9	0.006	18.4 ±4.5	17.9 ±4.1	20.9 ±5.3	0.137	0.828
%EWL	44.9 ±14.1	42.6 ±12.1	47.5 ±15.7	0.019	49.5 ±17.4	47.4 ±15.8	60.2 ±21.3	0.020	0.011

Table 4. Outcomes of questionnaires and weight loss *(continued)*

	Group A (n=272)				Group B (n=132)				p value*
	Total	CPAP use	No CPAP use	p-value**	Total	CPAP use	No CPAP use	p-value**	
6 months postoperative (n,%)									
ESS score	4.5 ±4.5	4.6 ±4.5	4.4 ±4.5	0.589	5.4 ±4.1	6.0 ±4.0	4.4 ±4.3	0.410	0.651
FOSQ score	20 (19.7-20)	20 (19.8-20)	20 (19.7-20)	0.536	20 (19.6-20)	20 (19.1-20)	20 (19.9-20)	0.174	0.186
Weight	96.7 ±19.4	101.1 ±20.5	94.6 ±18.4	0.138	96.2 ±19.1	99.1 ±19.9	90.0 ±14.7	0.283	0.734
BMI	32.8 ±5.3	34.2 ±5.3	32.1 ±5.0	0.636	31.4 ±5.4	32.4 ±5.6	29.2 ±3.8	0.209	0.994
%TWL	25.2 ±6.0	24.5 ±6.4	25.5 ±5.8	0.504	25.3 ±5.6	24.1 ±5.4	27.6 ±5.5	0.303	0.451
%EWL	61.9 ±18.2	57.2 ±17.1	64.2 ±18.3	0.128	67.1 ±20.8	62.4 ±19.2	76.5 ±20.8	0.106	0.721

*P-value of comparison between group A and group B

**P-value of comparison between CPAP users and non-users within in group A and group B, respectively.

Group A: patients with newly diagnosed OSA, Group B: patients with pre-existing OSA.

BMI Body Mass Index, *CPAP* Continuous Positive Airway Pressure, *%EWL* Percentage Excess Weight Loss, *ESS* Epworth Sleepiness Scale, *FOSQ* Functional outcomes of sleep questionnaire, *%TWL* Percentage Total Weight Loss

In the present study, the majority of patients stopped CPAP therapy without consulting their OSA physician, and often had no scheduled postoperative follow-up. Postoperative HSATs are important to monitor disease remission, as bariatric patients were often asymptomatic or did not recognize OSA symptoms to begin with. Timmermans et al. showed that remission of OSA (i.e., AHI <15 events/hour) after bariatric surgery is unrelated to improvement of sleepiness symptoms, weight loss or even self-initiated discontinuation of CPAP therapy (28). As our observational study showed, many patients cease their CPAP therapy due to these motives, emphasizing the need for clear guidelines on postoperative follow-up for this patient group to confirm either persistence or remission of OSA. We found that many of our patients did not receive a follow-up appointment or a postoperative polygraphy. As a possible explanation, this may be due to the fact that no guideline recommends a specific timeline in which patients should be re-evaluated (11). It could also derive from the relatively short follow-up duration that is being investigated in our study; six months after surgery might be too short to experience significant weight loss and perform consecutive polygraphy. Additionally, as the follow-up period of this study took place during the COVID-19 pandemic, is it possible that this type of elective care was postponed due to limited resources. In addition, we found that patients with pre-existing OSA were significantly more likely to stop CPAP than newly diagnosed patients without consultation of a physician, which could be explained by the fact that these patients are no longer regularly seen by their OSA physician, and thus a scheduled postoperative HSAT was omitted. These patients were presumably symptomatic at the time of diagnosis, which may have encouraged them to stop CPAP therapy when their OSA complaints resolved after substantial weight loss.

We acknowledge that our study has several limitations. First, the control group consisted of patients with pre-existing OSA before surgical consultation. These patients differed from newly diagnosed OSA patients in several baseline characteristics and more often reported OSA symptoms before HSAT. Although we aimed to correct for these differences in the logistic regression, it is possible that other factors that were not identified in our cohort also acted as confounders, such as neck circumference, pre- or postmenopausal status. Second, complications related to (untreated) OSA are rare, which is in concordance with the findings in the present study. This is a common finding in bariatric populations that adhere to Enhanced Recovery After Bariatric Surgery, a guideline that promotes bariatric surgery with low administration of drugs that induce breathing cessation, as well as early mobilization for optimal pulmonary recovery(9). Therefore, it is likely that a clinically relevant impact of CPAP therapy will only be visible in study populations with a much larger sample size. This also makes a future randomized trial that evaluates OSA-related complications quite unlikely or even infeasible, as sample size calculation using previous data

of OSA-related complications in a bariatric cohort, i.e. 0.6- 0.8%(29), results in group-sizes of 27,634 patients, containing 55268 patients in total. Third, it should be noted that the complication rate is potentially negatively influenced by a specific element of our perioperative strategy, i.e. pre-operatively diagnosed OSA patients who did not use CPAP, or used it insufficiently, were advised to use CPAP during the first night postoperatively. Patients that do not tolerate CPAP well, are at risk of enhanced sleep deprivation. This fragmentation of sleep can further aggravate the increase of AHI that is observed in the first postoperative week, long after patients are discharged from the hospital (30). Fourth, the adherence data of this study is partly based on questionnaires outcomes. We tried to refrain from using this data as questionnaires are less objective than data gained from telemonitoring. As we did not have objective quantifiable data through telemonitoring for all patients, this may have influenced our outcomes. Future studies should try to solely use adherence data from telemonitoring, as this is more objective and additionally has potential to better provide tailored advice for CPAP patients (31).

Rates of inadequate or no adherence in bariatric patients who are newly diagnosed with OSA were high in both the pre- and postoperative period. Given that routine preoperative OSA screening in all bariatric patients and consequent CPAP implementation is a time-consuming and costly intervention, the percentage of inadequately adherent patients suggests that this approach may not be the most cost-effective modality to prevent OSA-related complications. Future studies should elucidate whether optimization of CPAP use is the best strategy to minimize detrimental effects of untreated OSA in bariatric patients, or if alternative strategies to prevent OSA-related complications (i.e., no preoperative screening but for example intense postoperative monitoring, or development of an algorithm that has higher specificity and sensitivity than the existing screening questionnaires) can be used in bariatric practice (32).

Conclusion

Our results indicate that patients who are newly diagnosed with OSA are more likely to stop therapy or inadequately apply CPAP before and after surgery, compared to bariatric patients with pre-existing OSA. Strategies to increase CPAP adherence and scheduled post-operative HSATs may be of value when considering routine HSAT screening and subsequent peri-operative CPAP in patients undergoing bariatric surgery. Further studies focusing on efficacy and cost-effectiveness are needed to improve current guidelines on peri-operative OSA management in morbidly obese patients.

Statements and Declarations

All authors declare that they have no conflict of interest.

Ethical Statement
This study was performed in accordance with the 1964 Helsinki declaration and its later amendments, and was approved by the medical ethical review board.

Consent Statement
Informed consent was obtained from all participants included in the study.

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Data availability statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CHAPTER 7

Cost-effectiveness and safety of continuous pulse oximetry for management of undiagnosed obstructive sleep apnea in bariatric patients: a nationwide cohort study

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Submitted

ABSTRACT

Importance
Undetected obstructive sleep apnea (OSA) is highly prevalent in patients undergoing bariatric surgery and increases operative risks. Screening for OSA using preoperative polygraphy (PG) with subsequent continuous positive airway pressure (CPAP) is costly and time-consuming. Postoperative continuous pulse oximetry (CPOX) monitoring without OSA-screening is a less invasive, and is hypothesized to be a safe and cost-effective alternative.

Objective
To evaluate cost-effectiveness of CPOX compared with PG and CPAP as perioperative care for bariatric patients.

Design
Multicenter, prospective, observational cohort study with a non-inferiority design, with follow-up from baseline to one year postoperative. Propensity score matching was used to minimize selection bias.

Setting
Seven high-volume bariatric surgery centers in the Netherlands.

Participants
Adult patients with no prior OSA diagnosis.

Intervention/Exposure
In the intervention group, patients were postoperatively monitored using CPOX and received supplemental oxygen, without preoperative PG. In the control group, patients underwent preoperative PG and when OSA was diagnosed, CPAP was started. Patients were placed into a cohort based on local hospital protocols. A cost-effectiveness analysis was performed using quality adjusted life years (QALY) and healthcare costs.

Main outcomes
In total, 1390 patients were included, and 1090 patients remained after propensity score matching. QALYs were similar at baseline; both CPOX and PG group scored 0.77, and at one-year postoperatively, as scores increased to 0.87 and 0.88, respectively. Postoperative complications, and in particular OSA-related complications, did not differ between groups, neither did unanticipated ICU admissions or readmissions. The mean cost per patient/year in the CPOX group was €3,048, vs. €3,582 in the PG group; mean difference €-534 (95% CI €-896 to €-137). Higher costs in the PG group resulted from sleep studies, CPAP therapy, and subsequently more outpatient clinic appointments. Using outcomes of all 1390 patients in sensitivity analyses, similar findings for cost-effectiveness, complications and ICU admissions were observed.

Conclusion and relevance
This nationwide cohort study shows that CPOX and PG are similar in effectiveness, as CPOX is not associated with a higher complication or readmission rates. CPOX has lower costs from a healthcare perspective, and can therefore be considered a cost-effective alternative to routine OSA screening in this population.

Trial registration
Netherlands Trial Register, NTR6991, https://www.trialregister.nl/trial/6805

INTRODUCTION

Obstructive sleep apnea (OSA) is the most prevalent sleep-breathing disorder in surgical patients. As obesity is the main risk factor, it is not surprising that the prevalence of OSA is up to 70% in patients scheduled for bariatric surgery.(1-3) Obesity and OSA are both associated with significant healthcare costs. Identification of OSA in the general population is recommended because of impaired quality of life (QoL), increased risk of cardiovascular disease, and consequently increased utilization of healthcare resources throughout life.(4) However, these recommendations cannot be extrapolated to the bariatric population in which OSA is expected to reduce in severity or resolve completely as a result of weight loss.(4-6) The main challenge concerning OSA in bariatric patients is that the majority is undiagnosed and thus untreated, which increases the risk of cardiopulmonary and thromboembolic complications.(7, 8)

Most bariatric guidelines advocate preoperative OSA assessment using sleep studies such as polysomnography (PSG) or polygraphy (PG). If moderate or severe OSA is diagnosed, continuous positive airway pressure (CPAP) therapy is advised to prevent perioperative OSA-related complications. These guideline recommendations are mainly based on low-quality evidence, or are only consensus-based.(9, 10) Because sleep studies are costly and time-consuming, and in most high-volume bariatric centers limited in availability, OSA screening questionnaires have been developed. Unfortunately, these questionnaires lack high sensitivity and specificity in bariatric patients.(11, 12) An alternative to routine sleep studies or screening questionnaires is postoperative monitoring with continuous pulse oximetry (CPOX) and non-invasive supplementation of oxygen, without any form of OSA assessment before surgery. This strategy focusses on the early postoperative phase and oxygenation, and the termination of singular, long-lasting apneas that are feared by some clinicians.(13)

To date, no high-quality comparative studies are available that have evaluated the efficacy or cost-effectiveness of these perioperative strategies in bariatric patients with undetected OSA. In addition, no Because OSA-related complications are rare but potentially life-threatening, this creates a difficult discussion about whether an invasive and expensive perioperative strategy is justified.

We hypothesized that postoperative CPOX with supplemental oxygen can prevent desaturations leading to OSA-related complications, and can be cost-effective, compared with assessment with preoperative PG of all bariatric patients with consequential CPAP therapy.

METHODS

Study design

This is a prospective, multicenter, observational cohort study that was conducted in seven bariatric centers in the Netherlands. Patients were approached for study participation if they had no prior OSA diagnosis and fulfilled the criteria to undergo bariatric surgery (body mass index (BMI) ≥40 kg/m^2, or BMI≥35 kg/^{2} in presence of obesity-related comorbidity).(14) Exclusion criteria were previous bariatric surgery, the inability to speak the Dutch language, or undergoing concomitant procedures during bariatric surgery that could increase the risk of complications, such as hiatal hernia repair. The study design has been previously described.(15) Because of the non-randomized design, the main analyses were performed between groups that were propensity score-matched. In the logistic regression to form propensity scores, we used gender, BMI, age, hypertension, diabetes, hypercholesterolemia, alcohol consumption, and current smoking as potential confounders. We performed 1:1 nearest neighbor matching with a 0.1-width caliper. All patients provided written informed consent and the study was performed in accordance with the Declaration of Helsinki.(16)

Treatment allocation

Patients were placed in a cohort based on local protocols of their respective hospital. Patients in the CPOX group underwent postoperative continuous monitoring with CPOX immediately after return to the surgical ward, with additional oxygen supplied via a nasal cannula (2L/min SpO_2). Nurses were alarmed when saturation levels dropped <92% $SpO_{2,}$ during at least 10 seconds. Following an alarm, the attending nurse performed clinical evaluation, and long-lasting apneas were stopped by awaking the respective patient, or by providing additional supplemental oxygen via the non-invasive nasal cannula. If these minor interventions were not sufficient, the attending physician performed clinical evaluation, and other treatment options could be initiated, such as admission to the intensive care unit (ICU) for potential reintubation.

Patients in the PG group all underwent an ambulant PG. Several outcomes were monitored during PG; such as the occurrence of complete and partial cessations of breathing, respectively called apneas and hypopneas. The diagnosis of OSA was defined by the apneas or hypopneas index (AHI); an AHI <5/hour excludes OSA, AHI≥5/hour indicated mild OSA, AHI 15-30/hour indicated moderate OSA, and AHI>30/hour indicated severe OSA. In general, patients with moderate or severe OSA started CPAP therapy, which patients were required to use after surgery.

In this study, the laparoscopic Roux-en-Y gastric bypass and the laparoscopic sleeve gastrectomy were performed. All participating hospitals based their anesthetic regime on the principles of early recovery after bariatric surgery (ERABS). This included the minimization of opioids and other intra-operative drugs that could influence postoperative oxygenation. All participating bariatric centers used propofol for initial sleep induction, while using Rocuronium as muscle relaxant. Some hospitals also used propofol as maintenance of anesthesia. At the end of the surgical procedure, all participating centers measured residual relaxation related to neuromuscular blockade with train-of-four count, and applied reversal drugs, such as Sugammadex/Bridion®, if indicated. In the postoperative phase, all participating centers administered low-molecular-weight heparin (nadroparin) to all patients to prevent thrombosis.

Outcomes

The primary outcome was the cost-effectiveness of CPOX compared with PG from a societal perspective; evaluating health care costs made from baseline (i.e. start of bariatric care) until one year after surgery. QoL was measured as quality-adjusted life years (QALYs), where 1 QALY indicates one year in perfect health, and 0 QALY indicates death. The QALYs were assessed by using EuroQol 5 Dimensions – 3 level (EQ-5D-3L) questionnaires at several timepoints; preoperatively, and 1, 3, 6, and 12 months after surgery.(17) Healthcare costs were derived from hospital records and trial registration. Additionally, patients were asked to report medical costs outside the hospital (e.g. visits to the general practitioner or visits to another hospital) in a medical cost questionnaire. To assess the societal costs related to health, loss of income from a paid job, or productivity loss in unpaid activities, the productivity costs questionnaire was used (pICQ).(18) When differences in quality of life did not exceed the non-inferiority margin of 0.03, cost-effectiveness outcomes were expressed as incremental costs and no Incremental Cost-Effectiveness Ratio (ICER) values were calculated. Robustness of total cost outcomes was assessed using the 95% Credibility interval (CI) of the cost difference between both groups. All cost outcomes were analyzed from a societal perspective and a healthcare perspective. The healthcare perspective excluded productivity costs.

The secondary outcomes were surgical: complications until 30 days postoperatively, in particular cardiopulmonary and thromboembolic complications, as they can be the result of untreated OSA. In addition, admissions to the intensive or medium care unit (respectively ICU and MCU) were reported, length of stay, readmission, and reoperations. Outcomes of PG will also be documented, with AHI, oxygen desaturation index (ODI), and indication for CPAP treatment.

Sample size calculation

This study had a non-inferiority design to assess whether postoperative CPOX without a PG was non-inferior to PG in bariatric patients. As CPAP therapy should be initiated in patients with moderate or severe OSA, it should not only mitigate complication risks but also increase the general QoL. Sample size calculation is based on QALYs (obtained by using the EQ-5D score) reported in a study comparing CPAP to best supportive care alone (e.g. advice on sleep hygiene) in patients with OSA. The mean QALY in the CPAP group was 0.68 (95%CI 0.64 – 0.72).(19) We predefined a non-inferiority margin of 0.03 on the EQ-5D score, meaning that the upper boundary of the 95% CI of the absolute difference between the primary endpoint (i.e. the EQ-5D score) in the two study groups would be lower than 0.03. Calculating with 80% power to detect the predefined non-inferiority margin at a one-sided level of 0.05, 621 patients are needed in each study group. Assuming a loss to follow up of 10%, the total study population will be set at 1380 patients (690 per arm).

Statistical analysis

Data were analyzed using SPSS 25.0 for Windows, R (4.4) packages mice (3.14.0). Data were expressed as mean ± standard deviation, or median with interquartile ranges, based on normality. Baseline characteristics and complication parameters were compared between the two groups with an unpaired t test for continuous data or a chi-squared test for binary data. A p-value of <0.05 was considered significant. The 95% credibility interval was calculated using Monte Carlo simulations.

Health economic analysis

Data regarding QoL and cost data were analyzed from the inclusion date until one year after surgery. Data on all other healthcare costs (i.e. visits to other hospitals and general practitioners) and productivity losses were measured from the date of operation until one-year of follow-up. Unit costs of both healthcare costs and societal costs were translated into the year 2020 euros, using the Dutch consumer price index and are reported in the supplementary file; tables S1, S2, and Table 2. Missing data were imputed using 20 imputation sets. Next, the mean of the imputation sets was used as an outcome measure. Monte Carlo bootstrap simulation was performed 5,000 times by randomly (with replacement) selecting patients and randomly (without replacement) selecting 20 out of 200 imputation sets. Again, the mean of both groups was calculated. The 95% credibility interval was assessed using the percentile method on the simulation mean outcomes for both total costs and total QoL. As a sensitivity analysis, these analyses were repeated in the total number of included patients (N=1380), and in all complete cases analysis. Study conduct and reporting adhered to the Consolidated Health

Economic Evaluation Reporting Standards (CHEERS) checklist for economic evaluations.(20)

RESULTS

Between April 2018 and February 2020, 1389 patients were included, 699 in the CPOX cohort and 691 in the PG cohort. Patients' mean age was 45 years, median BMI 42.2 kg/m^2, and 79.2% were female. [Table 1] In the PG cohort, 338 patients (48.9%) had moderate or severe OSA and started CPAP treatment. Due to several differences in baseline characteristics between groups, i.e. age, gender, and hypertension, propensity score matching was performed. Out of the 1389 patients in total, 545 patients per cohort could be matched pairwise, resulting in 1090 patients in the propensity score analysis.

Table 1. Baseline characteristics

	CPOX		PG		P-value	
	All (n=699)	PSM (n=545)	All (n=691)	PSM (n=545)	All	PSM
Female gender **(n,%)**	571 (81.7)	442 (81.1)	530 (76.7)	428 (78.5)	0.025	0.327
Age**, in years (mean, SD)**	44.4 (±12.1)	44.6 (±12.0)	46.2 (±11.5)	45.5 (±11.6)	0.004	0.396
BMI**, in kg/m2 (median, IQR)**	42.5 (39.8-46.8)	42.4 (39.7-46.4)	42.0 (39.8-45.8)	41.9 (39.9-46.1)	0.081	0.422
Waist circumference**, in cm (mean, SD)**	128.5 (±14.2)	128.3 (±13.9)	128.6 (±13.9)	128.4 (±13.9)	0.937	0.643
Comorbidities **(n,%)**						
Hypertension	253 (36.2)	202 (37.1)	293 (42.4)	216 (39.6)	0.018	0.418
Type 2 Diabetes	114 (16.3)	94 (17.3)	132 (19.1)	103 (18.9)	0.262	0.688
NIDDM	67 (9.6)	57 (10.5)	85 (12.3)	66 (12.1)		
IDDM	47 (6.7)	37 (6.8)	47 (6.8)	37 (6.8)		
Dyslipidaemia	143 (20.5)	132 (24.2)	207 (30.0)	142 (26.1)	<0.001	0.530
GERD	199 (28.5)	155 (28.4)	211 (30.5)	162 (29.7)	0.411	0.689
Osteoartitis	333 (47.6)	259 (47.5)	385 (55.7)	300 (55.0)	0.003	0.015
Hypothyroidism	71 (10.2)	58 (10.6)	75 (10.9)	53 (9.7)	0.726	0.618
Asthma	91 (13)	68 (12.5)	81 (11.7)	61 (11.2)	0.371	0.454
COPD	20 (2.9)	19 (3.5)	17 (2.5)	10 (1.8)	0.620	0.091
AF	13 (1.9)	12 (2.2)	10 (1.4)	7 (1.3)	0.675	0.259
HF	5 (0.7)	3 (0.6)	3 (0.4)	1 (0.2)	0.726	0.624
CAD	16 (2.3)	13 (2.4)	15 (2.2)	9 (1.7)	0.881	0.519
OHS	0 (0)	0 (0)	2 (0.3)	1 (0.2)	0.248	0.318
DVT	38 (5.7)	31 (5.7)	22 (3.4)	17 (3.2)	0.035	0.042

Table 1. Baseline characteristics *(continued)*

	CPOX		PG		P-value	
	All (n=699)	PSM (n=545)	All (n=691)	PSM (n=545)	All	PSM
Myocardial infarction	17 (2.4)	14 (2.6)	21 (3.0)	13 (2.4)	0.514	0.849
History of psychiatric disorder	133 (19.0)	93 (17.1)	218 (29.1)	180 (33.0)	0.001	<0.001
History of carcinoma	41 (5.9)	33 (6.1)	31 (4.5)	24 (4.4)	0.278	0.276
CVA	8 (1.1)	6 (1.1)	6 (0.9)	4 (0.7)	0.790	0.753
Smoking (n,%)					0.307	0.555
Active smoker	58 (8.3)	44 (8.1)	45 (6.5)	35 (6.4)		
Former smoker	212 (30.3)	167 (30.6)	229 (33.1)	166 (30.5)		
Alcohol (n,%)	234 (33.5)	226 (41.5)	366 (53)	213 (39.1)	<0.001	0.802
Sleep study outcomes (median, IQR)						
AHI	N/A	N/A	11.3 (5.1-23.2)	10.4 (4.5-23.1)	N/A	N/A
AHI supine	N/A	N/A	12.5 (4.0-31.6)	11.3 (3.6-30.9)	N/A	N/A
ODI	N/A	N/A	12.3 (5.4-24.6)	11.4 (5.0-23.8)	N/A	N/A
TST supine in min	N/A	N/A	144 (63.5-239.2)	144 (62.1)	N/A	N/A
Average Sp02	N/A	N/A	94 (92-95)	94 (92-95)	N/A	N/A
Lowest SpO2	N/A	N/A	84 (78-88)	84 (78-88)	N/A	N/A
No. episodes Sp02 <90%	N/A	N/A	13 (1-46)	11 (1-42)	N/A	N/A
Total desaturation time in sec	N/A	N/A	221 (20-1506)	198 (18-1254)	N/A	N/A
No. episodes SpO2 4% below baseline saturation	N/A	N/A	59.5 (6.5-146.3)	44 (6-124)	N/A	N/A
OSA diagnosis + CPAP treatment (n,%)	N/A	N/A	338 (48.9)	258 (47.3)	N/A	N/A
Drug use (n, %)						
Oral antidiabetic agents	102 (14.6)	85 (15.6)	116 (16.8)	92 (16.9)	0.269	0.566
Insulin	49 (7.0)	39 (7.2)	46 (6.7)	36 (6.6)	0.832	0.721
Antihypertensive agents	244 (34.9)	190 (34.9)	273 (39.5)	202 (37/1)	0.070	0.448
Lipid lowering agents	124 (17.7)	106 (19.4)	121 (17.5)	87 (16.0)	0.888	0.132
Daily painkillers	140 (20.0)	100 (18.3)	122 (16.2)	88 (16.1)	0.070	0.379
of which: opoids	43 (6.2)	33 (6.1)	35 (5.1)	26 (4.8)	0.415	0.422
Anticoagulants	63 (9.0)	52 (9.5)	52 (7.5)	37 (6.8)	0.330	0.098
Type of procedure (n,%)					0.053	0.069
LRYGB	556 (79.5)	436 (80.0)	516 (74.7)	408 (74.9)		
LSG	143 (20.5)	108 (19.8)	175 (25.3)	137 (25.1)		

Abbreviations: AF atrial fibrillation, AHI apnea hypopnea index, BMI body mass index, CAD coronary artery disease, CDC Clavien Dindo classification, CPAP continuous positive airway pressure, CPOX continuous pulse oximetry, CVA cerebrovascular accident, DVT deep venous thrombosis, GERD gastroesophageal reflux disease, HF heart failure, IQR interquartile range, LRYGB laparoscopic Roux-en-Y gastric bypass, LSG laparoscopic sleeve gastrectomy, (N)IDDM (non) insulin dependent diabetes mellitus, ODI oxygen desaturation index, OHS obesity hypoventilation syndrome, OSA obstructive sleep apnea, PG polygraphy, PSM propensity score matched, SD standard deviation, TST total sleep time

Cost-effectiveness

At baseline, there were no differences in EQ-5D scores between the CPOX and PG group, both mean scores were 0.77. [Table 2] At one year postoperatively, both groups had significantly improved in QoL to 0.87 QALY in the CPOX group, and 0.88 QALY in the PG group (difference 0.005, 95%CI of the difference -0.019 – 0.006).

The total mean per patient cost from a healthcare perspective was lower in the CPOX group (€3,048) vs. the PG group (€3,582), with a mean difference per patient of €-534 (95%CI: €-896 - € -137). [Table 2] This difference mainly originated in the reduction of sleep studies, initiation of CPAP treatment, and outpatient clinic visits in the CPOX group.

Per-patient costs from a societal perspective were less clearly pronounced and favored the PG group. The PG total per-patient costs were estimated at €8,280 vs. €8,413 in the CPOX group, with a mean difference of €134, 95% CI: €-877 - €1,063). The cost differences were explained by higher observed productivity losses in the CPOX group, mainly caused by a small group of patients reporting higher productivity losses in day-to-day activities, such as caregiving for family members.

We did not calculate Incremental Cost Effectiveness Ratio's (ICERs), as no clinically relevant differences between QALY outcomes occurred between groups. We did perform a budget impact analysis based on the Dutch health care system. Annually, 12,000 bariatric procedures are performed, and approximately 10% of these patients have a medical history of OSA. Due to the lower costs of the CPOX group (€-534 per patient), we expect a potential cost saving of in total €5,767,200 per year in the Netherlands, from a healthcare perspective.

Surgical outcomes

The incidence of overall postoperative complications was 5.9% in the CPOX group, and 7.9% in the PG group, p=0.188. [Table 3] Fatalities within 30 days of surgery only occurred in the CPOX group, as one patient had a refractory septic shock due to a anastomotic leakage. Regarding OSA-related complications there were no significant differences between the groups. In the CPOX group, six patients experienced cardiopulmonary or thromboembolic events, compared with eight patients in the PG group (1.1% vs 1.5%, p= 0.789). Other types of complications, i.e. staple line leakage or bleeding, were also similar between groups. The severity of complications, based on the Clavien Dindo Classification, were not significantly different in the incidence of minor complications (class ≤2; 4.4% vs. 4.0%, p=0.440), and major complications (class >3A; 1.8% vs. 3.5%, p=0.065).

Total ICU admissions differed between groups, with a lower ICU admission rate in the CPOX group: 0.1% vs 1.7% in the PG group, p=0.021. However, this difference did not remain significant after the distinction between scheduled and unscheduled (unanticipated) ICU admissions was made. [Table 3] The difference was mainly explained by scheduled ICU admissions for PG patients, mainly due to CPAP intolerance; 6/9 patients. MCU admissions, length of stay, readmissions and reoperations were similar in both groups.

Table 2. Cost-effectiveness outcomes, expressed in QALYs and costs from healthcare and societal perspective.

		CPOX (n = 545)	**PG** (n = 545)		
QALY		Mean EQ5D score		Difference	95% CI
Pre-operative		0.77	0.77	0.003	
1 month		0.87	0.87	0.001	
3 month		0.88	0.87	0.003	
6 month		0.87	0.89	-0.021	
12 month		0.89	0.89	0.001	
Total (1 year follow-up)		0.873 (SD: 0.14)	0.880 (SD: 0.14)	-0.007	(-0.019 - 0.006)
Healthcare costs	**Unit cost**	**Mean cost**	**Mean cost**	**Difference**	**95% CI**
Trial reported pre-operative cost					
Polygraphy	133	0	133	-133	
Polygraphy follow-up consult	98	0	71	-71	
CPAP treatment	512	0	241	-241	
Trial reported follow-up costs					
PG no. follow-up mean	133	0	19	-19	
Follow-up healthcare costs in operation hospital					
Consultations	98	490	373	117	
Online consultations	98	57	47	10	
Day Treatment	299	14	20	-6	
Emergency visits	280	59	75	-16	
ICU	2179	0	207	-207	
Ward days	515	1456	1522	-66	

Table 2. Cost-effectiveness outcomes, expressed in QALYs and costs from healthcare and societal perspective. *(continued)*

		CPOX (n = 545)	**PG** (n = 545)		
Self-reported costs at other healthcare providers					
General practitioner	36	118	113	6	
Dietitian	32	65	75	-10	
Company Doctor	71	58	45	13	
Home care	NA*	218	155	64	
Emergency visits	280	86	85	1	
Ambulance	557	42	45	-4	
Consultations	98	65	69	-4	
Inpatient Days	515	319	287	32	
Total cost healthcare perspective		3048	3582	-534	(€-896 - €-137)
Unpaid productivity					
Unpaid productivity losses month 3	16	536	650	-114	
Unpaid productivity losses month 12	16	1966	1373	593	
Paid productivity losses month 3	41	1246	1144	102	
Paid productivity losses month 12	41	1617	1530	87	
Total productivity losses		5365	4697	668	(€-206 - €1,456)
Total cost societal perspective		8413	8280	134	(€-877 - €1,063)

Table 3. Surgical outcomes

	CPOX		PG		p-value	
	Complete case	PSM	Complete case	PSM	Complete case	PSM
Complications **(n,%)**	46 (6.6)	32 (5.9)	53 (7.7)	43 (7.9)	0.430	0.188
OSA-related complications*	7 (1.0)	6 (1.1)	8 (1.2)	8 (1.5)	0.983	0.789
Pulmonary	6 (0.9)	5 (0.9)	6 (0.9)	6 (1.1)		
Cardiac	1 (0.1)	1 (0.2)	2 (0.3)	2 (0.4)		
Thromboembolic	0	0	0	0		
Bleeding	17 (2.4)	11 (2.0)	20 (2.9)	15 (2.8)	0.592	0.552
Anastomotic leakage	1 (0.1)	1 (0.2)	3 (0.4)	2 (0.4)	0.380	0.739
GJS stenosis	5 (0.7)	4 (0.7)	8 (1.2)	8 (1.5)	0.535	0.476
Wound infection	1 (0.1)	1 (0.2)	4 (0.6)	4 (0.7)	0.223	0.289
Postoperative pain	3 (0.4)	2 (0.4)	3 (0.4)	2 (0.4)	0.858	0.761
UTI	5 (0.7)	3 (0.6)	3 (0.4)	2 (0.4)	0.343	0.417
Other*	7 (1.0)	4 (0.7)	4 (0.6)	2 (0.4)	0.134	0.230
Severity of complications						
Minor (CDC ≤2)	35 (5.0)	22 (4.0)	28 (4.1)	24 (4.4)	0.392	0.440
Major (CDC ≥3A)	11 (1.6)	10 (1.8)	25 (3.6)	19 (3.5)	0.016	0.065
ICU admission **(n,%)**	1 (0.1)	1 (0.2)	13 (1.9)	9 (1.7)	0.001	0.021
Scheduled	0	0	9 (1.3)	6 (1.1)	0.002	0.031
Unscheduled	1 (0.1)	1 (0.2)	4 (0.6)	3 (0.6)	0.216	0.624
MCU admission **(n,%)****	6 (0.9)	5 (0.9)	1 (0.1)	1 (0.2)	0.124	0.124
Readmission **(n,%)**	27 (3.9)	20 (3.6)	25 (3.6)	19 (3.5)	0.639	0.870
Reoperation **(n,%)**	7 (1.0)	6 (1.1)	15 (2.2)	11 (2.0)	0.134	0.328
Length of stay**, in days (median, IQR)**	1 (1-2)	1 (1-2)	1 (1-1)	1 (1-2)	0.051	0.321

* CPOX: fever without focus (3), internal herniation (1), kidney stones (1), incisional hernia (1), constipation (1)

* PPG: Postoperative urinary retention (1), incisional hernia (1), postoperative hyperglycaemia (2)

**all unscheduled admissions

Abbreviations: CDC Clavien Dindo classification, CPOX continuous pulse oximetry, GJS gastrojejunal stenosis, ICU intensive care unit, IQR interquartile range, MCU medium care unit, OSA obstructive sleep apnea, PG polygraphy, PSM propensity score matched, UTI urinary tract infection

Sensitivity analysis

For sensitivity analysis, we analyzed all patients (n=1390) included in this study. This analysis showed findings that were similar to the propensity score-matched cohorts: QALYs were similar for the CPOX and PG group. [Supplementary material, Table S2] CPOX was cost-effective from a healthcare perspective; €-586 compared with PG (95%CI €-933 - €-242). From a societal perspective PG was favored by € 379, but the confidence interval was wide, €-1,318 - €450,

similar to the main analysis in the propensity score matched cohort. In another sensitivity analysis, using complete cases, the health care costs for CPOX were € -724 compared with PG, and from a societal perspective, CPOX was unfavorable compared with the PG group by € -692. [Supplementary material, Table S3] Monte Carlo bootstrap simulations were performed using the propensity score matched group and the total group for cost-effectiveness analysis from a healthcare and societal perspective, and re-established our previous findings. [Supplementary material, Figures S1, S2, S3, S4]

Secondary outcomes in the cohort that contained all study patients were similar to the propensity score matched cohort. [Table 3] There were two different outcomes when compared with the results of the propensity score matched group. First, the incidence of major complications was 1.6% in the CPOX group vs. 3.6% in the PG group, p=0.0016, while this difference was not significant in main analysis (p=0.065). Length of stay showed a trend towards longer admissions in the CPOX cohort in complete case analysis, but this trend disappeared in the main analysis with propensity score matched cohorts.

DISCUSSION

The present study compared two perioperative care strategies for bariatric patients with no previous OSA diagnosis, and showed that postoperative CPOX without preoperative OSA-screening is safe and cost-effective compared with routine PG and CPAP treatment from a healthcare perspective. No difference in QoL was seen between groups, while costs were lower in de CPOX group, and the credibility interval showed that outcomes were robust (€-534, 95% CI: €-896 - € -137). In addition, secondary outcomes such as complications and unanticipated ICU admissions were similar between groups. Hence these data provide evidence that CPOX is a safe and cost-effective alternative in the perioperative management of bariatric patients who have no prior OSA diagnosis.

To our knowledge, this is the first study that compared postoperative outcomes in bariatric patients following routine OSA screening with no screening in the preoperative setting. Previous studies have mainly evaluated OSA in pre-selected patient groups or compared optimal care to low-intensity care, which makes surgical outcomes difficult to compare. For example, Shearer et al. have underlined that mandatory admission to an intensive care unit is unnecessary in bariatric patients with OSA, and that these patients can be safely managed at a general surgery ward with experience of bariatric surgery.(21) More recently, several studies investigated whether patients with mild or moderate OSA can safely undergo bariatric surgery without additional measures, when compared with patients with severe OSA with perioperative CPAP treatment.(22, 23)

Mostly, these studies did not find any consistent or significant differences in complications, but the intervention groups were not comparable to the control groups in disease-severity or a priori risk of complications. One study evaluated the effect of adding CPOX to standard care in their hospital; with preoperative OSA screening and consequent CPAP treatment, to standard care alone, and found significant reduction of cardiopulmonary complications.(24) It is important to note that the primary outcome was a composite of cardiopulmonary events that included prolonged hospital stay, which led to a very high event rate of 14.9% and 29.8% in the intervention and control group, and therefore cannot be compared with general bariatric complication rates.(25) In recent years, ERABS protocols are increasingly becoming standard care, leading to reduced administration of opioids and other sedative drugs and encouragement of early patient mobilization. Consequently, risks of developing cardiopulmonary complications are potentially reduced, although this has not yet been established specifically for patients with OSA.(26)

Studies on costs related to sleep breathing disorders such as OSA showed conflicting results. Mokhlesi et al. report a shorter hospital stay and reduced costs for OSA patients compared with patients with no OSA diagnosis.(27) This study was an analysis of a nationwide registry that selected sleep-breathing disordered patients based on ICD-coding, and did not specify methods used to identify or manage untreated or suspected OSA patients. Another study found that OSA was a predictive factor for laparoscopic gastric banding patients to be readmitted, which resulted in substantial increased costs.(28) Our data did not show an increased risk of readmission or difference in hospital stay in the CPOX patients compared with the PG patients.

Some authors advocate less invasive options for managing potentially undiagnosed OSA patients undergoing bariatric surgery with additional argument.(29) First, many patients who have undetected OSA before surgery, will only additionally benefit from CPAP treatment for several months, as weight loss is expected to reduced disease severity or induce complete remission within months after surgery. Second, CPAP treatment is not tolerated by all patients, or not sufficiently used to ensure clinical benefits, such as reduction of day-time sleepiness or reduction of cardiovascular effects of OSA.(30)

Although the present data show that CPOX is cost-effective in terms of health care costs, it is unclear whether this is also true from a societal perspective. PG patients had lower societal costs, in terms of unpaid loss of productivity, during the period between 3-12 months postoperatively. We initially hypothesized that if a difference in productivity would occur, this would be in the first postoperative period, when weight loss induced OSA remission would not yet have been

achieved during these months. However, productivity loss data showed high standard deviation within groups, large confidence intervals, low correlation between intervention and outcome given the timeframe, and the study was not powered to assess societal perspective of cost-effectiveness. Therefore, future studies are needed to further evaluate the societal perspective of these perioperative interventions.

Some limitations of this study should be acknowledged. First, due to the non-randomized design the groups were not comparable in complete count analysis for several baseline characteristics that are relevant in OSA prevalence. In the propensity score matching analysis we were unable to correct for neck-circumference, which is a well-known risk factor of OSA, due to incomplete data. This may have had an effect on comparability and pre-probability of OSA between the two groups. However, we believe that we have formed two comparable groups based on the other confounders in the propensity score matching. Second, all patients underwent bariatric surgery in high-volume centers which leads to low complication rates in general. Therefore, the low incidence of OSA-related complications (i.e. cardiopulmonary and neurovascular complications) additionally precludes us to make definitive statements on influence of perioperative management on these types of complications. Despite the large sample-size of our cohort, our study lacks statistical power to analyze these serious but rare complications, and can thus only be interpreted as hypothesis-generating. Third, cost-effectiveness analyses are depended on the type of data used for analyses. In this study, the analyses were performed using declaration data from hospital databases, which is less susceptible to human-errors than using clinical data directly gained from the trial. However, the pitfall of this type of data is that health care utilization should be billed properly in hospital databases and towards health care insurers. An example of missing data is visible in our outcomes of Table 2, when no expenses are presented for ICU admissions for the intervention group, even though one CPOX patient was admitted to the ICU after surgery (Table 3). The actual impact on costs would have been 0.75 cents per patient, which is rather minimal. Although a minor limitation, it is essential to be mentioned as these limitations should always be kept in mind when performing costing analyses.

Overall from a healthcare perspective, as per the budget impact analysis, we expect a potential healthcare cost saving of €5,767,200 per year in the Netherlands. As is common in cost-effectiveness analyses, purchase costs of CPOX equipment and one-time training of nurse staff is not included in the analysis, which could make the exact impact of this perioperative care strategy on the total costs less pronounced in real life.

With rising popularity of fast-track and day-care bariatric surgery, we underline that certain precautions are necessary to prevent severe OSA-induced complications, even though these might be rare.(31) In addition, with the rising obesity rates worldwide, an increase of general surgery patient that are also obese is very likely. This implicates that undiagnosed OSA and its related risks will become more frequent in the general surgery population, and that results of this study could potentially be extrapolated to other types of surgery that includes general anesthesia with breathing-depressing drugs. It is mandatory that future studies focus on the least invasive, safest and most cost-effective type of perioperative care of (bariatric) patients potentially at risk for OSA-related complications.

Conclusion

This nationwide cohort study shows that CPOX is a safe strategy in the perioperative management of bariatric patients with no prior OSA diagnosis. CPOX was similar in effectiveness, was not associated with a higher complication or readmission rates and has lower costs from a healthcare perspective compared with PG and CPAP therapy. Therefore, postoperative CPOX can be considered a cost-effective alternative for routine preoperative OSA screening in this bariatric population.

Conflict of interest

All authors declare that they have no conflict of interest

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Ethical Statement

This study was performed in accordance with the 1964 Helsinki declaration and its later amendments, and was approved by the medical ethical review board.

Consent Statement

Informed consent was obtained from all participants included in the study.

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SUPPLEMENTARY FILE

Table S1. Index of unit cost per CPAP and PG:

Costs CPAP		**Source**
Device	€146	De Vries et al.*, corrected into 2020 prices
CPAP chin straps	€24	Website Vivisol**
CPAP mask	€65	Website Vivisol estimation
Setting-up visit	€80	De Vries et al., corrected into 2020 prices
Check-up visits	€197	Estimation on average 2 check-up visits: 2 x €98.42, based on Dutch prices reported by Hakkaart et al.***, translated into 2020 prices
Total	**€512**	
Costs PG		
PG costs	€133	Correspondence to participating centers
Cost PG follow-up visit	€133	Correspondence to participating centers
Call consultation positive PG pre-operative	€98	Hakkaart et al.** translated into 2020 prices

Reference:

* de Vries GE, Hoekema A, Vermeulen KM, Claessen JQPJ, Jacobs W, van der Maten J, van der Hoeven JH, Stegenga B, Kerstjens HAM, Wijkstra PJ. Clinical- and Cost-Effectiveness of a Mandibular Advancement Device Versus Continuous Positive Airway Pressure in Moderate Obstructive Sleep Apnea. J Clin Sleep Med. 2019 Oct 15;15(10):1477-1485.

** Vivisol is marketleader in Home Respiratory Care in the Netherlands. Website: https://www.vivisol.nl

*** Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg In opdracht van Zorginstituut Nederland Geactualiseerde versie, (2015).12-64.

Table S2. Detailed cost information on total number of patients (n=1390)

		CPOX (n=699)	PG (n=691)		
QALY		Mean EQ5D score	Mean EQ5D score	Difference	95% CI
Pre-operative		0.77	0.76	0.002	
1 month		0.86	0.86	0.001	
3 month		0.88	0.87	0.004	
6 month		0.88	0.88	-0.009	
12 month		0.89	0.89	0.002	
Total 1 year follow-up		**0.873 (SD: 0.13)**	**0.874 (SD: 0.14)**	**-0.001**	**(-0.013 - 0.009)**
	Unit cost	Mean cost	Mean cost	Difference	95% CI
Trial reported preoperative cost					
Polygraphy	133	0	133	*-133*	
Polygraphy follow-up consult	98	0	74	*-74*	
CPAP treatment	512	0	251	*-251*	
Trial reported follow-up costs					
no. PG during follow-up	133	0	20	*-20*	
Follow-up healthcare costs in operation hospital					
Consultations	98	493	369	*124*	
Online consultations	98	60	50	*9*	
Day Treatment	299	16	19	*-2*	
Emergency visits	280	59	67	*-8*	
ICU	2179	0	196	*-196*	
Ward days	515	1459	1514	*-54*	

Table S2. Detailed cost information on total number of patients (n=1390) *(continued)*

		CPOX (n=699)	PG (n=691)		
Self-reported costs at other healthcare providers					
General practitioner	36	116	112	*3*	
Dietitian	32	66	79	*-13*	
Company Doctor	71	54	44	*10*	
Home care	NA*	251	256	*-5*	
Emergency visits	280	96	84	*13*	
Ambulance	557	50	43	*7*	
Consultations	98	67	69	*-2*	
Inpatient Days	515	306	300	*6*	
Total cost healthcare perspective		3094	3680	-586	(€-933 - €-242)
Unpaid productivity					
Unpaid productivity losses month 3	16	532	659	*-127*	
Unpaid productivity losses month 12	16	1869	1402	*467*	
Paid productivity losses month 3	41	1210	1127	*83*	
Paid productivity losses month 12	41	1546	1762	*-216*	
Total productivity losses		**5157**	**4950**	***207***	***(€-600 - €927)***
Total cost societal perspective		**8251**	**8630**	***-379***	***(€-1,318 - €450)***

**Home care consisted of a mix of domestic help (€108 per week), home care (€395 per week) and personal care at home (€270 per week). Sources for unit cost: table S1 (for CPAP and PG) and Kostenhandleiding (Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg In opdracht van Zorginstituut Nederland Geactualiseerde versie, (2015).12-64)*

Cost-effectiveness and safety of pulse oximetry as perioperative care in bariatric patients

Table S3. Sensitivity analyses

Summary results	**Incremental cost**	**95% CI cost**	**Incremental QoL (QALY)**	**95% CI QoL**
Base case, propensity score matched (n=1,090)				
Healthcare perspective	€ -534	(€-896 - €-137)	-0.007	(-0.019 - 0.006)
Societal perspective	€ 134	(€-877 - €1,063)	-0.007	(-0.019 - 0.006)
All subjects, no correction (n=1,390)				
Healthcare perspective	€ -586	(€-933 - €-242)	-0.001	(-0.013 - 0.009)
Societal perspective	€ -379	(€-1,318 - €450)	-0.001	(-0.013 - 0.009)
Complete cases (n=709)				
Healthcare perspective	€ -724	-	-0.010	-
Societal perspective	€ -692	-	-0.010	-

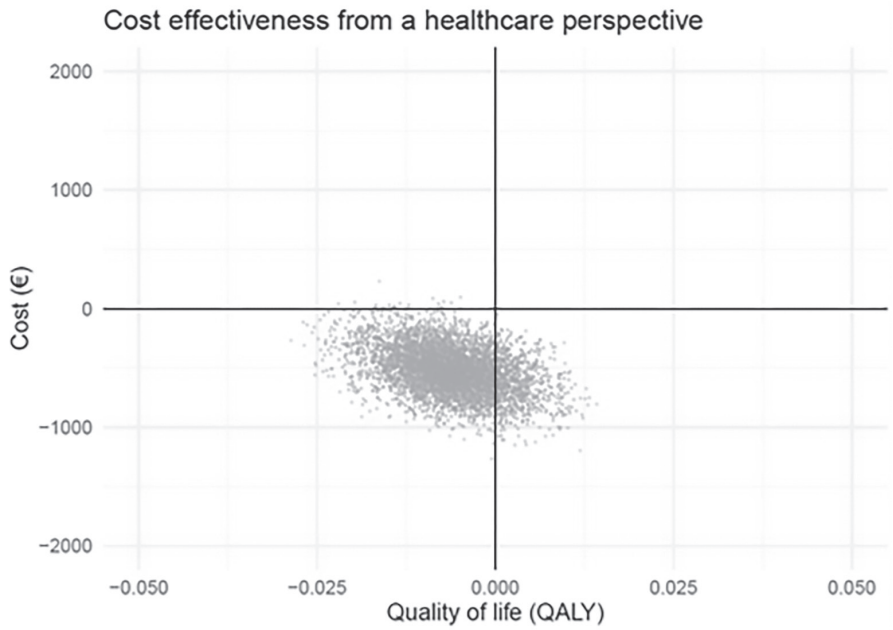


Figure S1: Bootstrap results of 5,000 resamples plotted on the cost effectiveness plane, from a healthcare perspective, based on propensity score matched cohort.

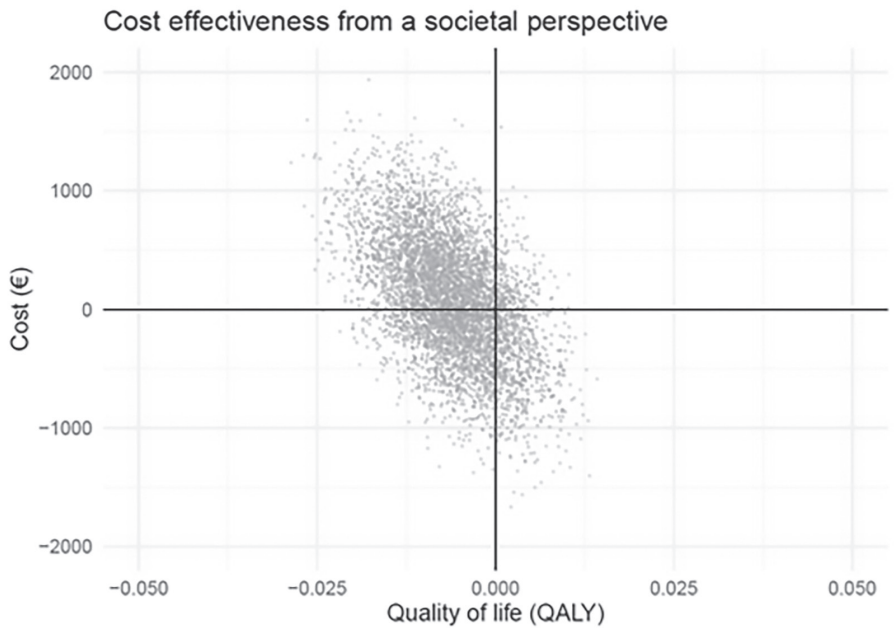


Figure S2: Bootstrap results of 5,000 resamples plotted on the cost effectiveness plane, from a societal perspective, based on propensity score matched cohort.

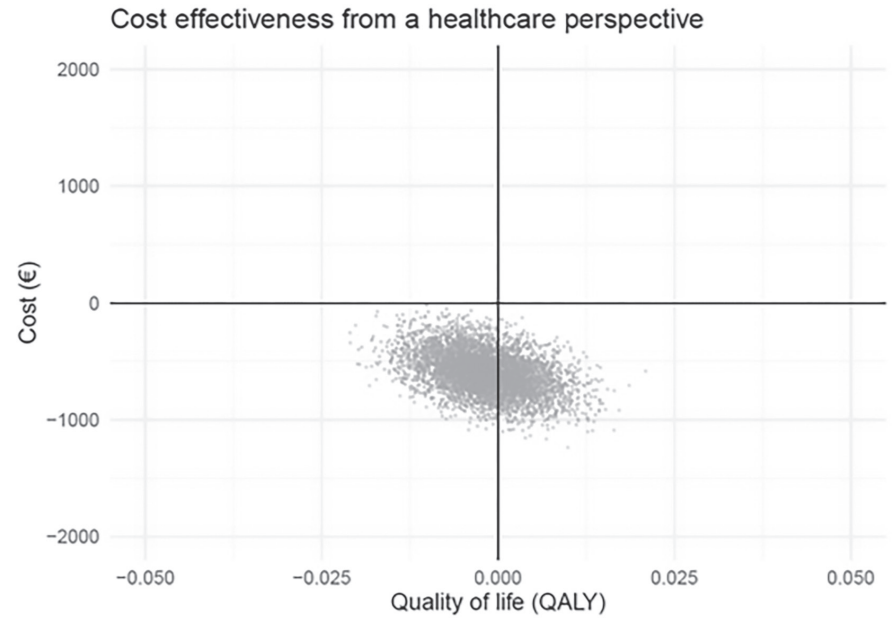


Figure S3: Bootstrap results of 5,000 resamples plotted on the cost effectiveness plane, from a healthcare perspective, analysis of all patients (N=1390).

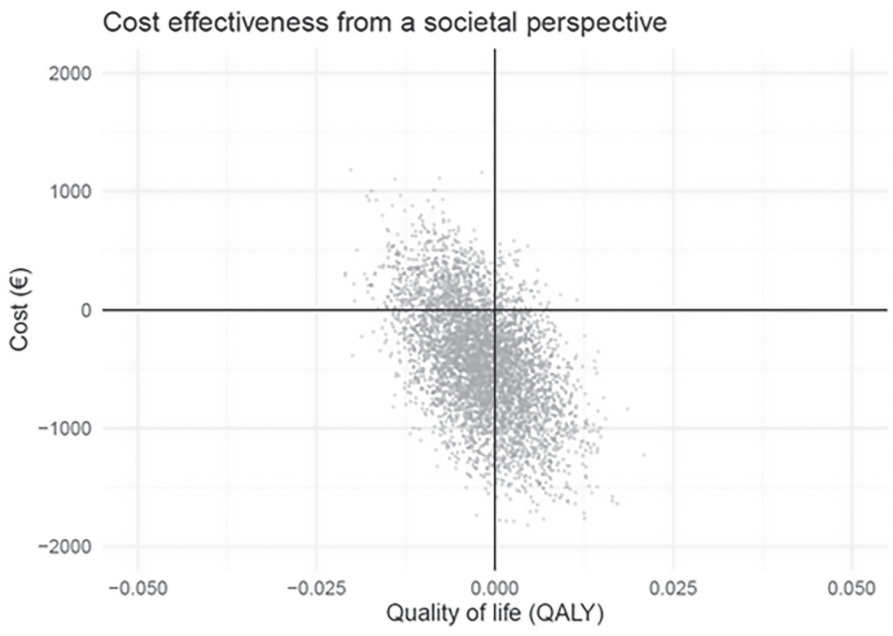
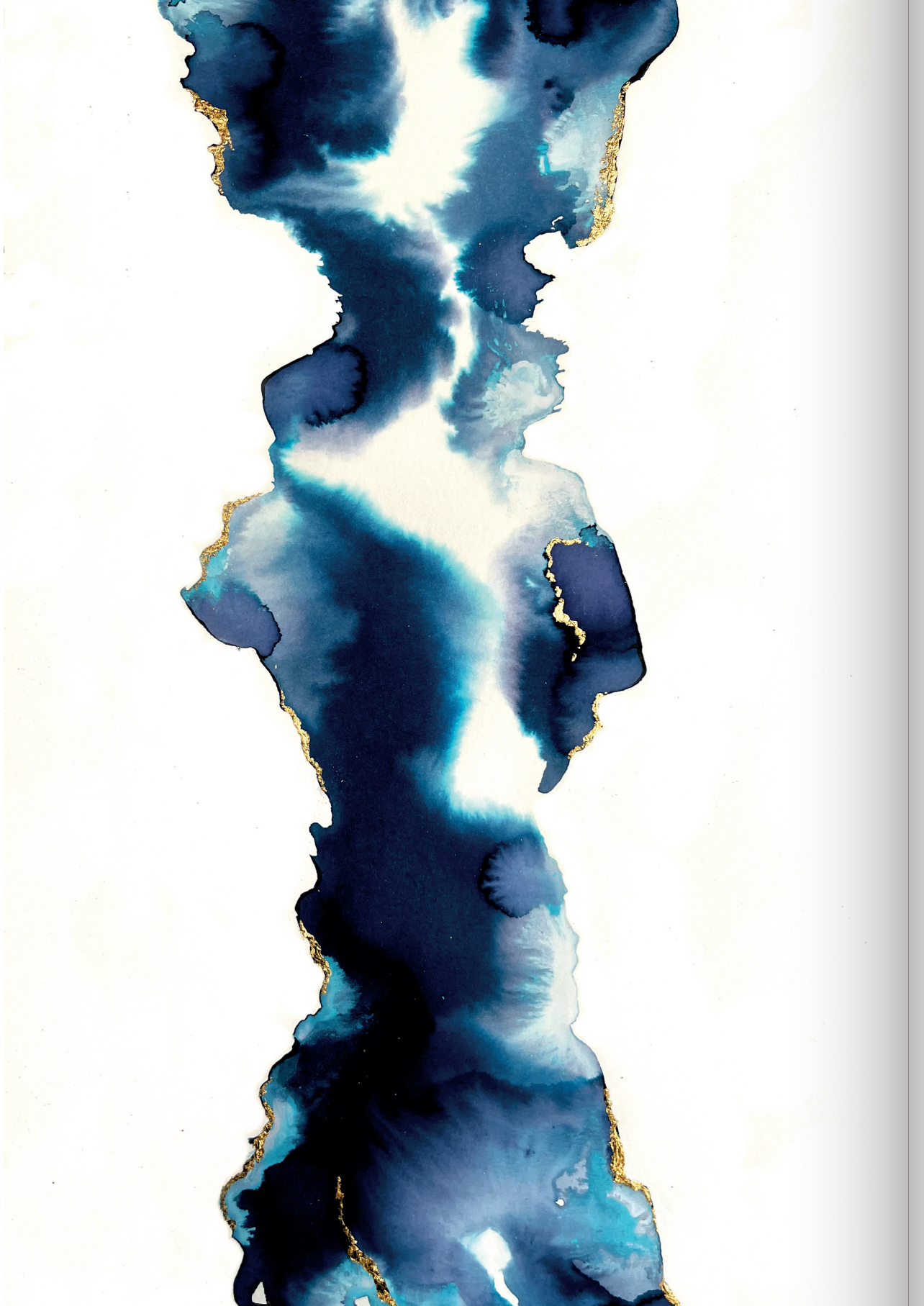


Figure S4: Bootstrap results of 5,000 resamples plotted on the cost effectiveness plane, from a societal perspective, analysis of all patients (n=1390).



PART B

CARDIOVASCULAR DISEASES AND RISK FACTORS IN BARIATRIC PATIENTS

CHAPTER 8

Preoperative cardiac screening using NT-proBNP in obese patients 50 year and older undergoing bariatric surgery: a study of 310 consecutive patients

Van Veldhuisen SL, van Woerden G, Hemels MEW, America YGCJ, de Boer RA, Rienstra M, van Veldhuisen DJ, Hazebroek EJ

Surgery for Obesity and Related Diseases, 2021.

ABSTRACT

Introduction
Obesity is associated with cardiovascular (CV) risk factors and diseases. Because bariatric surgery is increasingly performed in relatively elderly patients, a risk for per- and postoperative CV complications exists.

Objectives
We aimed to assess the value of plasma N-terminal-pro hormone BNP (NT-proBNP) as a CV screening tool.

Setting
High-volume bariatric center

Methods
Between June 2019 and January 2020, all consecutive bariatric patients aged ≥50 years underwent pre-operative NT-proBNP assessment in this cohort study, to screen for CV disease. Patients with elevated NT-proBNP (≥125 pg/ml) were referred for further cardiac evaluation, including electrocardiography and echocardiography.

Results
We included 310 consecutive patients (median age 56 years, 79% female, body mass index 43±6.5 kg/m^2). A history of CV disease was present in 21% of patients, mainly atrial fibrillation (7%) and coronary artery disease (10%). 72 patients (23%) had elevated NT-proBNP levels, and 67 of them underwent further cardiac work-up. Of these 67 patients, electrocardiography showed atrial fibrillation in 7 patients (10%). On echocardiography, three patients had left ventricular ejection fraction (LVEF) <40%, nine patients had LVEF 40-49%, and 13 patients had LVEF ≥50% with structural and/or functional remodeling. In two patients, elevated NT-proBNP prompted work-up leading to a diagnosis of coronary artery disease, and consequent percutaneous coronary intervention in one patient.

Conclusion
Elevated NT-proBNP levels are present in 23% of patients ≥50 years undergoing bariatric surgery. In 37% of them, there was echocardiographic evidence for structural and/or functional remodeling. Further studies are needed to assess if these preliminary results warrant routine application of NT-proBNP to identify patients at risk for CV complications after bariatric surgery.

INTRODUCTION

Obesity is associated with many cardiovascular (CV) risk factors such as hypertension, type 2 diabetes (T2D), dyslipidemia, and systemic inflammation [1-4]. The long-term consequences of these risk factors are increasingly recognized, and CV diseases such as heart failure, atrial fibrillation, coronary artery disease, but also valvular heart disease and stroke are common, particularly in the elderly. Obesity has become one of the largest healthcare problems worldwide. The prevalence of obesity (i.e. body mass index [BMI] ≥ 30 kg/m^2) is currently around 40%, and is still increasing [5]. As a result, obesity is increasingly recognized as a serious, and potentially treatable risk factor for CV disease [1,2].

Treatment of obesity is difficult, and currently, bariatric surgery is the only treatment option that renders significant and durable weight loss in obese patients with relatively low peri- and post-operative complications rates [6-8]. Anastomotic leakage and bleeding are the most common reported complications early after surgery, but vascular or cardiopulmonary problems can also occur [9]. The latter were reported to be present in up to 1.3% of all bariatric patients [9], although a larger study showed that during 90-day follow-up the percentage of CV deaths was much higher compared to those caused by leakage or bowel obstruction: 10/36 deaths were "heart related" (28%), and strongly related to CV risk factors and increasing age [8]. Although the majority of patients undergoing bariatric surgery are relatively young, a significant proportion of patients is older than 50 years of age, and these patients have a risk for CV diseases [10]. Given the significant number of patients with CV disease who will undergo bariatric surgery, screening for subclinical or unrecognized CV disease in patients ≥50 years may be beneficial.

Despite several review articles that have described possible diagnostic procedures in patients who undergo bariatric surgery, current bariatric guidelines do not provide details regarding preoperative cardiac work-up [6,11,12].

In the present study, we therefore aimed to determine the prevalence and incidence of CV diseases in patients ≥50 years who were undergoing bariatric surgery. Because cardiac examinations are not routinely performed in patients referred for bariatric surgery, we investigated whether a simple marker could provide useful information. Therefore, we measured N-terminal pro Brain Natriuretic Peptide (NT-proBNP) levels in consecutive patients ≥50 years old who were scheduled to undergo bariatric surgery. This biomarker is one the most sensitive markers to detect early CV disease [13], and has proven to be of important diagnostic value in patient groups undergoing non-cardiac (vascular) surgery [14, 15].

METHODS

All patients in the present study were referred to the Department of Bariatric Surgery, Rijnstate Hospital; Arnhem; the Netherlands, between June 2019 and January 2020, which is a high-volume bariatric center performing around 1300 bariatric procedures per year. For this prospective cohort study, only patients who were ≥50 years old, and who fulfilled the IFSO criteria (BMI ≥ 35 kg/m^2 with an obesity related comorbidity or BMI ≥40 kg/m^2), were considered eligible.

The cardiac screening protocol was approved by the Local Ethics Committee, and all patients gave informed consent. The present study was in concordance with the principles outlined in the Declaration of Helsinki. In patients who were deemed eligible, plasma NT-proBNP samples were collected and NT-proBNP concentrations in blood samples were measured by the Atellica® IM PBNP Essay, using the Atellica IM Analyzer (Siemens Healthineers, Erlangen, Germany). If the NT-proBNP value was 125 pg/ml or higher, patients were referred to the Department of Cardiology, Rijnstate Hospital for further cardiac work-up. This cut-off point is advocated by the European Society of Cardiology (ESC) for excluding heart failure. Although several confounders for NT-proBNP levels are known, including age, fat mass, and sex, this cut-off point has been shown to provide a reasonable performance [16,17].

If patients were referred to the cardiologist, a 12-lead standard electrocardiogram (ECG) was performed, as well as an echocardiogram. Transthoracic 2- and 3-Dimensional echocardiography was performed using Epiq Philips (EPIQ 7C Hardware en software version 5.02). HeartModel software was used to measure left ventricular (LV) and left atrial global volume at end-diastole and at end-systole, and to calculate the left ventricular ejection fraction (LVEF). All measurements were assessed according to the current recommendations for cardiac chamber quantification and assessment of diastolic function [18], and included LV systolic function (in particular LVEF), tricuspid annular plane systolic excursion for right ventricular function, and left ventricular diastolic function (E, A, E/A ratio, e′, and E/e′ ratio), valvular stenosis and/or regurgitation, and the peak pressure gradient across the tricuspid valve. Left atrial enlargement was defined as ≥34 ml/m^2, LV hypertrophy as LV mass index >95g/m^2 for women and >115g/m^2 for men, and diastolic dysfunction as mean septal and lateral ′e <9cm/s and/or E/e′ >13, all according to the current ESC criteria [19].

Heart failure was documented if patients had LVEF <40% (″heart failure with reduced LVEF, or systolic heart failure″), or LVEF 40-49% (″heart failure with mid-range EF″), or if they fulfilled the criteria of heart failure with preserved LVEF, i.e. ≥50%, and additional echocardiographic evidence for relevant structural heart

disease, including LV hypertrophy and/or left atrial enlargement and/or diastolic dysfunction, as described earlier in this section. [19].

Besides electrocardiography and echocardiography, additional diagnostic tests or interventions were performed when deemed necessary. Adverse events during the first 30 days after surgery were documented. We had particular interest in cardiovascular and pulmonary adverse events, including severe arrhythmias, acute heart failure, acute coronary syndrome, stroke or transient ischemic attack, pneumonia, deep vein thrombosis or pulmonary embolism, acute renal failure and reintubation. Severity of adverse events were scored according to the Clavien Dindo Classification, minor and major complications were respectively defined as class 1-2 and class ≥3A [20].

Normally and non-normally distributed data were described using means with standard deviations (SD) and medians with interquartile ranges (IQR). Continuous data were analyzed using independent t-tests, Mann Whitney U test or a Fishers' exact test, depending on the distribution. A p value of < 0.05 was considered as statistically significant. Statistical analyses were performed by using IBM SPSS Statistics, version 25.0 for Windows (SPSS. Chicago, IL).

RESULTS

Patient characteristics

Between June 2019 and January 2020, NT-proBNP levels were assessed in 310 consecutive patients referred for bariatric surgery (Figure 1). The median age of patients was 56 years, 72% were female, and mean BMI was 42.6 kg/m^2. Patients had a high prevalence of CV risk factors such as hypertension (58%), dyslipidemia (35%) and T2D (28%) (Table 1).

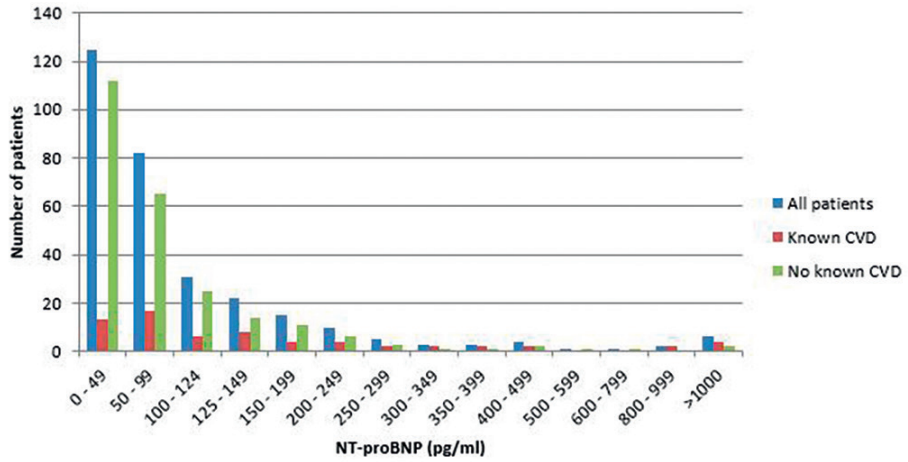


Figure 1: Distribution of NT-proBNP levels
NT-proBNP N-terminal-pro hormone brain natriuretic peptide, *CVD* cardiovascular disease

Table 1. Baseline characteristics and postoperative outcomes

	Total (n=310)	Elevated NT-proBNP (n=72)	Normal NT-proBNP (n=238)	*p*-value
Age (median, IQR) *	55,9 (53-61)	57 (54-62)	56 (53-60)	0.406
Gender, female (n,%)	224 (72.3)	57 (79.2)	167 (70.2)	0.088
BMI (mean, SD)	42,6 ±6.5	43,7 ±7.8	42,1 ±6.0	0.445
Abd. Circumference (mean, SD)	128 ±13	127 ±15	128 ±13	0.171
Smoking (n,%)				0.828
Current smoking	21 (6.8)	6 (8.3)	15 (6.3)	
History of smoking	151 (48.7)	34 (47.2)	117 (49.2)	
Medical history (n,%)				
Hypertension	179 (57.7)	47 (65.3)	132 (55.5)	0.173
Hypercholesterolemia	107 (34.5)	26 (36.1)	81 (34)	0.425
Diabetes	88 (28.4)	18 (25)	70 (29.4)	0.312
Obstructive Sleep Apnea	84 (27.1)	18 (25)	66 (27.7)	0.272
Chronic Kidney Disease	13 (4.2)	8 (11.1)	5 (2.1)	0.003
Chronic Obstructive Pulmonary Disease	19 (6.1)	7 (9.7)	12 (5)	0.163
History of cardiovascular disease(n,%)*	64 (20.6)	30 (41.7)	34 (14.3)	<0.001
Atrial Fibrillation	27 (8.7)	17 (23.6)	10 (4.2)	<0.001
History of AF	20 (6.4)	10 (13.9)	10 (4.2)	
Current AF	7 (2.3)	7 (9.7)	0	
Heart Failure (n,%)	6 (1.9)	5 (6.9)	1 (0.4)	0.003
Coronary artery diseases	31 (10)	9 (12.5)	22 (9.2)	0.126

Table 1. Baseline characteristics and postoperative outcomes (continued)

	Total (n=310)	Elevated NT-proBNP (n=72)	Normal NT-proBNP (n=238)	*p*-value
Angina Pectoris / no significant abnormalities on CAG	13 (4.2)	5 (6.9)	8 (3.4)	
MI / PCI / CABG	18 (5.8)	4 (5.6)	14 (5.9)	
Valvular disease	6 (1.9)	3 (4.2)	3 (1.3)	0.140
Other cardiovascular disease	5 (1.6)	2 (2.8)	3 1.3)	0.330
Medications				
ACEI or ARB	144 (46.5)	42 (58.3)	102 (42.9)	0.023
Beta-blocker	81 (26.1)	30 (41.7)	51 (21.4)	0.001
Diuretics	102 (32.9)	31 (43.1)	71 (29.8)	0.045
Lipid lowering agents	109 (35.2)	27 (37.5)	82 (34.5)	0.673
Oral anticoagulants	24 (7.7)	13 (18.1)	11 (4.6)	0.001
Platelet aggregation inhibitors	48 (15.5)	9 (12.5)	39 (16.4)	0.464
Insulin	33 (10.6)	7 (9.7)	26 (10.9)	0.772
GLP-1 agonist	11 (3.5)	3 (4.2)	8 (3.4)	0.180
Oral antidiabetic drugs	73 (23.5)	13 (18.1)	60 (25.2)	0.267
Procedure	266 (85.8)	57 (79.2)	209 (87.8)	0.646
LRYGB	223 (83.8)	46 (80.7)	177 (84.7)	
LSG	26 (9.8)	6 (10.5)	20 (9.6)	
Conversion LAGB to LRYGB	14 (5.3)	4 (7.0)	10 (4.7)	
Conversion LAGB to LSG	2 (0.8)	0	2 (1.0)	
Conversion LSG to SADI	1 (0.4)	1 (1.8)	0	

* Patients may have more than one cardiovascular disease
ACEI angiotensin-converting-enzyme inhibitors, *AF* atrial fibrillation, *ARB* angiotensin II receptor blockers, *BMI* body mass index, *CABG* coronary artery bypass grafting, *CAG* coronary angiography, *GLP-1 agonist* glucagon-like peptide-1 receptor agonists, *IQR* Interquartile range, *LAGB* laparoscopic adjustable gastric band, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *RYGB* Roux-en-Y gastric bypass, *SADI* single anastomosis duodenal ileal bypass, *SD* standard deviation , *SG* sleeve gastrectomy

Elevated NT-proBNP levels were observed in 72 patients (23%), the distribution of NT-proBNP levels is shown in Figure 1. A history of CV disease was present in 64 of the 310 patients (21%) (Table 1). Patients with elevated NT-proBNP levels more often had a history of CV disease (42% vs 14%) and also used more CV drugs. There were 31 patients with a history of coronary artery disease, but in general NT-proBNP levels were not increased in these patients. A history of atrial fibrillation was present in 22 patients, and 17 of them had elevated NT-proBNP levels. A history of heart failure was present in only six patients and five of them had elevated NT-proBNP levels. Use of CV drugs, in particular angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers and diuretics was more common in patients with elevated NT-proBNP compared to

patients with normal NT-proBNP values (all p<0.05) . Of the 72 patients who had elevated NT-proBNP levels, 67 patients were referred for further cardiac work-up (Figure 2). Two patients dropped out of the study (one patient with a BMI of 83 kg/m^2 who was not considered eligible for surgery, and one was lost to follow-up). In three other patients in whom NT-proBNP was marginally increased (between 125 and 150 pg/ml) further cardiac work-up was not performed at the discretion of the treating physician.

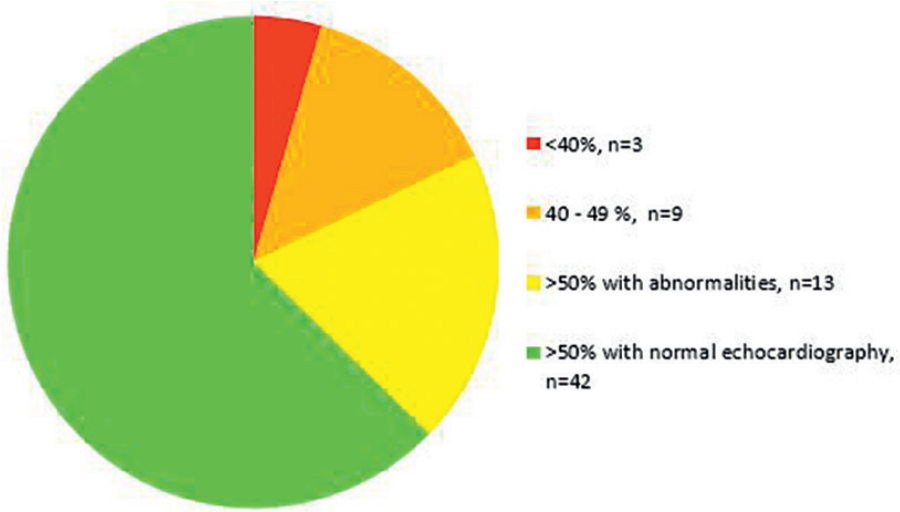


Figure 2: Distribution of LVEF in patients who underwent preoperative echocardiography
LVEF left ventricular ejection fraction

Findings during cardiac work-up

Of the 67 patients who were referred for further cardiac work-up, current atrial fibrillation/flutter was observed in seven patients on their ECG, which was in line with their medical history. In addition, eight patients had a history of these arrhythmias, but were in sinus rhythm on ECG.

On echocardiography, three of the 67 patients had systolic dysfunction, i.e. LVEF <40%, and nine patients had a LVEF of 40-49%, i.e. mild systolic dysfunction, whereas the majority of patients had LVEF ≥50%. 25 of 67 patients (37%) had evidence of structural and/or functional abnormalities on echocardiography. Only four of these 25 patients had a previous medical history of "heart failure".

Of the 55 patients with LVEF ≥ 50%, 13 had evidence for structural heart disease on echocardiography: left atrial enlargement (n=9), left ventricular hypertrophy (n=4), and/or evidence of diastolic dysfunction (n=3; patients may have more than

one criterion). Using our work-up, this means that the observed increased NT-proBNP levels in concert with the echo data, resulted in newly found biochemical and echocardiographic evidence for heart failure with preserved ejection fraction (HFPEF) [19] in 13 of these 55 patients (Figure 3).

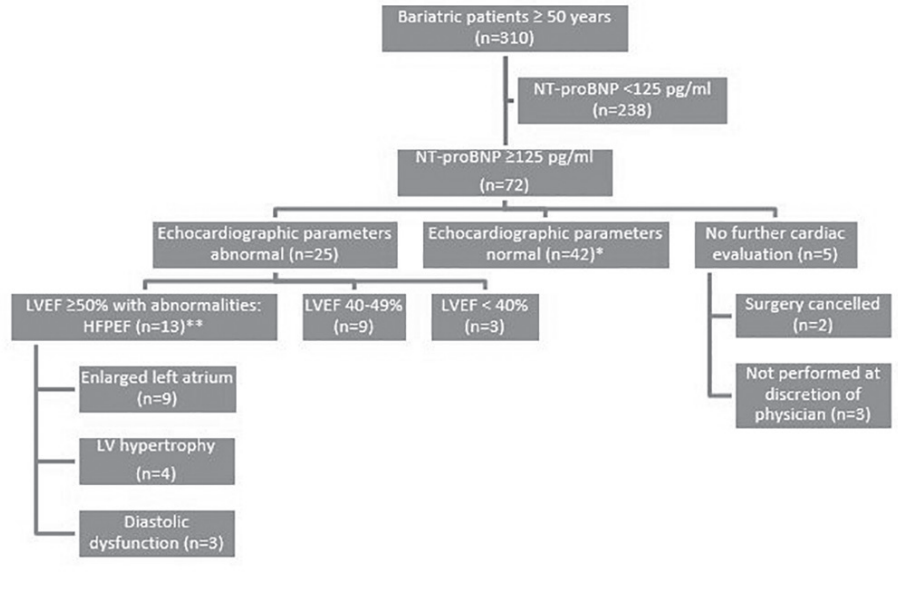


Figure 3: Flowchart and main outcomes of cardiac preoperative evaluation
* "Normal'was defined as'no significant abnormalities found on echocardiogram' following current ESC guidelines
** Patients may have more than one criterion
NT-proBNP N-terminal-pro hormone brain natriuretic peptide, LVEF left ventricular ejection fraction, LV left ventricle

In six of the 67 patients, additional diagnostic tests were done. One patient with a history of coronary artery bypass surgery had recurrent cardiac events of chest pain and myocardial ischemia, and underwent percutaneous coronary intervention. In two additional patients, coronary angiography was performed, which showed no coronary lesions, but both were found to have heart failure. Three patients had abnormalities on ECG, which led to 24-hour Holter ECG in two of them, and a cardiac MRI in the other, none of these three patients was diagnosed with a new CV disease. All six patients were subsequently accepted for surgery.

As a result of cardiac work-up, cardiovascular drug regimens were adjusted in nine patients. in seven patients, new drugs were prescribed (diuretics n=2, statins n=2, beta blocker n=1, ACE-inhibitor n=1, calcium channel blocker n=1). In the

remaining two patients, adjustment of beta blocker dosage was instructed for one, and a diuretic was ceased in another. In five other patients, the treating cardiologist ordered perioperative instructions on cardiovascular drugs, fluid balance or oral anticoagulants.

Surgical outcome

Of the 310 patients, 266 patients underwent bariatric surgery. In patients with an increased NT-proBNP, 57 of the 72 patients were operated, whereas 209 of the 238 with normal NT-proBNP were operated. Of the 44 non-operated patients, surgery was either cancelled (n=12) or postponed (n=32). Reasons for postponement of surgery were: need for further lifestyle changes or psychological management (n=10), additional cardiac work-up (n=2), and the covid-19 pandemic (n=20). During 30-day follow-up, no cardiac adverse events occurred. Total adverse events were found in four patients with elevated NT-proBNP levels, and in 15 with normal NT-proBNP levels, 7.0% and 7.2%, respectively, and none had a fatal outcome. Major adverse events occurred only in the group with normal NT-proBNP levels (5 of 209 patients; 2.4%), and were all surgical complications: stenosis of jejunojejunostomy (n=2), postoperative hemorrhage (n=1), anastomotic leakage (n=1), internal herniation (n=1).

DISCUSSION

The main purpose of this study was to determine the prevalence and incidence of subclinical or unrecognized CV disease in patients ≥50 years scheduled for bariatric surgery using plasma NT-proBNP. NT-proBNP was increased in 72 (23%) of the 310 patients. Of the 67 patients who underwent thorough cardiac evaluation, echocardiographic evidence of structural and/or functional remodeling was present in 25 patients (37%), and only four of these 25 patients had a medical history of heart failure. This means that this non-invasive, simple and cheap diagnostic tool could be used to detect new of structural and/or functional remodeling in a high-risk patient population that is evaluated for bariatric surgery.

Natriuretic peptides such as NT-proBNP and brain natriuretic peptide (BNP) are most often used for monitoring patients with established heart failure, and both have important clinical and prognostic value for long-term outcome [21]. In addition, these biomarkers are powerful tools to predict new onset heart failure [22]. Interestingly, in addition to heart failure and atrial fibrillation, NT-proBNP levels also strongly predict other CV events, such as myocardial infarction and stroke [23]. Therefore, NT-proBNP could be a reliable screening tool for CV disease. However, in our results we mainly observed elevated plasma NT-proBNP in patients with heart failure or atrial fibrillation, and to a lesser extend in patients

with coronary artery disease. Therefore, the use of NT-proBNP as a screening tool for CV diseases may be best used for new-onset heart failure.

NT-proBNP and BNP have been evaluated for their prognostic value as cardiac screening tools to predict the development of (major) cardiac events [14,24]. In our cohort, no CV events occurred in the postoperative phase, though unlikely, this might have been influenced by alterations in CV drugs during cardiac work-up. In general, there is limited data available on the incidence of cardiac complications following bariatric surgery, but in general the incidence is low, ranging between 0.1-1.7% [25,26]. So far, no studies have examined the association between pre-operative cardiac screening and outcome after bariatric surgery. Two meta-analyses concluded that single preoperative measurements of either NT-proBNP or BNP are both good predictors for cardiovascular complications [14,24]. These meta-analyses examined patients that were undergoing non-cardiac surgery, and several studies did evaluate patients undergoing (major) abdominal procedures, but not specifically patients undergoing bariatric surgery. Procedures that were examined in these meta-analyses were mainly classified as high risk for development of cardiac complications, while bariatric surgery is classified as a procedure with intermediate risk [14]. Elevated BNP or NT-proBNP levels were associated with an increased risk for the development of cardiovascular complications (odds ratio of 19.3 [95% CI 8.5-43.7]) [24], and an area under the curve (AUC) of the relative operating characteristic (ROC) for the predictive value of elevated BNP or NT-proBNP levels was 0.70 (95% CI 0.66 - 0.74) [14]. In a more recent prospective study including more procedures with an intermediate risk of cardiac complications, the AUC was 0.88 (95% CI 0.82-0.93) for preoperative NT-proBNP measurements [27]. Outcomes consistently show that heart failure is an independent predictor for major adverse cardiac events (MACE) [28]. As an alternative for a single measurement screening tool for major cardiac adverse events, several risk assessment tools have been tested in non-cardiac surgery patients, such as the 6-item Revised Cardiac Risk Index that indicates whether preoperative cardiac assessment should be performed [29]. Two newer prediction models are available as online tools for risk assessment of MACE and integrate 23 and 30 items [30,31]. However, none of these prediction tools are validated in bariatric study patients and might not be sensitive enough. Given the lack of a validated screening tool for CV disease and high prevalence of occult LV dysfunction (and heart failure) in our cohort, it is somewhat surprising that in the recently reported Clinical Practice Guidelines for patients undergoing Bariatric Surgery, standard preoperative evaluation of (high risk) patients in order to detect occult CV disease -in selected patients- is also not discussed [6].

With current acceptably low morbidity and mortality rates in the early phase after bariatric surgery, and the evident long-term improvements in weight

loss and CV disease, it is likely that the number of patients eligible for bariatric surgery will further increase. Moreover, it is conceivable that obese patients with specific CV diseases such as heart failure and atrial fibrillation, will be considered candidates for bariatric or metabolic surgery, not just to induce weight loss, but specifically to treat these comorbidities [6]. Especially for these patients at high-risk of developing CV complications, accurate pre-operative CV screening is important. Therefore, NT-proBNP assessment could prove to be the first choice as a screening tool, since it is cheap, easy and non-invasive.

There are some limitations that merit emphasis. First, this is a single center study with a relatively small sample size. Therefore, the results may not provide conclusive evidence whether cardiac screening is beneficial, in terms of reducing CV morbidity and mortality. Second, patients with normal NT-proBNP levels were not referred for ECG or echocardiography, therefore the presence of CV disease is unknown in these patients. However, it has been established that a normal BNP or NT-proBNP makes it very unlikely that a patient has CV disease, especially heart failure [19]. It should also be noted that NT-proBNP is a stronger predictor for heart failure than coronary artery disease and stroke, albeit we did identify two patients in our cohort that required intervention for coronary artery disease while using NT-proBNP [13,23]. Third, the aim of our study was to examine the value of NT-proBNP as a screening tool for CV disease, and was consequently not powered to examine a potential association with post-operative cardiovascular outcome. Fourth, NT-proBNP has an inverse relation with BMI [32], which means that patients with potential CV disease could have false negative outcome of cardiac screening with NT-proBNP. This implies that the reported 23% of patients with elevated NT-proBNP in our study is probably an underestimation of the actual number of patients with CV disease. Fifth, use of NT-proBNP as a single screening tool might be less predictive for CV disease than a prediction model that combines NT-proBNP with levels of additional laboratory measurements (such as troponins or highly sensitive C-reactive protein) and presence of comorbidities such as diabetes. However, we aimed to investigate NT-proBNP a simple and stand-alone diagnostic tool, and we thus did not add other parameters to the decision whether or not patients should be referred for cardiac work-up. Last, it is likely that our cohort of patients is slightly different than the general obese population. General practitioners may be reluctant to refer a patient for bariatric surgery if they have CV disease such as congestive heart failure or recent myocardial infarction, due to a higher risk of fatal complications following bariatric surgery [33].

Conclusion

Elevated levels of NT-proBNP levels are present in almost one fourth of obese patients aged ≥ 50 years undergoing bariatric surgery. In more than one third

of them, there was echocardiographic evidence for LV structural and functional remodeling. Further studies are needed to assess if these preliminary results warrant routine application of NT-proBNP to identify patients at risk for CV complications after bariatric surgery.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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CHAPTER 9

Bariatric surgery and cardiovascular disease: a systematic review and meta-analysis

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ABSTRACT

Aims

Obesity is a global health problem, associated with significant morbidity and mortality, often due to cardiovascular (CV) diseases. While bariatric surgery is increasingly performed in patients with obesity and reduces CV risk factors, its effect on CV disease is not established. We conducted a systematic review and meta-analysis to evaluate the effect of bariatric surgery on CV outcomes, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.

Methods and Results

PubMed and Embase were searched for literature until August 2021 which compared bariatric surgery patients to non-surgical controls. Outcomes of interest were all-cause and CV mortality, atrial fibrillation (AF), heart failure (HF), myocardial infarction, and stroke. We included 39 studies, all prospective or retrospective cohort studies, but randomized outcome trials were not available. Bariatric surgery was associated with a beneficial effect on all-cause mortality (pooled hazard ratio [HR] of 0.55; 95% confidence interval [CI] 0.49-0.62, p<0.001 vs. controls), and CV mortality (HR 0.59, 95% CI 0.47-0.73, p<0.001). In addition, bariatric surgery was also associated with a reduced incidence of HF (HR 0.50, 95% CI 0.38-0.66, p<0.001), myocardial infarction (HR 0.58, 95% CI 0.43-0.76, p<0.001), and stroke (HR 0.64, 95% CI 0.53-0.77,p<0.001), while its association with AF was not statistically significant (HR 0.82, 95% CI 0.64-1.06, p=0.12).

Conclusion

The present systematic review and meta-analysis suggests that bariatric surgery is associated with reduced all-cause and CV mortality, and lowered incidence of several CV diseases in patients with obesity. Bariatric surgery should therefore be considered in these patients.

INTRODUCTION

Obesity is rapidly becoming one of the biggest healthcare problems in the Western World, and is associated with significant morbidity and mortality.(1-4) In 2016, obesity was associated with 4 million deaths each year.(5) In the United States, the prevalence of obesity (defined as body mass index [BMI] ≥ 30 kg/m2) was 40% in adults in 2015-2016(6), and this will rise to around 50% in 2030.(7)

Obesity is associated with increased adipose tissue, also referred to as adiposopathy(8), and through several mechanisms this may be pathological to the CV system (figure 1). First, CV disease can be the result of the systemic effects of adipose tissue, due to the development of risk factors. Second, adipose tissue may also directly or locally act by epicardial and perivascular effects into the myocardium and blood vessels. (8, 9) And third, the accumulation of adipose tissue may cause (organ) compression(1), leading to hypertension and renal dysfunction(10), and obstructive sleep apnea.(11)

Of the CV risk factors associated with obesity, hypertension is the most common, followed by diabetes. Their prevalences increase with the severity of obesity and is generally present in 30-40% of patients.(12)Dyslipidaemia and increased inflammation are also common in obesity (around 20-40%).

CV diseases associated with obesity are atrial fibrillation (AF), heart failure (HF), coronary artery disease / myocardial infarction, and stroke. The hazard ratio to develop these CV diseases is at least 1.5-2.0, but this markedly increases to >6.0 in severe obesity, defined as BMI ≥40 kg/m2.(13-15) Obesity is also a well-known risk factor for stroke,(16-18) and has also been associated with increased incidence of aortic valve stenosis, but much fewer data are available on this topic. (19)

Treatment of obesity is difficult, and initially based on life-style change, diet and increased physical activity. (20) To achieve a sustained reduction of 5-10% of total body weight, is difficult if not impossible in most patients.(21) Pharmacological treatment of obesity can be considered, but only a few drugs have been approved(2, 20), because of side-effects and safety concerns.(22, 23)

Bariatric (or metabolic) surgery is an accepted treatment for patients with morbid obesity, i.e. BMI >40 kg/m2, or severe obesity, i.e. ≥35 kg/m2 in presence of obesity-associated comorbidities.(24) Since its introduction(25), techniques have improved, particularly with laparoscopic procedures, which has resulted in a low incidence of serious complications, and a 30-day mortality rate <0.5%.(20, 26, 27) A recent study of 9,710 patients reported mean total weight loss of around

25% after surgery.(28) Since obesity is increasingly common in patients with CV disease(29), the use of bariatric surgery is expected to increase in this population.

The effect of bariatric surgery on CV diseases (or CV mortality) has been examined in four other systematic reviews and meta-analyses,(30-33) but since that time important, prospective studies have been published, or recent reviews did not include all important CV outcomes, and/or did not have substantial follow-up duration. Therefore, we aimed to perform a comprehensive systematic review and meta-analysis of the available literature on the effect of bariatric surgery on CV disease and outcome.

METHODS

This systematic review and meta-analysis was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.(34) The PRISMA 2020 item checklist is detailed in the Supplementary material online (Figure S1). We conducted a search in Pubmed and Embase databases from inception to 28 August 2021. The search strategy composed the PICO method: Patients of interest were obese, adult (age ≥18 years old) patients, Intervention was bariatric surgery, Controls were obese patients who did not undergo bariatric surgery and Outcomes were defined as all-cause mortality, CV mortality, and incidence of CV disease, i.e. incident atrial fibrillation (AF), incident HF, incident myocardial infarction, incident stroke, and incident aortic stenosis. Further, for clarity reasons we investigated myocardial infarction, and not incident coronary artery disease, because it is very difficult if not impossible to define its onset, also this was not uniform across the studies. Somewhat similarly, we investigated stroke and not incident cerebrovascular disease. A few studies, however, further differentiated between ischemic vs haemorrhagic stroke, and thus we also separately investigated the effect on ischemic stroke. The full search strategy is detailed in the Supplementary material online. The protocol for this systematic review and meta-analysis was registered to PROSPERO (identification number: CRD42021277135). Our search was limited to studies conducted in adults, published in peer-reviewed journals and written in English.

Study selection

Studies were considered eligible if they were designed to study outcomes in obese patients who underwent a weight loss surgical intervention in comparison with an age, sex and BMI matched control group who did not undergo a weight loss surgical intervention. We searched for randomized controlled trials, prospective or retrospective longitudinal cohort studies, and case-control studies. For the control group, all non-surgical treatment options for obesity (e.g. intensive lifestyle intervention, standard of care or no specific therapy) were

accepted. Studies were excluded if 1) patients were not matched for age, sex and BMI, 2) the presence of one or more outcome parameters of interest (e.g. HF, AF, coronary artery disease) was required for inclusion, or 3) if the study groups were not representative in relation to the general population of patients with obesity (e.g. patients could only be included in presence of a specific comorbidity, for instance end-stage renal disease). The third criterium did not apply to T2DM, thus studies that only included patients with T2DM could be eligible for inclusion.

After removal of duplicates and non-English articles, conference abstracts, case reports, comments, review articles and editorials, all records were independently reviewed by two observers (T.G. and G.v.W.), and studies were subsequently excluded at title, abstract, or full text level. Disagreement was resolved by consensus. We also reviewed reference lists of included articles for relevant publications not identified by the initial search. Studies were specifically reviewed for potential overlap of study populations. If there was overlap of study population with identical outcome parameters of interest, the study with the longest follow-up duration for that endpoint was included. If one study population was described in various articles, but these articles analysed different outcome parameters, both articles could be included. However, for each study population, the hazard ratio (HR) for that specific outcome parameter could only be extracted once, so no overlap in HR of the same outcome within the same study population could occur. The HR with the longest follow-up duration for a specific endpoint was chosen.

Data extraction

The following data were extracted: 1) study characteristics (i.e. publication year, type of bariatric surgery, number of patients, mean age and BMI and the percentage of patients diagnosed with T2DM for both groups, study design, study cohort and recruitment period, major inclusion and exclusion criteria, primary and secondary outcome parameters and follow-up period), 2) event rate per outcome parameter for each group, 3) unadjusted and adjusted hazard ratios with their 95% confidence intervals for the association with outcome of interest, and 4) adjustment variables.

Quality assessment

The risk of bias for each study was assessed by two independent reviewers (S.v.V. and G.v.W.) using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies. Length of follow-up was set at a minimum of 5 years to be evaluated as adequate. Agreement for the quality assessment between both observers was tested and disagreement was resolved by consensus. The quality of evidence was assessed for each outcome parameter using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework.

(35) All study outcomes were assessed by two reviewers (S.v.V. and T.G.), and disagreement was resolved by consensus.

Statistical analyses

Continuous variables were reported as means ± standard deviation and categorical data as numbers or percentages. Hazard ratios were Log transformed, and the confidence interval (CI) was converted to standard error (SE) = (upper limit – lower limit) / 3.92. for 95% CI. In random effect models (DerSimonian and Laird), we analysed adjusted HR to generate pooled HRs for the association between bariatric surgery for outcome in comparison with controls. The pooled HRs were calculated using inverse variance weighted averaging and were depicted in forest plots. For the analyses that included <20 studies, the Hartung-Knapp-Sidik-Jonkman correction method of the DerSimonian and Laird random effect models was also applied, based on previous recommendation.(36) We performed a sensitivity analysis in which pooled HRs were primarily calculated in prospective and retrospective studies separately. We also performed a sensitivity analysis using only studies that were assessed to have good or fair quality, according to the Newcastle-Ottawa Quality Assessment Scale. Heterogeneity among effect sizes was assessed using the Q-statistic and magnitude of heterogeneity with I2. (37) Publication bias was tested with funnel plot asymmetry and Egger's regression test if a minimum of ten studies was included in the analysis.(38, 39) Inter-rater agreement for the quality assessment was tested using Cohen's kappa coefficient. Statistical analyses were performed using RevMan 5.4 and SPSS (Version 26).

RESULTS

Search results

The search strategy yielded 2,966 articles. After removing duplicates and screening of articles, 39 studies were included in the systematic review. Figure 1 shows the PRISMA flowchart for the literature search. There were no randomized, controlled trials that have examined the effect of bariatric surgery on mortality or CV disease. Our systemic search identified observational cohort studies that reported the effect of surgery. These were in mostly retrospective cohort studies (40-66), but several prospectively defined (matched) cohort studies(67-78) were also found. The key characteristics of all included studies are presented in Table 1. All outcomes regarding mortality and incidence of AF, HF, myocardial infarction, and stroke of all included studies are available in the supplementary material (Table S1). In our present search, we have not identified any reports which have examined the effect of bariatric surgery on incident valvular heart disease such as aortic stenosis.

In the quality assessment, 19 studies were assessed as 'good' quality, one study was assessed as 'fair' quality, and 19 studies were assessed as 'poor' quality

(Supplementary Table S2). The inter-rater agreement on the quality assessment was good/excellent: overall agreement 91.4% (329/360); Cohen's kappa was substantial: 0.800. The quality of evidence for all outcome parameters were assessed as "very low" quality. This was based on the observational design of all included studies and the substantial heterogeneity among studies per outcome parameter (Supplementary Table S3).

Heterogeneity among effect sizes was high for all outcome parameters Publication bias could only be assessed for all-cause mortality (given the criterium of a minimum of 10 studies per outcome parameter for Egger's test and funnel plots), which showed possible publication bias (Supplementary Table S4).

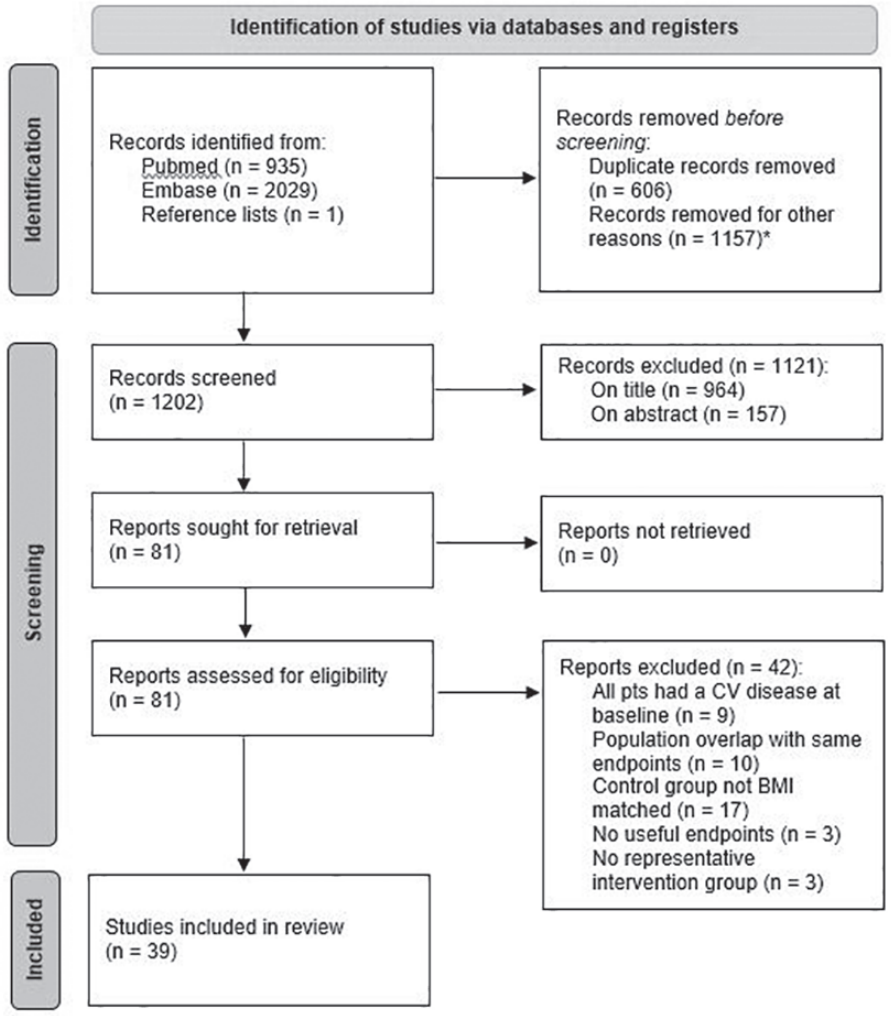


Figure 1: Flowchart of literature search according to PRISMA guidelines. BMI body mass index, CV cardiovascular

Effect on all-cause and cardiovascular mortality

A total of 28 studies examined the effect of bariatric surgery on mortality, both all-cause and CV mortality. Following bariatric surgery, all-cause mortality varied from 0.0-23.7%, and 1.4-28.2% for controls, with follow-up duration ranging between 2 years to 24 years (Supplementary Table S1). There were 21 studies that examined all-cause mortality, and reported adjusted hazard ratios, and were therefore suited for the meta-analysis, see Figure 2. These 21 studies included 133,524 patients after bariatric surgery, and 263,478 obese controls. The meta-

analysis showed that patients who had undergone surgery had a pooled HR of all-cause mortality of 0.55 (95% CI 0.49-0.62, p<0.001, I2=78%) compared to obese subjects in the control group. Three of these studies only reported adjusted hazard ratios for separate subgroups (i.e. diabetic vs. non-diabetic, or RYGB vs. sleeve gastrectomy) and are thus mentioned twice in the forest plot.(49, 54, 65) Seven studies investigated CV mortality, with incidences of 0.2-8.3% in bariatric patients and 0.5-12.9% in controls. The results in the meta-analysis showed that bariatric surgery also reduced CV mortality (HR 0.59, 95% CI 0.47-0.73, p<0.001, I2= 71%, see supplementary material, figure S3).

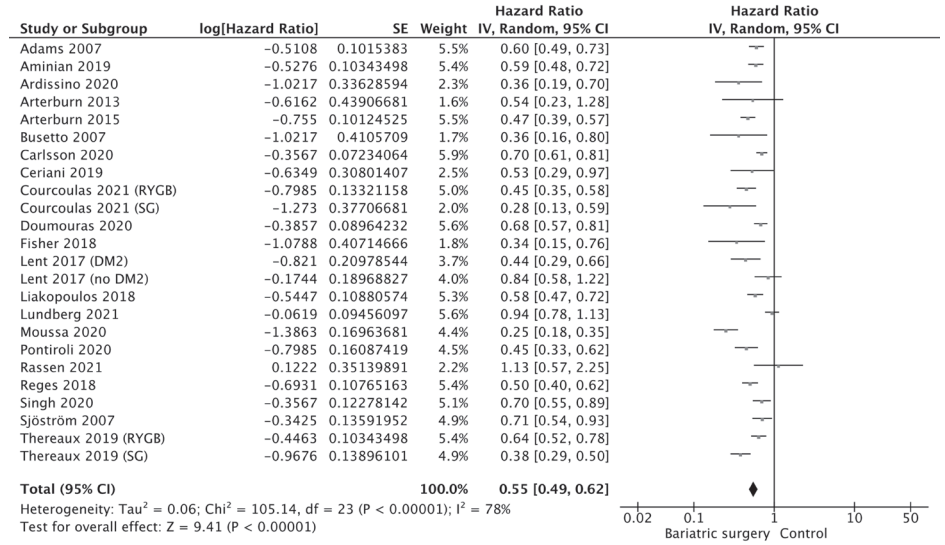


Figure 2: Forest plot of pooled HR of all-cause mortality
DM2 type 2 diabetes mellitus; HR hazard ratio, RYGB Roux-Y gastric bypass; SG sleeve gastrectomy

Effect on atrial fibrillation

A total of seven studies examined the effect of bariatric surgery on incidence of AF (Supplementary Table S1), which ranged from 0.8-12.4% in patients after bariatric surgery to 1.3-16.8% in control subjects. Five of these studies were suitable for the meta-analysis, which accumulated to 24,015 patients following bariatric surgery and 80,394 controls (Figure 3, upper left panel). The overall effect in the meta-analysis was a non-significant reduction after bariatric surgery vs. controls with regard to incidence of AF (HR 0.82, 95% CI 0.64-1.06, p=0.12, I2=76%).

Effect on heart failure

A total of 12 studies examined the effect of bariatric surgery on incidence of HF (Supplementary Table S1). Incidence rates that were reported ranged from 0.4-

9.9% in patients following bariatric surgery, as compared to 0.7-15.7% in controls. For the meta-analysis, eight studies fulfilled criteria and thus a total of 26,002 bariatric patients and 40,657 controls were examined. The pooled HR for incident HF following bariatric surgery vs. control subjects was 0.50 (95% CI 0.38-0.66, p<0.001, I2=71%, Figure 3, upper right panel).

It is important to mention that one large study that examined incident HF(78) was not included in the current meta-analysis since the authors only provided unadjusted HR in their results. Sundström et al. examined 25,804 patients who had undergone bariatric surgery, and compared them to a 13,701 controls.(78) During 4 years of follow-up, surgery led to a 46% reduction in HF incidence, but the overall incidence of events was very low, which may have been due to the design of the study (i.e. less stringent registration of events).

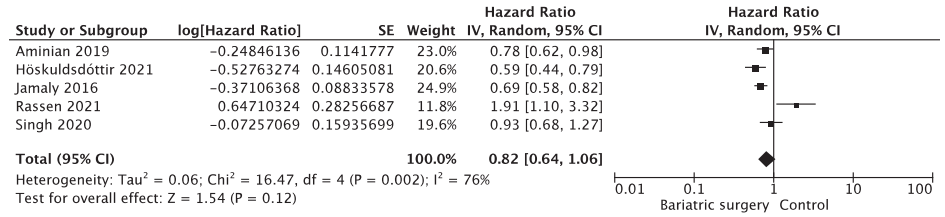
Effect on myocardial infarction

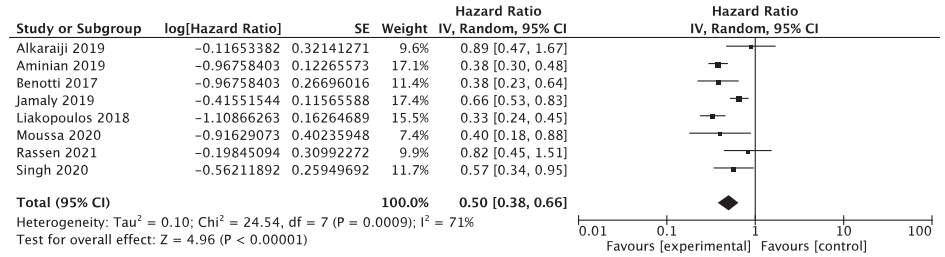
Nine studies reported on incident myocardial infarction after bariatric surgery and controls, and six on incident coronary artery disease. Incidence of coronary artery disease following bariatric surgery ranged from 1.5-13.7%, vs. 2.7-44.7% in controls (Supplementary Table S1), but these were not analysed further. Myocardial infarction after bariatric surgery occurred in 0.1-9.9% of patient, compared to 0.5-10.0% in controls,. For the meta-analysis of incident myocardial infarction after bariatric surgery, seven of the nine studies were suitable, involving 101,536 patients following bariatric surgery and 32,2551 controls. Bariatric surgery was associated with a lower incidence of myocardial infarction when compared to controls (HR 0.58, 95% CI 0.43-0.76, p<0.001, I2= 82%, Figure 3, lower left panel).

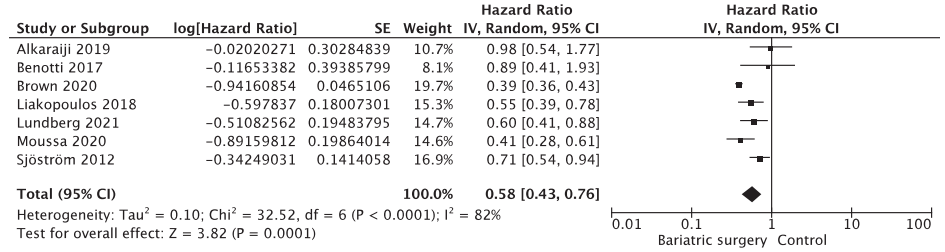
Effect on stroke

Incidence of stroke was investigated in 14 studies, and its incidence was much lower than other CV events (Table 1). Incidence of stroke ranged from 0.5 to 6.1% in bariatric patients, and 0.5 to 6.9% in controls. Nine studies were suitable for meta-analysis, involving 86,601 bariatric patients, and 318,599 controls. The pooled analysis showed that bariatric surgery reduced the incidence of (all) strokes (HR 0.64, 95% CI 0.53-0.77, p<0.001, I2=80%, Figure 3, lower right panel).

A few studies further investigated type of stroke, and so we performed additional analysis in studies that only reported on ischemic stroke. Interestingly, we observed an even more outspoken protective effect of surgery on ischemic stroke (HR 0.37, 95% CI 0.17-0.82, p=0.01, I2=92%), compared to the effect on all strokes combined (Supplementary material, figure S4).







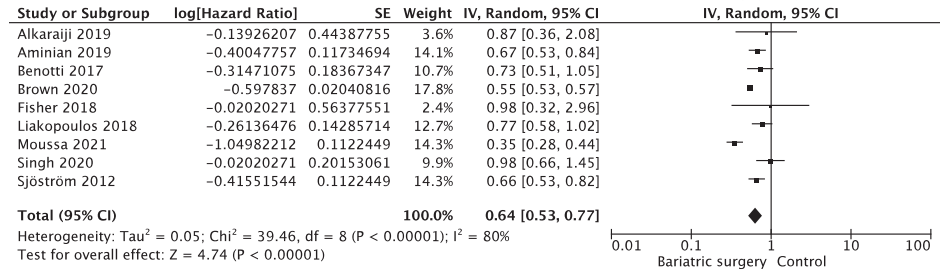


Figure 3: Forest plot of pooled HR of atrial fibrillation, heart failure, myocardial infarction, and stroke

Sensitivity analysis

As expected, small effect modification using the Hartung-Knapp-Sidik-Jonkman correction in the analyses with <20 studies changed the confidence intervals but not the overall effect estimate: for CV mortality (HR 0.59, 95% CI 0.45-0.77, p=0.004); for AF (HR 0.82, 95% CI 0.51-1.32, p=0.3); for HF (HR 0.50, 95% CI 0.37-0.68, p=0.001); for myocardial infarction (HR 0,58, 95% CI 0.42-0.80, p=0.006); and for stroke (HR 0.64, 95% CI 0.50-0.82, p=0.003).

In sensitivity analyses, we evaluated each outcome parameter for prospective and retrospective studies separately. The magnitude and direction of the pooled effect remained similar to all pooled HRs in comparison to prospective and retrospective studies for all-cause mortality (prospective studies: HR 0.60, 95% CI 0.43-0.83, p=0.002, I2=92%, and retrospective studies: HR 0.54, 95% CI 0.48-0.60, p<0.001, I2=59%). The same was observed in the analyses of CV related mortality (single prospective study: HR 0.78, 95% CI 0.64-0.96, p=0.02, and retrospective studies: HR 0.55, 95% CI 0.45-0.66, p<0.001, I2=53%), incident HF (prospective studies: HR 0.45, 95% CI 0.26-0.78, p=0.004, I2=84%, and retrospective studies: HR 0.54, 95% CI 0.38-0.77, p<0.001, I2=65%), and all types of stroke (prospective studies: HR 0.56, 95% CI 0.35-0.90, p=0.02, I2=92%, and retrospective studies: HR 0.02, 95% CI 0.00-0.31, p=0.005, I2=66%).

Differences in outcomes between prospective and retrospective studies were seen in incident AF (prospective studies: HR 0.66, 95 % CI 0.57-0.77, p<0.001, I2=0%, and retrospective studies: HR 1.04, 95% CI 0.69-0.1.56, p=0.87, I2=77%), as well as for incident myocardial infarction (prospective studies: HR 0.57, 95% CI 0.45-0.72, p<0.001, I2=42%, and retrospective studies: HR 0.66, 95% CI 0.32-1.35, p=0.25, I2=85%). For both outcomes, a protective effect following bariatric surgery was only found in prospective studies, and a non-significant (non-protective) outcome was seen in retrospective studies.

In sensitivity analysis that only assessed the studies of good or fair quality, outcomes were similarly beneficial following bariatric surgery for all-cause mortality (HR 0.50, 95% CI 0.43-0.59, p<0.001, I2=80%), CV mortality (HR 0.59, 95% CI 0.47-0.73, p=0.002, I2=63%), HF (HR 0.51, 95% CI 0.33-0.77, p=0.001, I2=56%), all types of stroke (HR 0.55, 95% CI 0.34-0.88, p=0.01, I2=90%), and ischemic stroke (single study: HR 0.32, 95% CI 0.25-0.41, p<0.001). For AF and myocardial infarction, outcomes of this sensitivity analyses (respectively; a single study on AF: HR 0.69, 95% CI 0.58-0.82, p<0.001, and multiple studies on myocardial infarction: HR 0.61, 95% CI 0.39-0.94, p=0.02, I2=67%) were in line with the pooled outcome of prospective studies, showing a lowered incidence of disease after bariatric surgery, but were different to the general pooled outcome.

DISCUSSION

Bariatric surgery is currently the only treatment option that achieves substantial and durable weight reduction in patients with obesity, in whom there is a markedly increased incidence of CV disease. The present systematic review and meta-analysis of 39 controlled cohort studies shows that bariatric surgery is significantly associated with reduction of not only mortality but also the incidence of CV disease, although it must be noted that no randomized outcome trials are available. Nevertheless, the data from the present systematic review and meta-analysis strongly suggest that bariatric surgery reduces the incidence of CV disease and lowers mortality during follow-up.

In recent years, four other systematic reviews have been published.(30-33) Zhou et al.(30) reviewed all studies until 2016 and reported all-cause mortality, cancer incidence and CV outcomes after bariatric surgery compared with obese controls. Their findings are in line with the current results, but clearly, their data are older, and many recent studies were not part of the analysis, particularly since a number of important studies have been published in the last two years. In addition, for CV disease they only examined 9 studies, and together these factors are the main limitation of their review. The meta-analysis by Wiggins et al.(31) published in 2020 focused on mortality and ischemic heart disease, and on CV risk factors such as diabetes, but they only included studies that drew their study population from nationwide registries as opposed to more precise hospital records, thereby missing many endpoints, and they only included 18 studies. Interestingly, using this approach, they observed a similar effect of bariatric surgery compared to controls as we did in the present analysis (i.e. a pooled odds ratio for all-cause mortality of 0.62 and 0.50 for CV mortality). In the third systematic review by Pontiroli (32), also published in 2020, the authors conducted a meta-analysis to evaluate outcome following bariatric surgery, and focused on the important issue of age at the time of surgery, and how that influences the effect of surgery on outcome. Using this approach the authors included 9 studies, and observed that the beneficial effect of surgery on outcome was mainly found in patients above the median age (around 40). It should be noted, however, that median follow-up duration in their meta-analysis was 8.7 years, and this may have been rather short, particularly in younger patients, since CV disease (and associated mortality) usually occurs later, even in obese patients. The review by Cardoso(33) from 2017, misses recent studies due to the publication date, and it only uses 8 studies for their outcome analysis. In addition, that study only examined short-term follow-up, and has very few endpoints.

Despite the potential favourable long-term effect of bariatric surgery, considering surgery for obesity, however, remains a significant step for patients. With the

increasing safety and relatively low incidence of (long-term) adverse outcomes, it can be an attractive alternative, however, for patients with morbid obesity (79). Bariatric surgery has been shown to reduce CV risk factors, and arguably, this should be accompanied by a reduction in CV events, but there are no randomized controlled trials that have prospectively examined the incidence of CV disease. This is understandable, since the average age of patients undergoing bariatric surgery is 40 years, and the onset of CV disease in patients below the age of 50 is relatively low. In other words, despite a probably significant and clinically relevant patient benefit, randomized controlled trials that examined the effect of bariatric surgery on CV disease outcome would require long-term (e.g. 5-10 years or maybe even longer) follow-up. The present meta-analysis shows a 25-58% reduction of CV events and a 35-40% reduction in mortality. It would be nice if these findings were supported in large-scale randomised clinical outcome trials, with substantial follow-up duration. But it will be challenging, and maybe even unlikely, that such a RCT will be conducted in the near future. The fact that bariatric surgery is already performed on a large scale (and that withholding bariatric surgery may sometimes seem unethical for patients with morbid obesity), will complicate matters further, and make an outcome trial very difficult. Hence, it will also be unlikely that a future systematic review and meta-analysis will render higher GRADE assessments for outcome parameters, even though this current review and future reviews consist of individual high-quality prospective studies.

An important factor in the beneficial effect of bariatric surgery, is whether this is only due to the absolute weight reduction, or whether additional, ancillary effects also play a role. A recent small mechanistic study suggested that benefits of bariatric surgery were all related to weight loss itself, with no other independent beneficial effects.(80) Many other studies, however, have suggested that ancillary factors associated with surgery are of influence, such as an altered profile in gut hormone expression, enhanced insulin sensitivity, and changed gut microbioma(81), and the procedure is therefore increasingly referred to as metabolic surgery.(82) Nevertheless, there is no question that the magnitude of weight loss is very important, and in one study it was calculated that in non-surgical obese patients, a 20% decrease in weight was required (only rarely achieved) to reduce long-term major CV events, while in surgical patients at least 10% weight reduction was required, which is generally easily achieved,(81) and underlines the hypothesis that other metabolic mechanisms contribute to the beneficial effects of surgery.

As pointed out before, despite these potential benefits of bariatric surgery to prevent (and possibly treat) CV disease, no randomized controlled studies have primarily investigated the effect of surgery on CV events or outcome.

At this moment, we are aware of only one ongoing randomized clinical trial in patients with morbid obesity and AF, who will undergo bariatric surgery six months prior to AF catheter ablation (Bariatric Atrial Restoration of Sinus Rhythm [BAROS], ClinicalTrial.gov identifier NCT04050969). In terms of prevention, bariatric surgery could potentially be useful in any (morbidly) obese patient with an increased risk of CV disease. Regarding treating clinically present disease, surgery could possibly be useful to treat patients with HF, but also AF, as discussed above. The recently published guideline for prevention of CV disease by European Society of Cardiology(83) states that 'bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss', i.e. a 2A recommendation. This is a major change from the previous guideline of 2016,(84) in which diet and lifestyle are advocated as main-stay therapy options, and bariatric surgery did not receive a formal recommendation. In addition, prevention or treatment of CV disease has so far not affected the recommendations for surgery.(85) The strongest recommendation for metabolic surgery is for patients with obesity and type 2 diabetes, and in this patient population, it is now considered a valid addition to existing standard therapy.(86)

There are some limitations that should be mentioned regarding the present systematic review and meta-analysis. First, all data regarding bariatric surgery that are discussed here stem from non-randomized studies, albeit many of them are prospective in design. Second, some of the studies in obese subjects only enrolled patients with (type 2) diabetes, which may have affected the findings (see also Supplementary Table 1). Indeed, it has been suggested that bariatric surgery may be more effective in terms of reducing outcome in patients with diabetes, as compared to those without diabetes.(54) However, this was not reported in another study(74) and the present meta-analysis does not provide an answer on this. Third, recent studies with new drugs like glucagon-like peptide 1 (GLP1) agonists or sodium glucose cotransporter 2 (SGLT2) inhibitors, have shown promising results in patients with diabetes and obesity, but no large studies are currently available on the (additive) effect of bariatric surgery in the population. But it is conceivable that these drugs may affect outcome in this population. Fourth, we only examined the effect of surgical techniques combined, and did not investigate potential differences between techniques. Fifth, we did not specifically analyse HR of coronary artery disease in addition to MI. This decision was based on the fact that the data on coronary artery disease was relatively scarce, and as coronary artery disease can occur silently, this may have been difficult to report in large (national) cohorts. We hypothesized that coronary artery disease is underreported to some extent, and therefore future studies could add valuable information regarding coronary artery disease following bariatric surgery. Last, some analyses should be interpreted with caution, as some

sensitivity analyses consisted of single studies analysis, for example CV related mortality in the analysis of prospective studies.(73) In addition, publication bias was not assessed for the majority of our outcome parameters, as the Egger's test and funnel plots are not appropriate in analysis containing less than 10 studies. For interpretation of funnel plots, it should be noted that asymmetry can also originate from other sources than publication bias.(39)

In summary, the results of this systematic review and meta-analysis of 39 studies suggest that bariatric surgery reduces mortality and incidence of CV disease in patients with obesity compared to non-surgical treatment. Bariatric surgery should therefore be considered in these patients.

Disclosure

The authors declare no relevant conflicts of interest, and no funding or payment was obtained for this review.

The Department of Cardiology, UMCG, has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals Gmbh, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche. Some of the ongoing clinical trials are in the field of diabetes and CV disease, but none of them (specifically) in obesity, and none in bariatric surgery. At the department of the Experimental Cardiology, UMCG (chair RADB) some studies in obesity are ongoing, none of them related to bariatric surgery.

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SUPPLEMENTARY FILE

Figure S1. PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary F2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5-6

Figure S1. PRISMA 2020 checklist *(continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5-6

Figure S1. PRISMA 2020 checklist *(continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6-7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6-7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6-7

Figure S1. PRISMA 2020 checklist *(continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7+ Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7 + suppl. Table S4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8-10, figure 2+3, suppl. table S1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-10, figure 2+3, suppl. table S1 +S4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	10-11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	7-11
DISCUSSION			

Figure S1. PRISMA 2020 checklist *(continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11
	23b	Discuss any limitations of the evidence included in the review.	13-14
	23c	Discuss any limitations of the review processes used.	13-14
	23d	Discuss implications of the results for practice, policy, and future research.	14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4 (of note: reg.no. is not yet known)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	15
Competing interests	26	Declare any competing interests of review authors.	15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	In part: suppl. Fig S2, table S1, Data collection forms are not available

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S2: Search strategy

Pubmed

("Overweight"[Mesh] OR obes*[tiab] OR overweight[tiab] OR body mass index[tiab] OR BMI[tiab] OR "Body Mass Index"[Mesh])

AND

("Bariatric surgery"[Mesh] OR bariatric surg*[tiab] OR bariatric operat*[tiab] OR "Gastric Bypass"[Mesh] OR gastric bypass*[tiab] OR gastroileal bypass*[tiab] OR gastrojejunostom*[tiab] OR gastroplast*[tiab] OR jejunoileal bypass*[tiab] OR ileojejunal bypass*[tiab] OR intestinal bypass*[tiab] OR biliopancreatic bypass*[tiab] OR biliopancreatic diversion*[tiab] OR duodenal switch*[tiab] OR pancreatobiliary bypass*[tiab] OR gastric banding*[tiab] OR stomach banding*[tiab] OR laparoscopic adjustable silicone banding*[tiab] OR bariatric operat*[tiab] OR bariatric procedure*[tiab] OR obesity surg*[tiab] OR obesity operat*[tiab] OR sleeve gastrectom*[tiab] OR gastric sleeve*[tiab] OR metabolic surg*[tiab] OR stomach surg*[tiab] OR weight loss operat*[tiab] OR weight loss surg*[tiab] OR weight reduction operat*[tiab] OR weight reduction surg*[tiab])

AND

("Control Groups"[Mesh] OR "Weight Loss"[Mesh] OR "Standard of Care"[Mesh] OR "Conservative Treatment"[Mesh] OR "Weight Reduction Programs"[Mesh] OR "Life Style"[Mesh] OR non-surgical*[tiab] OR nonsurgical*[tiab] OR conventional therap*[tiab] OR conventional care[tiab] conventional treatment*[tiab] OR standard care[tiab] OR standard therap*[tiab] OR standard treatment*[tiab] OR regular care[tiab] OR regular therap*[tiab] OR regular treatment*[tiab] OR conservative treat*[tiab] OR conservative therap*[tiab] OR conservative care[tiab] OR normal care[tiab] OR normal treatment*[tiab] OR normal therap*[tiab] OR weight low*[tiab] OR weight reduction*[tiab] OR weight loss[tiab] OR losing weight[tiab] OR control*[tiab] OR medical intervention*[tiab] OR lifestyle*[tiab] OR diet*[tiab] OR compar*[tiab] OR matched control*[tiab] OR "Diet, Fat-Restricted"[Mesh] OR calor*[tiab])

AND

("Mortality"[Mesh] OR cardiovascular event*[tiab] OR cardiovascular outcome*[tiab] OR "Heart Failure"[Mesh] OR heart decompensation*[tiab] OR myocardial failure*[tiab] OR heart failure*[tiab] OR "Atrial Fibrillation"[Mesh] OR atrial fibrillation*[tiab] OR Auricular Fibrillation*[tiab] OR "Myocardial Infarction"[Mesh] OR myocardial infarct*[tiab] OR Cardiovascular Stroke*[tiab] OR Heart Attack*[tiab] OR "Coronary Artery Disease"[Mesh] OR Coronary Artery Disease*[tiab] OR Coronary arteriosclerosis[tiab] OR "Aortic Valve Stenosis"[Mesh] OR aortic valve stenosis[tiab] OR aortic stenosis[tiab] OR aortic valvular stenosis[tiab] OR major adverse cardiac event*[tiab] OR major adverse cardiovascular event*[tiab] OR major cardiovascular event*[tiab] OR major cardiac event*[tiab] OR MACE[tiab] OR ischemic stroke*[tiab] OR ischemic cerebrovascular accident*[tiab] OR ischaemic stroke*[tiab] OR ischaemic cerebrovascular accident*[tiab] OR myocardial ischaemia*[tiab] OR myocardial ischemia*[tiab] OR mortalit*[tiab])

AND

("Randomized Controlled Trial" [Publication Type] OR "Matched-Pair Analysis"[Mesh] OR "Case-Control Studies"[Mesh] OR "Propensity Score"[Mesh] OR "Cohort Studies"[Mesh] OR randomi*[tiab] OR randomly[tiab] OR trial[ti] OR cohort[tiab] OR Propensity Score*[tiab] OR MatchedPair*[tiab] OR

matched-pair*[tiab] OR paired comparison*[tiab] OR case-control[tiab] OR retrospective*[tiab] OR prospective*[tiab] OR longitudinal*[tiab] OR observational*[tiab] OR follow-up[tiab])

NOT

("Review" [Publication Type] OR "Systematic Review" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Editorial" [Publication Type] OR "Case Reports" [Publication Type] OR "Comment" [Publication Type]) NOT (("Child"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh]) NOT ("Pediatric Obesity"[Mesh] OR "Pregnancy"[Mesh] OR "Conversion to Open Surgery"[Mesh] OR "Safety"[Mesh] OR conversion*[tiab] OR safety[tiab] OR technique*[tiab] OR surgery type*[tiab] OR efficacy[tiab] OR maternal[tiab] OR pregnan[tiab])

Embase
('obesity'/exp OR 'body mass'/exp OR (obes* OR 'overweight' OR 'body mass index' OR BMI):ab,ti,kw)

AND

('bariatric surgery'/exp OR 'gastric bypass surgery'/exp OR 'gastrojejunostomy'/exp OR 'stomach surgery'/exp OR 'collis gastroplasty'/exp OR 'vertical banded gastroplasty'/exp OR 'intestine bypass'/exp OR 'gastric sleeve'/exp OR 'endoscopic sleeve gastroplasty'/exp OR 'one-anastomosis gastric bypass'/exp OR ('bariatric surg*' OR 'bariatric operat*' OR 'gastric bypass*' OR 'gastroileal bypass*' OR gastrojejunostom* OR gastroplast* OR 'jejunoileal bypass*' OR 'ileojejunal bypass*' OR 'intestinal bypass*' OR 'biliopancreatic bypass*' OR 'biliopancreatic diversion*' OR 'duodenal switch*' OR 'pancreatobiliary bypass*' OR 'gastric banding*' OR 'stomach banding*' OR 'laparoscopic adjustable silicone banding*' OR 'bariatric operat*' OR 'bariatric procedure*' OR 'obesity surg*' OR 'obesity operat*' OR 'sleeve gastrectom*' OR 'gastric sleeve*' OR 'metabolic surg*' OR 'stomach surg*' OR 'weight loss operat*' OR 'weight loss surg*' OR 'weight reduction operat*' OR 'weight reduction surg*'):ab,ti,kw)

AND

('control group'/exp OR 'body weight loss'/exp OR ('non-surgical*' OR 'nonsurgical*' OR 'conventional therap*' OR 'conventional treat*' OR 'conventional care' OR 'standard therap*' OR 'standard treat*' OR 'standard care' OR 'regular therap*' OR 'regular care' OR 'regular treat*' OR 'conservative therap*' OR 'conservative treat*' OR 'conservative care' OR 'normal treat*' OR 'normal care' OR 'normal therap*' OR 'weight low*' OR 'weight reduction*' OR 'weight loss' OR 'losing weight' OR 'control*' OR 'medical intervention*' OR 'lifestyle*' OR 'diet*' OR 'compar*' OR 'matched control*' OR 'calor*'):ab,ti,kw)

AND

('controlled clinical trial'/exp OR 'Propensity Score'/exp OR 'Cohort Analysis'/exp OR 'intervention study'/exp OR 'case control study'/exp OR (randomi* OR randomly OR trial OR cohort OR 'Propensity Score*' OR MatchedPair* OR matched-pair* OR 'paired comparison*' OR case-control OR prospective* OR observational* OR longitudinal* OR retrospective* OR follow-up):ab,ti,kw)

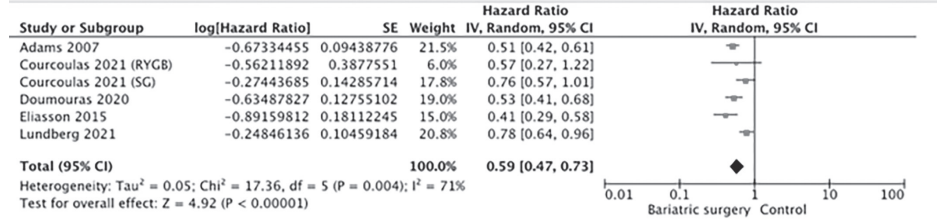
AND

('mortality rate'/exp OR 'all cause mortality'/exp OR 'cardiovascular mortality'/exp OR 'prognostic factor'/exp OR 'survival rate'/exp OR 'outcome'/exp OR 'major adverse cardiac event'/exp OR 'heart failure'/exp OR 'atrial fibrillation'/exp OR 'heart infarction'/exp OR 'cerebrovascular accident'/exp OR 'coronary artery disease'/exp OR 'coronary artery atherosclerosis'/exp OR 'aortic stenosis'/exp OR 'heart muscle ischemia'/exp OR ('cardiovascular event*' OR 'cardiovascular outcome*' OR 'heart decompensation*' OR 'myocardial failure*' OR 'heart failure*' OR 'atrial fibrillation*' OR 'auricular fibrillation*' OR 'myocardial infarct*' OR 'cardiovascular stroke*' OR 'heart attack*' OR 'coronary NEXT/1 disease*' OR 'coronary arteriosclerosis' OR 'aortic NEXT/1 stenosis' OR 'cardiac event*' OR 'MACE' OR 'ischemic stroke*' OR 'ischemic cerebrovascular accident*' OR 'ischaemic stroke*' OR 'ischaemic cerebrovascular accident*' OR 'myocardial ischaemia*' OR 'myocardial ischemia*' OR mortalit*):ab,ti,kw)

NOT

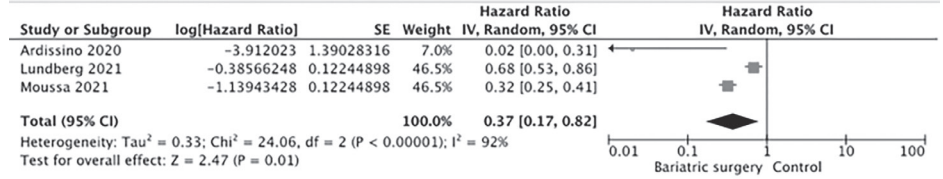
('review'/exp OR 'meta analysis'/exp OR 'editorial'/exp OR 'case report'/exp OR 'pregnancy'/exp) NOT (('child'/exp OR 'adolescent'/exp OR 'infant'/exp) NOT 'adult'/exp) NOT ('childhood obesity'/exp OR 'conversion to open surgery'/exp OR 'risk assessment'/exp OR (conversion* OR safety OR technique* OR 'surgery type*' OR efficacy OR maternal OR pregnan*):ab,ti,kw)

Figure S3. Forest plot of pooled hazard ratio (HR) of cardiovascular mortality



CI confidence interval; HR hazard ratio, RYGB Roux-en-Y gastric bypass, SG sleeve gastrectomy

Figure S4. Forest plot of pooled HR of ischemic stroke



CI confidence interval; HR hazard ratio

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Adams 2007 [40]	All-cause mortality	2.7%	4.1%	NR	NR	0.60 [0.45 - 0.67]	Age, sex, BMI, index year	<0.001
	CV mortality	0.7%	1.3%	NR	NR	0.51 [0.36 - 0.73]		<0.001
Alkharaiji 2019 [41]	MI	9.9%	8.8%	1.03 [0.57 - 1.86]	NR	0.98 [0.54 - 1.77]	Age, sex, diabetes duration, Townsend deprivation status, marital status, smoking, alcohol use	0.94
	Stroke	6.1%	6.9%	0.77 [0.34 - 1.72]	NR	0.87 [0.36 - 2.10]		0.75
	CAD	13.7%	44.7%	0.31 [0.19 - 0.52]	NR	0.29 [0.16 -0.52]		<0.001
	HF	9.9%	15.7%	0.81 [0.44 - 1.49]	NR	0.89 [0.47 - 1.70]		0.73
Aminian 2019 [42]	MACE	0.2%	0.3%	NR	NR	0.61 [0.55 - 0.69]	Age, sex, BMI, index date, index site, race, annual zip code income, multiple comorbidities (e.g. HTN, HF, AF, CAD, MI, CDK, stroke), clinical and laboratory data (e.g. HbA1c, HDL-C, BP), drugs use (e.g. insulin)	<0.001
	All-cause mortality	4.9%	9.7%	NR	NR	0.59 [0.48 - 0.72]		<0.001
	CAD	NR	NR	NR	NR	0.69 [0.54 - 0.87]		0.002
	HF	NR	NR	NR	NR	0.38 [0.30 - 0.49]		<0.001
	Cerebrovascular disease	NR	NR	NR	NR	0.67 [0.48 - 0.94]		0.02
	AF	NR	NR	NR	NR	0.78 [0.62 - 0.97]		0.03

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Ardissino 2020 [43]	ASCVD	3.5%	5.6%	NR	NR	0.53 [0.30 - 0.95]	Age, BMI, sex, index date, HTN, HCL, hyperlipidemia, AF, CKD, family history of CVD, smoking, alcohol use, and use of anti-DM, anti-HTN, anti-HCL and anticoagulant drugs	0.03
	CAD	2.5%	2.9%	NR	NR	0.69 [0.32 - 1.46]		0.3
	Cerebrovascular event	0.2%	0.7%	NR	NR	0.02 [0.00009 - 5.45]		0.2
	All-cause mortality	2.4%	5.9%	NR	NR	0.36 [0.19 - 0.71]		0.003
Arterburn 2013 [44]	All-cause mortality	NR	NR	NR	NR	0.54 [0.22 - 1.23]	Age, BMI, sex, site and year of eligibility, DM duration, HbA1c, DM drugs	NS
Arterburn 2015 [45]	All-cause mortality	10.5%	17.1%	NR	NR	0.47 [0.39 - 0.58]	Age, BMI, sex, DM, race, index site, marital status, DCG score, multiple comorbidities (e.g. DM, HTN, HCL, CAD)	<0.001

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Benotti 2017 [46]	CVD event	3.7%	6.4%	0.69 [0.50 - 0.94]	0.02	0.58 [0.42 - 0.82]	Age, BMI, sex,	0.002
	Stroke	1.8%	2.8%	0.77 [0.49 - 1.21]	0.25	0.73 [0.45 - 1.17]	Framingham Risk	0.2
	MI	0.7%	1.0%	0.85 [0.41 - 1.79]	0.7	0.89 [0.41 - 1.92]	Score, smoking, anti-HTN drugs, DM,	0.8
	HF	1.4%	3.2%	0.53 [0.33 - 0.85]	0.009	0.38 [0.22 - 0.64]	index year	0.0003
Brown 2020 [47]	CVD event	2.3%	5.4%	NR	NR	0.48 [0.45 - 0.51]	Age, sex, race,	<0.0001
	MI	0.9%	2.8%	NR	NR	0.39 [0.35 - 0.42]	CAD, HTN, HF, valvular disease, PAD,	<0.0001
	Stroke	1.5%	3.1%	NR	NR	0.55 [0.45 - 0.51]	DM, PCD, index year	<0.0001
Busetto 2007 [48]	All-cause mortality	1.0%	4.4%	NR	NR	0.36 [0.16 - 0.80]	Age, BMI, sex	NR
Carlsson 2020 [67]							Age, BMI, sex, marital status, education level, smoking, index year, waist:hip ratio, CVD, DM, HTN, laboratory data, substance abuse, psychiatric	
	All-cause mortality	23.7%	26.4%	0.77 [0.68 - 0.87]	<0.001	0.70 [0.61 - 0.81]	disease or -drugs	<0.001
	CV mortality	8.3%	10.8%	0.70 [0.57 - 0.85]	NR	NR	NR	NR
Ceriani 2019 [60]	All-cause mortality	7.2%	12.9%	0.64 [0.44 - 0.93]	0.02	0.53 [0.29 - 0.97]	Age, sex, BMI, DM, BP, CAD, eGFR	0.04
	CV mortality	0.8%	3.2%	0.26 [0.09 - 0.72]	0.001	NR	NR	NR

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Courcoulas 2021 [48]9(SG)	All-cause mortality	1.0%	2.7%	NR	NR	0.28 [0.13 - 0.57]	Age, BMI, sex, index site, DM, HTN,	NR
	CV mortality	NR	NR	NR	NR	0.57 [0.19 - 1.71]	insulin use, race,	NR
Courcoulas 2021 [49] (RYGB)	All-cause mortality	1.8%	4.5%	NR	NR	0.45 [0.35 - 0.59]	smoking, combined comorbidity score, prior health care	NR
	CV mortality	NR	NR	NR	NR	0.76 [0.53 - 1.09]	utilization	NR
Douglas 2015 [50]	MI	0.1%	0.5%	0.28 [0.10 - 0.74]	0.01	NR	NR	NR
	Stroke	0.5%	0.5%	0.91 [0.47 - 1.76]	0.9	NR	NR	NR
	All-cause mortality	1.4%	1.4%	0.97 [0.66 - 1.43]	0.9	NR	NR	NR
Doumouras 2020 [51]	All-cause mortality	1.4%	2.5%	NR	NR	0.68 [0.57 - 0.81]	Age, BMI, sex, DM duration, extensive demographic, socioeconomic, and clinical	<0.001
	CV mortality	0.2%	0.5%	NR	NR	0.53 [0.34 - 0.84]	characteristics	0.007

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Eliasson 2015 [52]	All-cause mortality	1.3%	4.7%	NR	NR	0.42 [0.30 - 0.57]	Age, BMI, sex, index year, BP, laboratory	<0.001
	MI	0.3%	0.7%	NR	NR	0.49 [0.24 - 1.01]	data, hospital admissions due to MI / HF / stroke, smoking, anti-HTN or DM drugs, marital status, education	0.054
	CV mortality	0.2%	1.1%	NR	NR	0.41 [0.19 - 0.90]	level, yearly income	0.03
Fisher 2018 [53]	Macrovascular disease	2.0%	4.0%	NR	NR	0.52 [0.28 - 0.97]	Age, BMI, sex, race, index site and	NR
	CAD	1.5%	2.7%	NR	NR	0.50 [0.24 - 1.06]	year, DM duration,	NR
	Cerebrovascular event	0.7%	1.5%	NR	NR	0.98 [0.37 - 2.58]	smoking, laboratory data, use of DM or anti-HTN drugs, BP, PAD, HCL, microvascular disease due to DM,	NR
	All-cause mortality	1.3%	4.2%	NR	NR	0.34 [0.15 - 0.74]	prior health care utilization	NR

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Höskuldsdóttir 2021 [68]	AF	2.0%	2.6%	NR	NR	0.59 [0.44 - 0.78]	Age, MBI, sex, DM duration, HbA1c, BP, smoking, physical performance, DM associated complications, DM/ anti-HTN or -HCL drugs, education, income, and country of birth.	<0.001
	HF	0.9%	2.8%	NR	NR	0.27 [0.19 - 0.38]		<0.001
Jamaly 2016 [70]	AF	12.4%	16.8%	0.71 [0.60 - 0.83]	<0.001	0.69 [0.58 - 0.82]	Age, BMI, sex, waist circumference, DM, HTN, CVD, laboratory data	<0.001
Jamaly 2019 [69]	HF	9.4%	13.1%	0.65 [0.54 - 0.79]	<0.001	0.66 [0.51-0.81]	Age, BMI, sex, waist-hip ratio, BP, laboratory data, smoking, DM, menopause, HTN, alcohol use	<0.001
Lent 2017 (DM2) [54]	All-cause mortality	NR	NR	0.42 [0.28 - 0.63]	<0.0001	0.44 [0.29 - 0.66]	Age, BMI, sex, DM, smoking, anti-HTN or -HCL drugs	<0.001
Lent 2017 (no DM2) [54]	All-cause mortality	NR	NR	0.92 [0.64 - 1.32]	0.6	0.84 [0.58 - 1.22]		0.4

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Liakopoulos 2019 [71]	All-cause mortality	3.4%	6.6%	NR	NR	0.51 [0.43 - 0.62]	Age, BMI, sex, socioeconomic factors (income, marital status, education level and country of origin)	<0.0001
	MI	1.0%	1.6%	NR	NR	0.55 [0.39 - 0.79]		0.001
	HF	2.0%	4.2%	NR	NR	0.49 [0.39 - 0.62]		<0.0001
	AF	3.8%	4.0%	NR	NR	0.93 [0.76 - 1.14]		0.5
	Stroke	1.1%	1.3%	NR	NR	0.77 [0.54 - 1.10]		0.2
Liakopoulos 2020 [72]	HF	1.6%	4.4%	NR	NR	0.33 [0.24 - 0.46]	Age, BMI, sex, eGFR, marital status, income, education, and country of birth.	<0.0001
	All-cause mortality	3.4%	6.6%	NR	NR	0.58 [0.47 - 0.72]		<0.0001
Lundberg 2021 [73]	MI	0.3%	1.2%	NR	NR	0.60 [0.41 - 0.88]	Age, BMI and sex	NR
	Stroke	0.5%	1.2%	NR	NR	0.68 [0.48 - 0.96]		NR
	Mortality	1.8%	4.1%	NR	NR	0.94 [0.78 - 1.13]		NR
	CV mortality	0.7%	2.4%	NR	NR	0.78 [0.60 - 1.01]		NR
Lynch 2019 [55]	AF	0.8%	2.9%	NR	NR	NR	NR	NR
MacDonald 1997 [56]	Mortality	9.1%	28.2%	NR	NR	NR	NR	NR
Michaels 2020 [57]	MI	1.8%	10.0%	NR	NR	NR	NR	NR
	PCI	0.4%	7.8%	NR	NR	NR	NR	NR
	CABG	0.6%	2.3%	NR	NR	NR	NR	NR

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Moussa 2020 [74]	Combined MI/ Stroke	1.0%	2.5%	NR	NR	0.41 [0.27 - 0.62]	Age, BMI, sex, HTN, HCL, DM, AF, smoking, alcohol or cocaine use, exercise level. Use of anti-HTN, anti-HCL, hormone replacement, or anticoagulant drugs.	<0.001
	MI	1.0%	2.5%	NR	NR	0.41 [0.28 - 0.61]		<0.001
	Stroke	0.4%	0.1%	NR	NR	0.54 [0.16 - 1.75]		0.3
	HF	0.6%	1.2%	NR	NR	0.40 [0.18 - 0.90]		0.03
	All-cause mortality	1.2%	4.9%	NR	NR	0.25 [0.18 - 0.35]		<0.001
Moussa 2021 [75]	Major cerebrovascular event	0.5%	1.3%	NR	NR	0.35 [0.20 - 0.64]	Age, BMI, sex, HTN, HCL, DM, AF, smoking, alcohol or cocaine use, exercise level. Use of anti-HTN, anti-HCL, hormone replacement, or anticoagulant drugs.	0.001
	Ischemic cerebrovascular event	0.3%	0.9%	NR	NR	0.32 [0.16 - 0.64]		0.001
	Hemorrhagic cerebrovascular event	0.1%	0.4%	NR	NR	0.44 [0.15 - 1.33]		0.1
	All-cause mortality	1.3%	4.1%	NR	NR	0.28 [0.20 - 0.40]		<0.001
Perry 2008 [58]	All-cause mortality	4.5%	8.6%	NR	NR	NR	NR	NR

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Pontiroli 2020 [59]								
	All-cause mortality	NR	NR	NR	NR	0.45 [0.33 - 0.62]	Age, DM, RR, e-GFR, history of CAD	0.001
Rassen 2021 [61]	MACE	25.3%	36%	NR	NR	0.99 [0.76 - 1.30]	Age, BMI, sex, race, annual income, smoking, comorbidities (e.g. AF, CADm MI, HTN, HF, PAF, stroke), laboratory data, use of anti-DM, anti-HTN, anti-HCL or anticoagulant drugs	NR
	All-cause mortality	3.8%	4.0%	NR	NR	1.13 [0.57 - 2.26]		NR
	CAD	8.9%	8.5%	NR	NR	1.10 [0.67 - 1.80]		NR
	HF	5.5%	7.2%	NR	NR	0.82 [0.44 - 1.52]		NR
	AF	9.3%	5.2%	NR	NR	1.91 [1.10 - 3.33]		NR
Reges 2018 [62]							Age, BMI, sex, DM, HTN, HCL, CVD, SES, immigrant status, smoking, laboratory data	
	All-cause mortality	1.3%	2.3%	1.97 [1.59 - 2.42]	NR	2.02 [1.63 - 2.52]		NR
Sampalis 2006 [63]	All-cause mortality	3.4%	4.8%	NR	NR	NR	NR	NR

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Singh 2020 [64]	CVD event	1.8%	2.4%	0.78 [0.61 - 1.00]	0.045	0.80 [0.62 - 1.02]		0.07
	Ischemic heart disease	1.0%	1.3%	0.82 [0.59 - 1.14]	0.2	0.85 [0.61 - 1.19]	Age, BMI, sex, smoking, alcohol consumption, ethnicity and social deprivation status	0.3
	HF	0.4%	0.7%	0.55 [0.33 - 0.90]	0.02	0.57 [0.34 - 0.96]		0.03
	Stroke	0.7%	0.8%	0.91 [0.62 - 1.35]	0.6	0.98 [0.66 - 1.45]		0.9
	All-cause mortality	1.7%	2.8%	0.67 [0.53 - 0.85]	0.001	0.70 [0.55 - 0.89]		0.004
	AF	1.2%	1.3%	0.94 [0.69 - 1.28]	0.7	0.93 [0.68 - 1.27]		0.7
Sjöström 2007 [76]							Sex, age, weight, height, smoking, DM, previous cancer, biometric data (e.g. circumference of hip, waist, neck), RR	
	All-cause mortality	5.0%	6.3%	0.76 [0.59 - 0.99]	0.04	0.71 [0.54 - 0.92]		0.01
Sjöström 2012 [77]	CV mortality	1.4%	2.4%	0.56 [0.35 - 0.88]	0.01	0.47 [0.29 - 0.76]	Age, BMI, sex, smoking, DM, history of stroke, waist/hip ratio, RR, laboratory data, and use of anti-HT, -DM, or -HCL drugs	0.002
	MACE	9.9%	11.5%	0.83 [0.69 - 1.00]	0.05	0.67 [0.54 - 0.83]		<0.001
	MI	6.1%	6.7%	0.88 [0.69 - 1.12]	0.30	0.71 [0.54 - 0.94]		0.02
	Stroke	4.6%	5.4%	0.82 [0.62 - 1.08]	0.15	0.66 [0.49 - 0.90]		0.008
Sundström 2017 [78]	HF	NR	NR	0.54 [0.36 - 0.82]	NR	NR	NR	NR
	MACE	NR	NR	0.58 [0.46 - 0.74]	NR	NR	NR	NR

Table S1. Summary of the effects of bariatric surgery on major cardiovascular endpoints *(continued)*

First author / pub year	Event	Event rate intervention group	Event rate control group	Unadjusted hazard ratio for endpoint	p value	Adjusted hazard ratio for endpoint	Variables used in adjustment model	p value
Thereaux 2019 [65]	All-cause mortality (RYGB)	NR	NR	0.64 [0.52 - 0.78]	<0.0001	NR	NR	NR
	All-cause mortality (SG)	NR	NR	0.38 [0.29 - 0.50]	<0.0001	NR	NR	NR
Wong 2021 [66]	All-cause mortality	0%	6.8%	NR	NR	NR	NR	NR
	CV disease	3.6%	9.1%	0.53 [0.25 - 0.86]	0.015	NR	NR	NR
	MI	0.7%	1.5%	0.53 [0.13 - 2.28]	0.397	NR	NR	NR
	Stroke	0.7%	2.8%	0.81 [0.37 - 1.79]	0.605	NR	NR	NR
	HF	2.3%	3.4%	0.28 [0.07 - 1.17]	0.082	NR	NR	NR

AF atrial fibrillation; ASCVD atherosclerotic cardiovascular disease; BMI body mass index; BP blood pressure; CAD coronary artery disease; CKD chronic kidney disease; CV cardiovascular; DCG Diagnostic Cost Group; DM Diabetes Mellitus; HbA1c hemoglobin A1c; HCL hypercholesterolemia, HF heart failure; HTN hypertension; MACE major adverse cardiovascular event; MI myocardial infarction; NR not reported; PAD peripheral arterial disease; PCI percutaneous coronary intervention; PCD pulmonary circulation disease; RYGB Roux-en-Y gastric bypass, SES socioeconomic status, SG sleeve gastrectomy

Table S2. Summary of the qualitative assessment according to Newcastle-Ottawa Scale

Studies	Selection				Comparability	Outcome			Conclusion
Author/pub year	**1**	**2**	**3**	**4**	**1**	**2**	**1**	**2**	**3**	
Adams 2007	1	0	1	1	0	1	1	1	0	Good
Alkharaiji 2019	1	1	1	1	1	1	0	1	0	Poor
Aminian 2019	1	1	1	1	0	1	1	0	0	Poor
Ardissino 2020	1	1	1	0	0	1	1	0	0	Poor
Arterburn 2013	1	1	1	1	0	1	0	0	0	Poor
Arterburn 2015	1	1	1	1	1	1	1	1	0	Good
Benotti 2017	1	1	1	1	0	1	1	1	0	Good
Brown 2020	1	1	1	0	0	1	1	0	0	Poor
Busetto 2007	1	0	1	1	0	1	1	1	1	Good
Carlsson 2020	1	1	1	1	1	1	1	1	0	Good
Ceriani 2019	1	1	1	1	0	1	1	1	0	Poor
Courcoulas 2021	1	0	1	1	0	1	1	1	0	Fair
Douglas 2015	1	1	1	1	0	1	1	0	1	Good
Doumouras 2020	1	0	1	1	0	1	0	0	1	Poor
Eliasson 2015	1	0	1	1	0	1	1	0	0	Poor
Fisher 2018	1	0	1	0	0	1	1	0	0	Poor
Höskuldsdóttir 2021	1	0	1	1	0	1	1	0	0	Poor
Jamaly 2019	1	1	1	1	0	1	1	1	1	Good
Jamaly 2016	1	1	1	1	0	1	1	1	1	Good
Lent 2017	1	1	1	1	0	1	1	1	0	Good
Liakopoulos 2018	1	1	1	0	0	1	1	0	0	Poor
Liakopoulos 2020	1	1	1	1	0	1	1	0	0	Poor
Lundberg 2021	1	1	1	1	0	1	1	0	0	Poor
Lynch 2019	1	0	1	1	0	1	1	1	0	Good
MacDonald 1997	1	1	1	1	0	0	1	1	0	Poor
Michaels 2020	1	1	1	0	0	1	1	1	0	Good
Moussa 2020	1	1	1	0	0	1	1	1	0	Good
Moussa 2021	1	1	1	0	0	1	1	1	0	Good
Perry 2008	1	1	1	1	0	1	1	0	0	Poor
Pontiroli 2020	1	0	1	1	0	1	1	1	0	Good
Rassen 2021	1	0	1	1	0	1	1	0	0	Poor
Reges 2018	1	0	1	1	0	1	1	0	1	Good
Sampalis 2006	1	0	1	1	0	1	1	0	0	Poor
Singh 2020	1	1	1	1	0	1	1	0	0	Poor
Sjöström 2007	1	1	1	1	0	1	1	1	1	Good

Table S2. Summary of the qualitative assessment according to Newcastle-Ottawa Scale *(continued)*

Studies	Selection				Comparability		Outcome			Conclusion
Author/pub year	**1**	**2**	**3**	**4**	**1**	**2**	**1**	**2**	**3**	
Sjöström 2012	1	1	1	0	0	1	1	1	1	Good
Sundström 2017	1	0	1	1	1	1	1	0	1	Good
Thereaux 2019	1	1	1	1	0	1	1	1	1	Good
Wong 2021	1	1	1	1	0	1	1	0	0	Poor

The Newcastle-Ottowa scale accredits a 1 (=yes, when adequate quality was assessed) or 0 (=no) for specific point in three subcategories.

Selection

1. Representativeness of the exposed cohort
2. Selection of the non-exposed cohort
3. Ascertainment of exposure
4. Demonstration that outcome of interest was not present at start of study

Comparability of cohorts on the basis of the design or analysis controlled for confounders

1. The study controls for age, sex and marital status
2. Study controls for other factors

Outcome

1. Assessment of outcome
2. Was follow-up long enough for outcomes to occur? Minimum of 5 years
3. Adequacy of follow-up of cohorts

The Newcastle-Ottawa scales was than converted to good, fair, and poor quality study based on combining scores from these subcategories:

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Table S3. Evidence profile assessment according to GRADE framework[1]

		Quality assessment					Summary of findings*			Quality
Outcome	No. of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	Publications bias	HR (95% CI)	p-value	Plausible confounding	
All-cause mortality	21 (observational studies)	No serious limitations	Serious inconsistency: I^2=78%, p<0.001	No serious indirectness	No serious imprecision	No serious publication bias	0.55 (0.49-0.62)	<0.001	No plausible confounding	Very low
Atrial fibrillation	5 (observational studies)	No serious limitations	Serious inconsistency: I^2=75%, p=0.002	No serious indirectness	Serious imprecision: wide confidence intervals	No serious publication bias	0.82 (0.64-1.06)	0.120	No plausible confounding	Very low
Heart failure	8 (observational studies)	No serious limitations	Serious inconsistency: I^2=71%, p<0.001	No serious indirectness	No serious imprecision	No serious publication bias	0.50 (0.38-0.66)	<0.001	No plausible confounding	Very low
Myocardial infarction	9 (observational studies)	No serious limitations	Serious inconsistency: I^2=82%, p<0.001	No serious indirectness	No serious imprecision	No serious publication bias	0.58 (0.43-0.76)	<0.001	No plausible confounding	Very low
Stoke	9 (observational studies)	No serious limitations	Serious inconsistency: I^2=80%, p<0.001	No serious indirectness	No serious imprecision	No serious publication bias	0.64 (0.53-0.77)	<0.001	No plausible confounding	Very low

*Assessment of dose-response was not applicable in this systematic review and meta-analysis and was thus left out of the GRADE assessment

[1]Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD. PMID: 18436948; PMCID: PMC2335261.

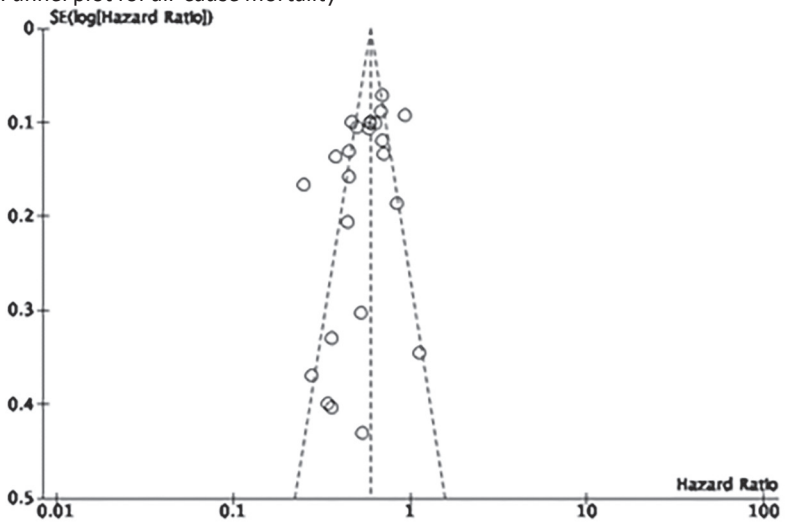
Table S4. Analysis of heterogeneity and publication bias

Heterogeneity and publication bias

Outcome parameter	Chi-squared	df	p-value	I^2	Egger's test
All-cause mortality	109.49*	23	<0.00001	79%	0.026

*P<0.05

Funnel plot for all-cause mortality



CHAPTER 10

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Obesity is a multifactorial, complex disease that affects millions worldwide. The prevalence of obesity has more than doubled since 1980 and has not yet reached a plateau phase.(1) Moreover, over the next decades, obesity prevalence is expected to increase even further. A recent study focusing on obesity prevalence in the Unites States predicted an increase in obesity prevalence (BMI 30-35 kg/m^2) to 49% in the general population, and that severe obesity (BMI>35 kg/m^2) will affect 24%.(2) Countless initiatives to treat or mitigate the increase of obesity have not yet proved efficient enough to alter the course of this obesity pandemic. Bariatric surgery is currently the most efficient treatment option for patients with severe obesity. However, non-operative therapy to prevent or treat overweight or obesity should be the main focus of future research. Drugs that induce weight loss and metabolic improvements are promising, especially drugs that were originally developed for treatment of type 2 diabetes mellitus, like glucagon-like peptide 1 agonist (GLP-1) receptor agonist and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. For example semaglutide, a GLP-1 inhibitor, has shown to effectively reduce weight in patients with obesity, even those who are non-diabetic.(3) Other trials have shown that liraglutide, another GLP-1 receptor agonist, cannot only effect body weight but in doing so also reduces AHI in known OSA patients, who are obese but non-diabetic.(4) Still, these results are less effective than those rendered by surgery. On the other hand, application of drugs is less invasive, and may therefore pose a great treatment option in the future for patients with pre-morbid obesity, or those with a lower BMI but with an obesity-related comorbidity, such as OSA or cardiovascular (CV) disease. In addition, considering that in most countries only 1% of patients that is suitable for bariatric surgery has access to surgery, and that the general population is aging with multi-comorbidities with potentially unfavorable operative risks, non-surgical treatment of obesity hopefully provides a (partial) answer to the growing demand for treatment. However, confirmation of these findings in large studies, and long-term results of weight loss, comorbidity remission, and drug-related adverse events are needed to establish the role of these drugs. Currently, bariatric surgery remains the mainstay of treatment for severe obesity. Despite sustainable and significant effects of surgery with an acceptable safety profile, progress can still be made in this field. Therefore, this thesis focused on providing more insight in specific obesity-related comorbidities, i.e. obstructive sleep apnea and several cardiovascular diseases, in order to optimize perioperative care and postoperative outcomes.

Part A - Obstructive sleep apnea in patients undergoing bariatric surgery

For surgeons and other health care providers in bariatric surgery centers, a strong argument in the choice of perioperative care is safety. The identification

of obesity-related comorbidities during preoperative evaluation is aimed at eliminating preventable adverse events after surgery. In part A of this thesis, we evaluated postoperative outcomes in relation to different types of perioperative care strategies that target (suspected) OSA. In **Chapter 2** we found a very low occurrence of adverse events (0.6%) that were potentially related to OSA, when patients who underwent bariatric surgery were under postoperative surveillance with pulse oximetry and supplemental oxygen. This seems acceptable, given that patients with a history of OSA and CPAP treatment had a complication rate of 0.8% in this study. In **Chapter 3,**. In this study we compared two types of preoperative assessment of unrecognized OSA in bariatric patients; polysomnography (PSG) and polygraphy (PG). In this study, we found no difference in OSA related complications. PG is a less invasive diagnostic test that patients can undergo at home instead of in-laboratory. Due to the omission of electroencephalography in PG, the distinction of sleep and awake state cannot be made, which makes the measurements of apneas and hypopneas less sensitive, and usually results in lower AHI scores. Therefore, some patients with mild OSA might stay undiagnosed. Comparative studies of these diagnostic tools have not been performed in bariatric patients, but in accordance with literature of general OSA patients, we found that PSG renders higher rates of OSA and more patients with moderate or severe disease. However, a relation to clinical outcomes such as higher rates of complications or more admissions to the intensive care unit (ICU) was not found. It can be hypothesized that patients prone to OSA-related complications due to their severe undiagnosed disease, are identified either way. This however is not unequivocally supported by current literature, that often fails to find a connection between OSA severity and incidence of complications. In future studies, it would be interesting to investigate if there is a correlation between OSA severity in bariatric patients and occurrence in postoperative complications. In **Chapter 4**, we retrospectively analysed 2872 patients who had undergone formal sleep studies (polygraphy or polysomnography). We did not find a significant correlation between disease severity and complications. However, we did find slightly higher percentages of OSA-related complications in the group with moderate or severe OSA, i.e. 1.3% and 1.4%, compared to patients with no OSA or mild disease, respectively 0.7% and 0.3%. We also looked at predictors for OSA prevalence in this bariatric population. Previous studies have evaluated this too, but only in relatively small studies. We confirmed predictors reported by other authors such as male gender, age, preoperative BMI, preoperative waist circumference, and hypertension. However, we also found a new predictor: dyslipidaemia. Non-bariatric studies have suggested a correlation between OSA and deregulation of lipid metabolism due to intermittent hypoxia.(5) Unfortunately, even combined with data from a large cohort, data on this correlation are too not conclusive, and should be confirmed in larger cohorts before dyslipidaemia can be incorporated in screening questionnaires for OSA in

bariatric patients. This raises the question whether future research should focus on improving or adjusting currently used screening questionnaires. In many ways, a high quality screening questionnaire would solve a large part of the clinical issue of undiagnosed OSA in bariatric patients. Only patients at high-risk of having clinically relevant OSA would then have to undergo a sleep study. It seems logical that many bariatric clinics currently apply screening questionnaires. The STOP-BANG questionnaire is most frequently used, and is accepted as an effective screening tool in general surgery patients with a normal BMI (i.e. 18 – 25 kg/m^2). However, as obesity and obesity-related risk factors are criteria for the STOP-BANG cut off score, sensitivity and specificity to identify moderate or severe OSA are lower in bariatric patients: 86% and 28%, respectively.(6) In a large bariatric cohort of, the area under the curve for the STOP-BANG questionnaire was 0.74 (0.691-0.788), and other evaluated tools had similar outcomes.(7) The generally accepted lower boundary for an area under the curve of 0.8 in diagnostic models is thus not achieved by current screening tools. It seems unlikely that these prediction models can completely substitute routine sleep studies (i.e. PG or PSG) in these patients.

Looking towards a solution, we hypothesized if continuous pulse oximetry (CPOX) following bariatric surgery could substitute preoperative routine OSA-screening with PG. In **Chapter 5**, this hypothesis is elaborately discussed in the protocol of the POPCORN study. Applying CPOX as perioperative care, all bariatric patients are assumed to have OSA, do not undergo preoperative screening, and postoperative care is aimed at preventing long-lasting apneas that could induce hypoxemia and consequently, an adverse event. In the POPCORN trial, CPOX is compared with routine PG and consequent start of CPAP treatment if OSA is diagnosed. We hypothesized that CPOX is similar in effectiveness compared with routine screening with PG and CPAP, but related to lower costs as no polygraphy has to be performed, and patients do not have to visit a pulmonologist or dedicated CPAP-nurse in the outpatient clinic. Outcomes of the POPCORN study are described in **Chapter 6 and 7**. The main findings are that these perioperative care strategies are similar in outcomes: quality-adjusted life years are similar, but costs related to routine PG testing are higher. Also, more scheduled ICU admissions are necessary, as not all patients tolerate CPAP treatment. Unscheduled ICU admission was similar in both groups, as were general complication rates and OSA-related complications. Patients' self-reported outcomes such as quality of life, sleep-related quality of life and sleepiness symptoms are similar between groups at all timepoints; from preoperative baseline measurements to one year after surgery. This shows that a hypothesized result of leaving patients undiagnosed with OSA in the CPOX group, does not result in clinically worse outcomes. In **Chapter 6**, we analyzed the effectiveness of CPAP implementation in preoperatively diagnosed patients

and established that adherence to CPAP was lower than expected. Remarkably, despite (consensus-based) bariatric guidelines that advocate routine PG and CPAP treatment, no large cohorts have ever evaluated the adherence of bariatric patients to CPAP in the perioperative period. This is surprising because of the well-known low adherence rates in the symptomatic general OSA population. CPAP is difficult to tolerate by some, due to nasal congestion, claustrophobia and impact on relational sleeping environment. Even though bariatric patients can be expected to be motivated to use CPAP because this is a prerequisite to safely undergo surgery, one could also argue that bariatric patients are often asymptomatic and are therefore clinically less rewarded for therapy compliance. Regardless of motives, effect of this type of perioperative care is completely dependent on good CPAP compliance. Therefore, the aim of this subgroup analysis was to compare CPAP adherence in POPCORN patients with newly diagnosed OSA with bariatric patients with a history of OSA. We found significantly lower rates of CPAP adherent patients at all time points in preoperatively diagnosed patients. Before surgery, 15% had no or inadequate adherence, which increased to 73% of patients within six months of surgery. Therefore, our results add clinically important data to the subject of perioperative care of OSA, as CPAP adherence is not routinely mentioned in bariatric studies. We hope that the data and conclusions from our prospective study, mainly presented in **Chapter 7**, will be incorporated in future bariatric guidelines. The most recent guideline (8) only evaluates two topics with regard to OSA. First, the question whether patients should be screened for OSA or not is answered with a conditional recommendation due to low grade evidence with high risk of bias. The two evaluated options are: a STOP-BANG questionnaire or a preoperative PSG. The authors of the guideline concluded that a STOP-BANG questionnaire can be considered, as they anticipate that this is more cost-effective than routine PSG. However, if OSA is suspected, a PSG should be performed. Unfortunately, no other alternatives were explored, which we think is a pity as alternatives like CPOX show promising results and access to costly and time-consuming PSGs may be restricted in bariatric clinics. Second, the authors state in a strong recommendation that perioperative CPAP should be considered in patients with severe OSA. Again, no other alternatives than CPAP compared with no treatment are explored.

An important and recurrent limitation mentioned in **Chapters 2, 3, 4, 6, and 7**, merits attention. The sample size of all cohorts are too small to make a definitive statement on safety comparing several types of OSA management and preventing OSA-related adverse events. Despite large patients cohorts, with respectively 5682, 1464, 2872, 404, and 1390 patients (disclaimer: Chapter 3 and 4 had some overlap in patients, as well as Chapter 6 and 7), and low OSA-related complication rates (ranging from 0.6 to 1.5%) in all types of comparisons between

types of OSA management, the studies were never adequately powered. As mentioned in the discussion of **Chapter 6**, a sample size calculation to make such a definitive statement would require a study including 27,634 patients per treatment group, resulting in 55,268 patients in total. This does not seems feasible in prospective, randomized controlled trials. A systematic review and meta-analysis addressing this issue may be a valuable alternative, not to mention that this would result in a higher form of evidence. However, in absence of comparative studies, this is also not expected to be published in the next years. These facts make an evidence-based, high-quality guideline unlikely, and will leave room for discussion on perioperative OSA care in the next coming years. Future studies should focus on large, national comparative studies or cohorts, facilitating a future systematic review and meta-analysis. In this review, new perioperative strategies such as pulse oximetry, should be included and compared with other, more conventional strategies such as using routinely performed sleep studies or STOP-BANG-selected patient groups undergoing bariatric surgery.

In general, the majority of this thesis is dedicated to management of undiagnosed OSA in the bariatric population. Global obesity is still increasing and so is the average BMI of the general surgery patient. It may seem counterproductive to have elaborate literature on undiagnosed OSA in bariatric patients, while general surgery patients with same BMI classes and similar risk factors do not receive similar attention in preoperative assessment. Several notes can be made on similarities and differences between these two populations. The most striking difference is that bariatric care is centralized in the Netherlands. This enables healthcare professionals to form dedicated teams and organize care via highly standardized protocols. Additionally, since the introduction of laparoscopic procedures, the most important development in bariatric care has been the application of enhanced recovery after bariatric surgery (ERABS). In light of ERABS protocols, patients are better educated before hospital admission, allowing faster discharge post-surgery, and healthcare workers are better educated too. Strict protocols have been developed focusing on minimization of per- and postoperative drug administration such as opioids, which enables faster recovery. For OSA patients, less opioids result in less negative influence on respiratory pathways. Early mobilization after returning to the surgical ward is also important to prevents adverse events. The success of ERABS protocols have enabled the next step in bariatric surgery; day care surgery. Despite the previously mentioned differences between bariatric and general surgery, these differences will increasingly dissolve once bariatric procedures are performed in day-care setting. Until now, pilot studies have shown that same day discharge can be safely performed in pre-selected patient groups undergoing sleeve gastrectomy or Roux-en-Y gastric bypass.(9, 10) In all studies reporting outcomes of day-care surgery, only low-risk patients were deemed eligible, meaning that patients with

comorbidities are not represented in these studies. OSA was routinely assessed via sleep studies in all studies, and patients with moderate or severe OSA were excluded. Therefore, future studies should focus on patient-centralized best care, and should be formulated with respect to local facilities and possibilities. Some countries, such as the Netherlands, are well suited for day-care surgery, with close proximity to a hospital in the entire country. Other countries might not be as suitable and there the focus should lie on the least invasive, most cost-effective and safest form of perioperative care, which will probably be an overnight stay in the hospital, compared to a same day discharge. Introduction of day-care will also have implications for OSA strategies and therefore requires more studies. If patients are discharged on the same day of surgery, some form of OSA-screening has to be performed to ensure a safe discharge.

Part B - Cardiovascular diseases and risk factors in bariatric patients

In this part of the thesis, we aimed to critically assess the actual prevalence of CV disease in the elderly population of patients undergoing bariatric surgery. In **Chapter 8**, we described a cohort of 310 patients aged 50 years and older who were scheduled to undergo bariatric surgery. All patients underwent laboratory testing of a single biomarker that is considered most sensitive to detect early or eminent CV disease: N-terminal probrain natriuretic peptide (NT-proBNP). In our cohort, 23% of all patients had elevated levels of NT-proBNP, and were thoroughly assessed by a cardiologist. The work-up included electrocardiography and echocardiography, and showed signs of left ventricular structural and functional remodelling in one third of patients. Although these findings should be regarded as preliminary, with the side-note that future research is needed to confirm our findings in cohorts with different and / or age cut-off limits, these are interesting findings. Many patients that had elevated NT-proBNP levels, did not have a history of CV disease. Given that NT-proBNP has an inverse relation with BMI, this could have the implication that these patients are at risk of development of CV disease later in life. This could also explain the findings of our own systematic review and meta-analysis in **Chapter 9**. In this study, outcomes showed that bariatric surgery reduces (all-cause, and CV-related) mortality and incidence of CV disease in patients with obesity compared with non-surgical treatment. Despite many well conducted and large cohort studies, it became clear that many CV outcomes still warrant more research in bariatric surgery. Randomized controlled trials that aimed to described CV outcomes in patients in randomized controlled trials that compared bariatric surgery with non-surgical care was not available. This is mind-blowing as CV disease (ischemic heart disease) is the leading cause of death worldwide, followed by stroke, and both diseases are related to obesity. Nevertheless, our meta-analysis showed that bariatric surgery can be very effective in reducing incidence of future CV disease, and even all-cause mortality. However, despite the need for prospective, adequate, randomized controlled

trials, it is quite unlikely such a large study will be conducted in the near future. This is due to the fact that it could be regarded as unethical to withhold proven superior treatment (i.e. bariatric surgery) to the control group, in which patients would be suitable to undergo bariatric surgery but are provided with non-surgical care. Potentially, future research including randomized controlled trials might be possible in patients with an obesity class that are currently not eligible for bariatric or metabolic surgery. In the field of metabolic surgery, interesting research on type-2 diabetes has recently been performed in obesity class 1, i.e. BMI 30-35 kg/m^2, with excellent results: diabetes remission was similar in patients with BMI<35 kg/m^2 vs. BMI>35kg/m^2.(11) Arguably, it should be critically reviewed whether invasive surgery can be performed in patients with hypothetical risk of losing too much weight, risk of malabsorption, the burden of life-long indication for taking supplemental vitamins, and safety concerns including risk of major adverse events. The international diabetes guideline was recently re-written, as previous guidelines did not mention bariatric surgery as a treatment option for type 2 diabetes.(12) The guideline states that substantial literature is available (based on randomized controlled trials) that surgery achieves adequate glycemic control, and should be recommended in patients with BMI ≥40 kg/m^2, or patients with BMI 35.0-39.9 kg/m^2, when hyperglycemia is inadequately controlled by non-surgical treatment. Authors of the new guideline even state that bariatric surgery can be considered for patients with type 2 diabetes and BMI 30.0-34.9 kg/m^2 if optimal non-surgical treatment cannot control hyperglycemia. To circle back to surgery in patients with CV disease and at high-risk of development of a major adverse cardiac events (MACE) later in life (myocardial infarction, stroke, heart failure), research that involves patients in lower BMI classes might provide a unique opportunity to analyze the metabolic component of bariatric surgery and the long-term effect on CV outcomes. Metabolic effects of bariatric surgery, aside from weight loss, were illustrated in a retrospective, but large single center study including more than 7,000 patients, comparing bariatric surgical patients to patients with dietary and lifestyle interventions. Their findings showed that a substantial role for metabolic effects following bariatric is plausible in preventing MACE (a composite endpoint including all-cause mortality, coronary artery and cerebrovascular events, HF, nephropathy and AF).(13) In surgical patients, the risk of developing MACE was decreased significantly after losing 10% of their weight, while non-surgical patients needed to lose 20% to achieve the same reduction. Subgroup analysis showed even more outspoken effects; surgical patients required 5% weight reduction to achieve the same decrease in all-cause mortality compared to 20% in conservatively managed patients. In many ways, it will be interesting and necessary to review the effect of bariatric, or metabolic, surgery on CV outcomes.

We also noted in **Chapter 9**, that of all outcomes, only AF did not show a significant reduction in hazard ratio (HR) following bariatric surgery: for surgery patients compared with controls HR was 0.82, 95% confidence interval 0.64 – 1.06, P= 0.12. This can be somewhat surprising, as other observational studies not only show correlation between AF and obesity, but also mention a potential link to OSA. Treatment for OSA increases the success rate of treatment for AF by ablation, and vice versa. Future research should be performed to further evaluate the link between obesity, AF and OSA, and the effect of weight reduction on both disorders to personalize care for patients with multi-comorbidity.

Another mediating factor between obesity, CVD and particularly HF with mid-range or preserved ejection fraction, appears to be increased volumes of epicardial fat. There is a growing body of evidence that shows that epicardial fat plays an important role in the development of obesity-related HF.(14) The effect of bariatric surgery on epicardial fat depots seems effective in pilot studies, and might form an interesting subject for future research.(15)

Another interesting debate is bariatric surgery in elderly patients: potentially higher risks, but also higher gains? Patients in bariatric surgery are usually referred to as 'elderly' when aged >60 or >65 years, and are frequently considered unsuitable for bariatric surgery. A recent study showed that patients with an average age of 62 had significant HR in all endpoints compared with no surgery: in mortality, new-onset HF, and myocardial infarction.(16) These endpoint were achieved during 4 years of median follow-up, which is relatively short for the incidence of CV outcomes. These results might indicate that obese patients with a high risk profile of development of MACE might greatly benefit from surgically induced weight loss and metabolic effects of bariatric surgery, but more data are needed to confirm these findings and alter guidelines for elderly patients.

Conclusion and future perspectives

This thesis has evaluated several options of perioperative care of OSA and CV disease in patients undergoing bariatric surgery, and reflected on the related outcomes. Our results demonstrate that minimally invasive strategies to handle potentially undetected OSA are cost-effective and safe compared with standard care. Additionally, many patients undergoing bariatric surgery suffer from CV risk factors, and benefits of bariatric surgery on CV outcomes (mortality and incidence of CV disease) seem evident.

Further research should focus on novel challenges that are introduced by day-care with regard to perioperative care of undetected OSA. Studies should also attempt to elucidate the best type of treatment for obese patients at risk of developing CV disease that might potentially entail offering surgery to patients

in lower BMI-classes. Lastly, future research should focus on therapy options that prevent evolvement of overweight into obesity, and should explore non-surgical treatment options.

All of these future studies should bear in mind that the quality of bariatric care is dependent on a multidisciplinary approach, as is in accordance with the current guidelines.(8, 12, 17, 18) Additionally, as bariatric (or metabolic) surgery is an evolving field in a globally expanding obese population, research should justify the utilization of health care resources to apply the available funds in the best way possible.

In conclusion, pulmonary and cardiovascular diseases are highly related to obesity and thus highly prevalent in bariatric patients, but also benefit greatly from surgically-induced weight loss. Care for bariatric patients prone to cardiopulmonary disease should be provided in a multidisciplinary approach, and should be further evaluated to be as safe, cost-effective, and minimally invasive as possible.

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CHAPTER 11

Summary

SUMMARY

This thesis aimed to provide new insights in preoperative assessment of both obstructive sleep apnea (OSA) and cardiovascular disease in patients undergoing bariatric surgery. In addition, other relevant aspects, such as incidence of these diseases at time of screening for a bariatric surgery, risk profiles, and effectiveness of weight reduction on disease were also evaluated. Many of the studies focused on providing evidence-based tools to provide optimal patient care, but also on sensible utilization of healthcare resources.

Part A - Obstructive sleep apnea in patients undergoing bariatric surgery
In **Chapter 2** we retrospectively evaluated the surgical outcomes of patients who are unaware of their OSA status, who were not preoperatively assessed for disease prevalence, but rather monitored with continuous pulse oximetry (CPOX) after surgery. We compared these patients with patients with a history of OSA who adhered to continuous positive airway pressure (CPAP) treatment adequately. Outcomes showed that patients who had CPOX after surgery had 0.6% OSA-related complications, versus 0.8% of patients with OSA and CPAP. This was not a significant difference, and demonstrates that CPOX did not increase perioperative risk in this population, as all outcomes, such as mortality, intensive care unit (ICU) admissions, and all other complications were similar between groups.

Chapter 3 and 4 reported surgical outcomes of bariatric patients who underwent screening for OSA before surgery using homed-based polygraphy or in-hospital polysomnography. In **Chapter 3**, the comparison between these two types of sleep studies is made, and we found several differences in clinical outcomes. Using polygraphy, patients can undergo the sleep study at home instead of in the hospital like is the case with polysomnography. Although polygraphy is less invasive for patients to undergo, several measurements are eliminated compared with polysomnography, because the latter also conducts an electroencephalography. This enables the distinction between sleep and awake state, which makes the measurements of apneas and hypopneas more sensitive, and usually results in higher and thus more severe forms of diagnosed OSA. We saw that OSA was diagnosed in 79% of 271 patients undergoing polysomnography, compared with 64% of 1193 patients undergoing polygraphy (p<0.001). This led to implementation of CPAP in 52% and 27% of patients, respectively. We also analysed predictors for initiation of CPAP treatment using the entire study population (n=1464). The predictors identified in this analysis were all well-known risk factors for OSA: male gender, BMI ≥ 50, hypertension, and age ≥ 50, but also the diagnostic tool polysomnography, compared with polygraphy. No difference was seen in OSA-related complications between

groups. In **Chapter 4**, we retrospectively analysed 2872 patients who underwent preoperative OSA-screening, and aimed to elucidate risk factors for prevalence of OSA and analyse incidence of OSA-related complications. We found that male gender, age, preoperative BMI, preoperative waist circumference, hypertension, and dyslipidaemia were significant predictors for prevalence of OSA. Related complications in different AHI classes (no OSA vs. mild, moderate and severe OSA) were not significantly different, although patients with no or mild disease had less complications compared with moderate or severe disease; 0.7% and 0.3% versus 1.3% and 1.4%, p=0.100.

The protocol for a prospective study (POPCORN) that compared continuous pulse oximetry (CPOX) with routine OSA screening using polygraphy (PG) was described in **Chapter 5**, and outcomes are presented in **Chapter 6 and 7**. The aim was to evaluate the cost-effectiveness of these two perioperative care strategies. The hypothesis behind this study was that bariatric centres can either screen every patient for the presence of OSA, as is standard care in many facilities, or all patients can be considered potentially having OSA, and the focus of postoperative care is to prevent long lasting apneas that induce severe hypoxemia and consequently result in cardiopulmonary or thromboembolic complications. Surgical patients are at risk of experiencing these types of complications because of respiratory depressant drugs that are administered during surgery. In addition, cost-effectiveness, quality of life, sleepiness symptoms, and surgical outcomes such as complications, unscheduled transfers to ICU for cardiopulmonary reasons, reoperations and readmissions in the first 30 days after surgery were evaluated.

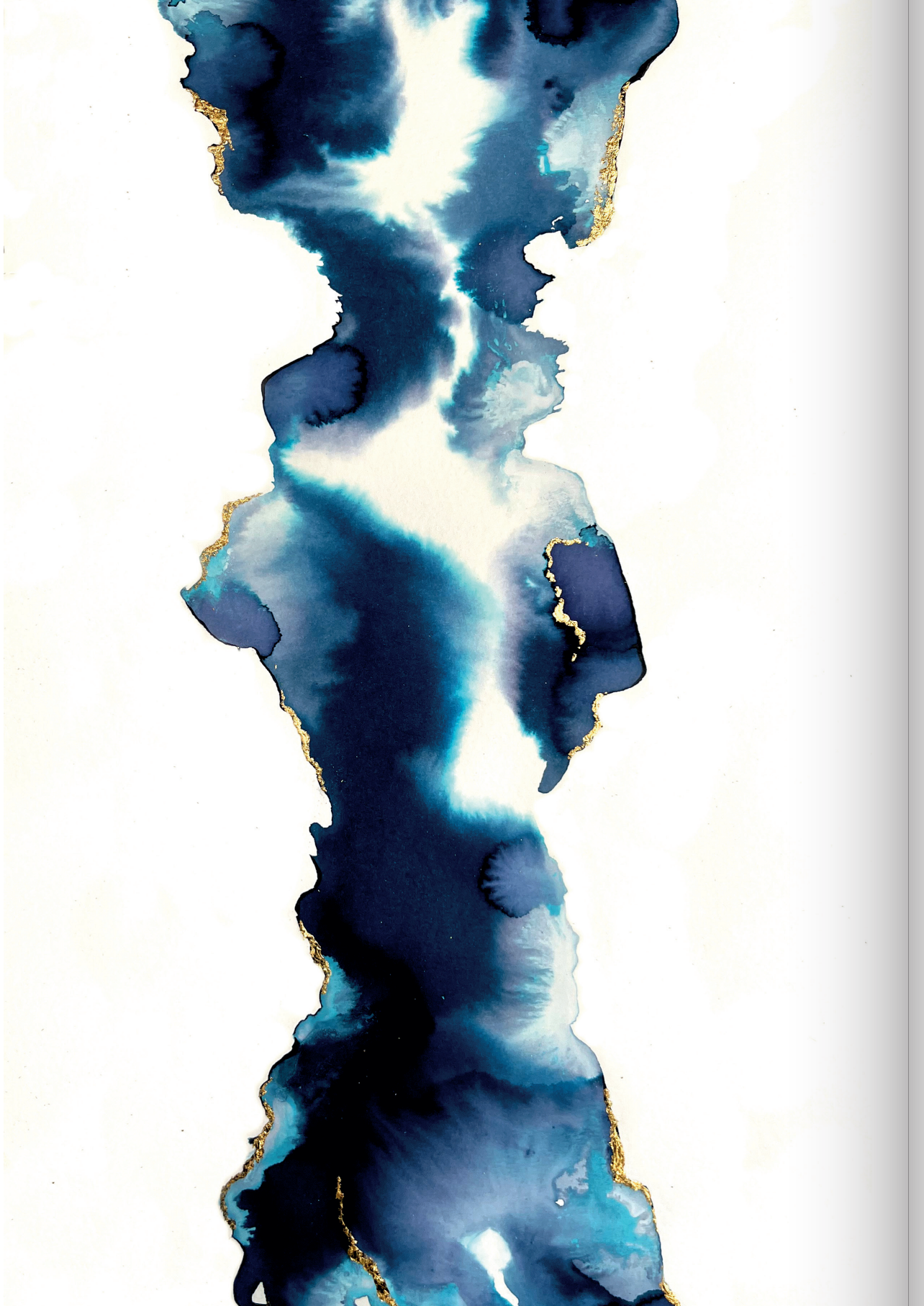
To assess the clinical impact of preoperative PG with consequential CPAP treatment, we performed a subgroup analysis of patients from the POPCORN study in **Chapter 6**. This study describes CPAP adherence in patients who were preoperatively diagnosed with OSA, and these were compared to patients who had a history of OSA and CPAP treatment. In order for CPAP treatment to be adequate, it should be applied at least 4 hours a night. Before surgery, the group with newly diagnosed patients had significantly more inadequate CPAP users (n=41, 15%) compared with known OSA patients (n=5, 4%, p=0.049). This number accumulated to 73% for newly diagnosed patients at six months after surgery, compared with 39% for patients with pre-existing OSA, respectively (p<0.001). No clinical consequences of inadequate or non-adherence to CPAP were found in the other outcomes, i.e. complications, quality of life, and signs of daytime sleepiness. The primary outcome of the POPCORN study, cost-effectiveness, was reported in **Chapter 7.** Because several baseline characteristics were significantly different between the CPOX group and the PG group, propensity score matching was performed and main outcomes were described in 1090

patients. Analyses showed that patients in both intervention arms had similar quality adjusted life years at one year after surgery; with an increase from 0.77 (same baseline measurement in both arms) to 0.88 and 0.89 in the CPOX and PG arm, respectively. Other clinical outcomes such as complications, unanticipated ICU admissions, readmissions, and (sleep-related) quality of life were similar between the groups. Although the effectiveness was thus the same, costs were different. From a healthcare perspective, CPOX was lower in costs; €-534 (95% CI €-896 to €-137). This difference in favor of CPOX originated from the additional costs that were encountered in the PG group: the actual sleep study, more outpatient clinic appointments with the pulmonologist and dedicated CPAP nurse, as well as several scheduled ICU admissions in patients who were diagnosed with moderate to severe OSA, but were unable to tolerate CPAP.

Part B - Cardiovascular diseases and risk factors in bariatric patients

Obesity is increasingly recognized as a risk factor for almost all cardiovascular (CV) diseases. However, hardly any research on the incidence of specific CV diseases in bariatric patients has been performed and guidelines do not provide specific advice on cardiac pre-operative assessment. In **Chapter 8**, we therefore aimed to determine the prevalence and incidence of subclinical or unrecognized CV disease in patients undergoing bariatric surgery. We preoperatively assessed a biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients aged 50 years and older, as NT-proBNP is a well-known indicator to detect early CV disease. In this study, 310 consecutive patients were analyzed, of whom 72 patients (23%) had elevated levels of NT-proBNP. These patients were referred to a cardiologist for thorough assessment, including an electrocardiogram (ECG) and an echocardiography. Six patients underwent additional diagnostics, including 24-hour Holter ECG, functional MRI, and coronary angiography with or without percutaneous coronary intervention. Of the 67 patients who underwent thorough cardiac evaluation, we found echocardiographic evidence of structural and/or functional remodeling in 25 patients (37%). Interestingly, only four of these 25 patients had a medical history of heart failure. Clinical consequences of the screening were mostly drug-related; drug regimens were altered in nine patients. We concluded that NT-proBNP can be used as a noninvasive, simple, and inexpensive diagnostic tool that can detect new structural and/or functional cardiac remodeling in a high-risk patient population. Compared to most literature in cardiologic journals, patients described in **Chapter 8**, aged of 50 to 65 years, are regarded as relatively young. However, given the high number of risk factors for development of CV disease, such as obesity, hypertension, diabetes, systemic inflammation, we were interested in the effect that surgically induced weight loss would have on CV outcomes. In **Chapter 9** we performed a systematic review and meta-analysis to answer this question, and more specifically look into the difference between obese subjects, comparing long term outcomes of bariatric

patients to their obese counterparts that did not undergo bariatric surgery. We found that bariatric patients have a pooled hazard ratio (HR) of all-cause mortality of 0.55 compared to controls. For CV-related mortality, HR was 0.59. Other outcomes were all in favor of bariatric surgery; HR for heart failure was 0.50, myocardial infarction HR 0.58, and stroke HR 0.64. Only the outcomes of atrial fibrillation did not show significant difference; bariatric patients had an HR 0.82 when compared with controls (95% confidence interval 0.64–1.06, P= 0.120).



APPENDIX

Samenvatting in Nederlands

SAMENVATTING

Het doel van dit proefschrift was om nieuwe inzichten te verkrijgen in de zorg van zowel obstructief slaap apneu (OSA) als cardiovasculaire aandoeningen bij patiënten die bariatrische chirurgie ondergaan. In dit proefschrift zijn daarom de specifieke zorg rondom de operatie, de incidentie van deze ziekten in patiënten met obesitas, de risicoprofielen, en de effectiviteit van gewichtsreductie op deze ziekten geëvalueerd. Veel van deze studies richten zich op evidence-based manieren om optimale en veilige patiëntenzorg te leveren, maar bekijken ook hoe we beschikbare middelen in de gezondheidzorg op de juiste manier in kunnen zetten.

Deel A - Obstructief slaap apneu in patiënten die bariatrische chirurgie ondergaan

In **Hoofdstuk 2** hebben we retrospectief data geanalyseerd die gaan over chirurgische uitkomsten van patiënten die bariatrische chirurgie ondergingen. Deze patiënten wisten niet wisten of ze wel of niet OSA hadden, en er werd geen preoperatieve evaluatie verricht om hierachter te komen. In plaats daarvan werden deze patiënten na de operatie gemonitord met een continue pulsoximeter (CPOX), wat het zuurstofgehalte in het bloed meet. We vergeleken deze patiënten met andere patiënten die wel een OSA diagnose hadden en daar ook behandeling voor kregen, namelijk continuous positive airway pressure (CPAP). De resultaten lieten zien dat 0,6% van de patiënten die na de operatie gemonitord werden met CPOX een OSA-gerelateerde complicatie opliepen, versus 0,8% van de patiënten met OSA die daarvoor CPAP gebruikten. Het verschil tussen de groepen was niet significant, en laat zien dat CPOX het risico op OSA-gerelateerde complicaties niet verhoogt in deze populatie. Ook waren de andere uitkomsten, zoals mortaliteit, opnames op de intensive care, en alle andere complicaties hetzelfde in beide groepen.

Hoofdstuk 3 en 4 beschrijven de chirurgische uitkomsten van bariatrische patiënten die preoperatief gescreend werden op OSA d.m.v. een slaaponderzoek. Patiënten ondergingen een polygrafie, een onderzoek dat thuis uitgevoerd kan worden, of een polysomnografie, wat in het ziekenhuis uitgevoerd moet worden. In **Hoofdstuk 3** worden deze twee slaaponderzoeken met elkaar vergeleken, waarbij we meerdere verschillende resultaten vonden tussen beide onderzoeken. Een polygrafie is een minder invasief onderzoek voor patiënten, maar sommige metingen die bij polysomnografie wel worden gedaan, kunnen niet verricht worden tijdens een polygrafie, zoals een elektro-encefalografie. Dit meet de elektrische activiteit van de hersenen, en kan daarvoor het onderscheid maken tussen wakker zijn en slapen. Dit zorgt ervoor dat de apneu en hypopneu metingen nauwkeuriger zijn, welke de ernst van OSA indexeren. Daarom is een diagnose

verkregen door een polysomnografie vaker een ernstigere vorm van OSA, vergeleken met polygrafie. In onze resultaten zagen we dat OSA gediagnosticeerd werd in 79% van de 271 patiënten die polysomnografie ondergingen, vergeleken met 64% van de 1193 die polygrafie ondergingen ($p<0.001$). Naar aanleiding van deze uitkomsten werd CPAP gestart in respectievelijk 52% en 27% van de patiënten. Geen verschil werd gevonden in OSA-gerelateerde complicaties tussen de groepen. We hebben ook analyses gedaan om te voorspellen welke patiënten uit de gehele populatie CPAP moesten gebruiken (n=1464). We hebben daarbij de volgende voorspellers geïdentificeerd, welke allen al bekenden risicofactoren zijn voor het ontwikkelen van OSA: mannelijk geslacht, BMI ≥ 50, hypertensie, leeftijd ≥ 50 jaar, maar ook keuze van slaaponderzoek: namelijk polysomnografie. De conclusie is dat polygrafie weliswaar mensen met een milde OSA diagnose kan missen, en dat minder patiënten met CPAP hoeven te starten, maar dat in onze data er geen aanwijzingen zijn dat dit leidt tot meer OSA-gerelateerde complicaties. In **Hoofstuk 4** hebben we retrospectief alle data geanalyseerd van 2872 bariatrische patiënten die preoperatieve screening voor OSA ondergingen, waarbij risicofactoren geïdentificeerd hebben voor de prevalentie van OSA en complicaties gerelateerd aan OSA. We zagen dat mannelijk geslacht, leeftijd, preoperatief BMI, buikomvang, hypertensie en dyslipidemie significante voorspellers waren voor prevalentie van OSA. Hieraan gerelateerde complicaties waren niet significant verschillend tussen de verschillende groepen; geen OSA vs. milde, gematigde en ernstige OSA, al waren de cijfers voor geen en milde ziekte iets lager dan in de groep met matig of ernstige ziekte; 0,7% en 0,3% vs. 1,3% en 1,4%, p=0,100.

Het studieprotocol van een prospectieve studie die continue pulsoximetrie (CPOX), vergeleek met routinematige screening voor OSA met polygrafie (PG), de POPCORN studie, wordt beschreven in **Hoofdstuk 5**. De uitkomsten hiervan worden beschreven in **Hoofdstuk 6 en 7**. Het doel was om de kosteneffectiviteit van deze twee typen perioperatieve zorg te evalueren. De hypothese hierachter is dat veel bariatrische centra elke patiënt screenen op de aanwezigheid van OSA middels PG, maar je anderzijds ook elke bariatrische patiënten als een potentiële OSA patiënt kan beschouwen. De focus van perioperatieve zorg komt dan te liggen op het voorkomen van langdurende apneus die ernstige hypoxie tot gevolg hebben, en kunnen resulteren in cardiopulmonale of trombo-embolische complicaties. Chirurgische patiënten hebben een toegenomen risico op deze complicaties vanwege de medicatie die tijdens de narcose wordt toegediend, en als nadeel heeft dat de ademprikkel onderdrukt wordt. We hebben gekeken naar uitkomsten: kosteneffectiviteit, kwaliteit van leven, symptomen van slaperigheid en chirurgische uitkomsten zoals complicaties, opnames op de intensive care voor cardiopulmonale problemen, heroperaties en heropnames binnen de eerste 30 dagen na de operatie.

Om het echte effect van een preoperatieve PG met daaropvolgende start van CPAP te analyseren, hebben we een subgroep analyse verricht van patiënten uit de POPCORN studie in **Hoofdstuk 6.** Dit artikel beschrijft de therapietrouw aan de CPAP behandeling van patiënten die voor de operatie de OSA diagnose hebben gekregen, en werden vergeleken met patiënten die al jaren OSA hadden met CPAP therapie. Adequate therapietrouw werd gedefinieerd als minimaal 4 uur gebruik van het CPAP masker per nacht. Voor de operatie hadden de patiënten met een nieuwe OSA diagnose significant meer inadequate therapietrouw vergeleken met de patiënten met bekende OSA: n=41, 15% vs. N=5, 4%, p=0,049. Zes maanden na de operatie was dit percentage van inadequate therapietrouw opgelopen tot 73% voor nieuw gediagnosticeerde patiënten en 39% voor bekende OSA patiënten, p<0,0001. Er werden geen klinische consequenties gezien van inadequate of geheel geen gebruikte CPAP qua complicaties, kwaliteit van leven of symptomen van slaperigheid overdag. De primaire uitkomst van de POPCORN studie, namelijk de kosteneffectiviteit, wordt beschreven in **Hoofdstuk 7**. Aangezien meerdere basiskarakteristieken van de patiëntengroepen significant verschillend waren, hebben we propensity score matching toegepast. De primaire resultaten zijn dan ook beschreven in deze gematchte groep van 1090 patiënten. De resultaten lieten zien dat de quality adjusted life years gelijk waren tussen de groepen ten tijde van één jaar na de operatie, waarbij de basiswaarden van 0,77 in beide groepen is gestegen naar 0,88 in de CPOX groep en 0,89 in de PG groep. Andere uitkomsten zoals complicaties, ongepland intensive care opnames, heropnames en (slaap gerelateerde) kwaliteit van leven waren hetzelfde in beide groepen. De effectiviteit van de interventies was dus gelijk. Echter, de kosten waren verschillend. Vanuit het oogpunt van de gezondheidszorg waren de kosten lager in de CPOX groep: €-534 (95% CI €-896 to €-137), vergeleken met de PG groep. Dit verschil ontstond met name door de extra kosten die de PG groep maakte; de slaaponderzoeken, poliklinische afspraken met longarts of CPAP verpleegkundige, maar ook meer geplande intensive care opnames indien een patiënt matige of ernstige OSA bleek te hebben, en de CPAP behandeling niet verdroeg.

Deel B - Cardiovasculaire aandoeningen en risicofactoren in bariatrische patiënten

Obesitas wordt in toenemende mate herkend als een risicofactor voor bijna elke cardiovasculaire aandoening. Echter, er is tot op heden nog weinig onderzoek gedaan naar de incidentie van de verschillende cardiovasculaire aandoeningen in de bariatrische populatie. Richtlijnen geven daarom weinig specifieke adviezen voor preoperatieve cardiologische analyse. In **Hoofdstuk 8** hebben we daarom gepoogd de prevalentie van subklinische en niet-herkende cardiovasculaire ziekten te identificeren. We hebben preoperatief de biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) bepaald in elke patiënt die bariatrische

chirurgie onderging én ouder was dan 50 jaar, aangezien NT-proBNP een bekende indicator is van vroege cardiovasculaire ziekte. In deze studie hebben we 310 patiënten geanalyseerd, waarvan 72 patiënten een verhoogde waarde van NT-proBNP hadden (23%). Deze patiënten werden vervolgens verwezen naar een cardioloog voor grondige evaluatie, inclusief een elektrocardiogram (ECG) en een echocardiografie. Zes patiënten ondergingen nog aanvullende diagnostiek; zoals een 24-uur Holter ECG, een functionele MRI, en coronaire angiografie met of zonder percutane interventie. Van de 67 patiënten die cardiologische evaluatie ondergingen, vonden we in 25 patiënten (37%) echocardiografische aanwijzingen van structurele en/of functionele remodellering van het hart. Interessant genoeg hadden maar vier van deze patiënten een voorgeschiedenis van hartfalen. De screening resulteerde het meest in aanpassingen van medicijnen, waarbij negen patiënten veranderingen kregen in de cardiovasculaire medicatie. We concludeerden van deze studie dat NT-proBNP gebruikt kan worden als non-invasieve, simpele en goedkope diagnostische meting om nieuwe structurele of functionele remodellering van het hart op te sporen in een hoog-risico populatie. Vergeleken met de meeste cardiologische publicaties, worden de patiënten die in **Hoofdstuk 8** beschreven worden gezien als relatief jong, met een leeftijd tussen 50 en 65 jaar. Echter, gezien de hoge prevalentie van risico factoren voor cardiovasculaire aandoeningen die in deze populatie voorkomt, zoals obesitas, hypertensie, diabetes en systemische inflammatie, waren we erg geïnteresseerd in het effect van gewichtsverlies op het ontstaan van cardiovascuclaire aandoeningen. In **Hoofdstuk 9** hebben we een systematic review en meta-analyse gedaan om deze vraag te beantwoorden. Hierbij keken we specifieker naar de uitkomsten op langer termijn van patiënten die bariatrische chirurgie ondergingen, en vergeleken we deze uitkomsten met vergelijkbare individuen die geen chirurgische behandeling voor obesitas ondergingen. De resultaten lieten zien dat bariatrische patiënten een gepoolde hazard ratio (HR) hadden van 0,55 op algemene sterfte, vergeleken met de controlegroep. Voor sterfte gerelateerd aan cardiovasculaire aandoeningen was de HR 0,59. Andere uitkomsten waren ook allen in het voordeel van de bariatrie groep; HR van hartfalen was 0,59, voor myocardinfarct 0,58, en voor herseninfarct 0,64. Alleen de resultaten van atriumfibrilleren waren niet significant verschillend: bariatrische patiënten hadden een HR van 0,82 vergeleken met de controlegroep, met 95% confidence interval 0,64-1,06, p=0,120.

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Overview of completed training activities

Discipline specific activities

Oral presentations	Year
Congress of Dutch Society for Metabolic and Bariatric Surgery	2018
Congress of International Federation for the Surgery of Obesity and Metabolic Disorders	2018
Congress Chirurgendagen organized by Nederlandse Vereniging van Heelkunde	2019
Congress of Symposium Experimenteel Onderzoek Heelkundige Specialismen	2019
European Congress on Obesity & International Congress on Obesity	2020
Congress of International Federation for the Surgery of Obesity and Metabolic Disorders	2020
Congress of Dutch Society for Metabolic and Bariatric Surgery	2020

Poster presentations	
Congress of European Association for Endoscopic Surgery (EAES)	2019

Conference attendance	
Congress Chirurgendagen organized by Nederlandse Vereniging van Heelkunde	2018
Congress Najaarsdagen organized by Nederlandse Vereniging van Heelkunde	2018
Congress of Dutch Society for Metabolic and Bariatric Surgery (DSMBS)	2019
Up to Date congress on obstructive sleep apnea (OSA)	2019
Congress of International Federation for the Surgery of Obesity and Metabolic Disorders	2019

Participation in masterclass workshop	
Research Talent Academy during congress European Association for Endoscopic Surgery	2018-2019

General courses

Name of the course	Year
Good Clinical Practice (GCP), GCP Central	2018
Robot Surgery - Assistant level, Intuitive Surgical, Inc	2018
Essential Medical Statistics, University of Oxford	2020-2021
Presenting with Impact, Wageningen Graduate Schools	2019
Scientific Writing, Wageningen Graduate Schools	2019-2020
Advanced Trauma Life Support, Advanced Life Support Groep	2020

Assisting in teaching and supervision activities	Year
Supervision of MSc students: Paulina Planjer	2019
Jolien Jonckheere	2020

Other activities	Year
Preparation of research proposal and grant applications	2018-2021
International scientific meetings: participation in international research on benchmark outcomes for bariatric surgery	2019
International scientific meetings: participation in Research Talent Academy course	2018-2019
Scientific meetings, seminars, colloquia Rijnstate	2018-2021
Societally relevant exposure: interview in hospital magazine	2019

Dankwoord

DANKWOORD

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Mijn lieve **Paranimfen**, Leontien en Charlotte. Wat een toppers allebei. Lieve **Le**. Ik had nooit gedacht zo'n ontzettend waardevolle vriendin tijdens mijn promotie te vinden. Jij bent echt een power-mens, heel daadkrachtig, eerlijk en toch heel lief, ik vind het een hele mooie en bijzondere combinatie. In de afgelopen jaren heb ik erg genoten van alle avonden met chardonnay en pasta, wandelingen of koffiedrinken met kleine Stef, of korte werkoverlegjes tijdens het inlopen van hockey, maar bovenal veel lachen. Ik ben trots op hoe je alles combineert en ben heel blij dat je er vandaag bij bent als mijn paranimf. Op naar nog vele jaren vriendschap! Lieve **Char**; mijn twinnie en nu ook paranifm, waar moet ik beginnen? Als kleine kids waren onze favo films al degene waar tweelingen de toon zetten (it takes two & the parent trap), hadden wij een gezamenlijk liefde voor de kleur roze, hockey, kattenfilmpjes, en zelfs tegenwoordig hebben vaak we toch ineens weer dezelfde trui gekocht, en misschien is het daarom ook niet verassend dat we naast alle dingen die wij delen, wij ook dezelfde passie qua werk hebben. Dit resulteerde in gezamenlijke koffiedates in het OLVG, en tegenwoordig ook in het AMC. Ik ben super trots op je, met je recente opleidingsplek chirurgie in de pocket en een prachtig proefschrift in the making! Maar hoe trots ik ook ben, ik waardeer nog veel meer dat jij aan een half woord genoeg hebt, ontzettend attent en liefdevol voor iedereen in je omgeving bent, maar ook iedereen ontzettend kan laten lachen door een goed getimede foto op het strand van Tarifa te midden van pogingen tot kiten, of een lekker diva-achtige outfit niet kan laten liggen. Bedankt voor alles dat je in mijn leven betekent en vandaag hier bent als mijn paranimf.

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het overlijden van Caroline en de overgang naar jouw leven als pensionado, maar je hebt je hier echt ongelooflijk knap doorheen geslagen. Als het even tegenzat in Arnhem en ik belde weer vanuit de trein, was er niets zo fijn dan dat jij mij even verzekerde van het feit dat het allemaal écht goed ging komen. Dankjewel, ook dat jij met al je warmte en aandacht van het nieuwe huis weer ons nieuwe familiethuis weet te maken. Lieve **Pap**, je was tijdens mijn promotietijd niet alleen mijn vader met wie ik altijd kan praten over alles van persoonlijke perikelen, muziek en sporten, maar nu ook tot aan de wetenschap. Ik heb het al een ongelooflijk voorrecht gezien dat we zo veel hebben samengewerkt tijdens mijn proefschrift. Wat begon als een interessant telefoongesprek over de relatie van obesitas en hartfalen, heeft zich uitgemond in een samenwerking tussen jouw afdeling en de bariatrie in Arnhem. We zijn inmiddels meerdere inspirerende meetings, studies met bijbehorende publicaties en een op handen zijnde RCT verder, en ik denk dat we er allebei ontzettend van genieten om samen te werken. Ik ben heel trots op alles wat je hebt bereikt in je carrière, maar dat je daarnaast ons gezin en al je passies ook op de voorgrond hebt weten te houden, zodat er nooit een hockeywedstrijd of balletvoorstelling werd overgeslagen. Lieve Pap en Mam, bedankt voor alles!

Curriculum Vitae

CURRICULUM VITAE

Sophie Laura van Veldhuisen was born on 31st of October 1990 in Groningen, and grew up in the small town of Eelde Paterswolde with her parents and twin sister Charlotte. After obtaining her high school diploma at the Preadinius Gymnasium in Groningen, she went to Seville, Spain for several months to learn Spanish. Afterwards, she went to Costa Rica to do volunteer work and to travel, before returning to the Netherlands.

In 2010, Sophie started her medical studies at the University of Amsterdam. During the bachelor, she participated in research in surgical repair of congenital heart disease. After obtaining her bachelor's degree, she had to wait for 18 months before she could start her master. During this period, she studied Art History at the University of Amsterdam for a year, but also participated in research on chronic pancreatitis. At the end of this waiting period, she went to Cape Town, South Africa, for an internship at the Pediatric Department of the Groote Schuur Hospital. In 2015, Sophie started with her master's degree, wherein she was fascinated by general surgery the most. Her clinical rotations led her to Antwerp, Belgium and to Sydney, Australia, where she did an elective internship in upper gastrointestinal surgery.

After obtaining her medical degree, Sophie started working on her PhD project, conducting research in bariatric surgery, which is described in this thesis. She was supervised by prof. dr. E.J. Hazebroek from the department of surgery, Rijnstate Ziekenhuis, Arnhem, and by dr. S.M.M. de Castro, department of surgery, OLVG, Amsterdam. While this was a great time, Sophie was very excited about the return to clinical patient care as a surgical resident not in training in 2020, at the Spaarne Gasthuis.

Sophie also really enjoys her life outside of the hospital, spending time with her friends and family, playing field hockey, going kite surfing, participating in challenges of long-distance ice skating, playing tennis and lots more.

In January 2022, Sophie started as a surgical resident in training at Amsterdam UMC, location AMC, which she will continue her residency at the Rode Kruis Ziekenhuis, Beverwijk in January 2023.

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