BMJ Open

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.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038830
Article Type:	Protocol
Date Submitted by the Author:	25-Mar-2020
Complete List of Authors:	van Veldhuisen, Sophie; Rijnstate Hospital, Department of Surgery / Vitalys Clinic Kuppens, Kim; St Antonius Hospital, Department of Pulmonary Medicine de Raaff, Christel; Albert Schweitzer Hospital, Department of Surgery Frederix, Geert; Universitair Medisch Centrum Utrecht, Department of Public Health, Julius Center Research Program Methodology Hazebroek, Eric; Rijnstate Hospital, Vitalys Clinic, Department of Surgery / Vitalys Clinic; Wageningen University and Research, Division of Human Nutrition and Health
Keywords:	Sleep medicine < ANAESTHETICS, SLEEP MEDICINE, Adult surgery < SURGERY, RESPIRATORY MEDICINE (see Thoracic Medicine)

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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.

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 multicenter 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

Article summary

Strengths and limitations of this study

- This study is the first prospective study to compare and analyze cost-effective methods for perioperative care of obese patients with no known OSA history. Giving the growing worldwide epidemic of obesity, all aspects of bariatric surgery need to be assessed for costs and efficacy in order to achieve affordable and high-quality health care for patients with morbid obesity.
- Results of this study will provide insight in many aspects of pre- and perioperative interventions that is currently lacking, such as the impact on postoperative complications, influence on QOL, change of sleepiness symptoms, and adherence rates to CPAP in patients who were asymptomatic or did not experience recognized symptoms.
- This study includes a large population that will be monitored to evaluate OSA care in bariatric patients. For a study that evaluates a perioperative intervention, the duration of follow-up of one year is relatively long.

- Despite the non-randomized design, we hypothesize that both cohorts will embody the average patient that is scheduled for a primary bariatric procedure due to the ample size and few exclusion criteria for study participants. Therefore, data gathered in these cohorts will probably be applicable to the general bariatric population.

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, multicenter, 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).

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 paraoesophageal 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 Center, 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.

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 centers 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). No other primary procedures are performed in the participating hospitals. 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. 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). 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 (37). 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 center. 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 analyzed. 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 (38).

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(39). Sleep-related QOL will be assessed with the Functional Outcome Sleep Questionnaire-10(40). 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(41).

OSA-related outcomes

The main symptom of OSA, daytime sleepiness, will be assessed by the Epworth Sleepiness Scale questionnaire(42). 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 analyzed 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 and daily use of opioids 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(43). 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. 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.

Sensitivity analysis will be carried out to correct all potential confounders, such as gender, age, preoperative BMI, comorbidities, choice of bariatric center, intraoperative and postoperative administered opioids, smoking status, previous ENT surgery.

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 analyzed 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 $p < 0.05$.

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

A non-profit organization for OSA patients was consulted during the process of writing the protocol.

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, 44, 45). 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(46). 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, 47). 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 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.

Author contributions

EJH conceived and designed the study, with support of CALDR and KK. SVV wrote and developed the protocol together with EJH, CALDR, KK, GJWF and LR. EJH is the principal investigator and SVV is the main investigator. All authors critically reviewed the content and approved the final manuscript.

Acknowledgements

We would like to thank our collaborators (e.i. clinical Investigators) who are contributing greatly to the POPCORN study. All collaborators are involved in recruitment and care of study participants: dr. M.J. Wiezer, Department of Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands; dr. S.M.M. de Castro, Department of Surgery, OLVG, Amsterdam, the Netherlands; dr. R.N. van Veen, Department of Surgery, OLVG, Amsterdam, the Netherlands; dr. D.J. Swank, Dutch Obesity Clinic, the Hague, the Netherlands, dr. A. Demirkiran, Department of Surgery, Rode Kruis Hospital, Beverwijk, the Netherlands, dr. E.G. Boerma, Department of Surgery, Zuyderland Hospital, Heerlen; dr. F.M.H. van Dielen, Department of Surgery, Máxima Medical Center, Veldhoven, the Netherlands.

Funding

This work was supported by ZonMw, grant number '843004110'.

Competing interests

Not applicable for any of the authors

430

431
432
433

References

1. WHO. Obesity and overweight; Fact sheet. . 2018.
2. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. Jama. 2004;292(14):1724-37.
3. Maciejewski ML, Arterburn DE, Van Scoyoc L, Smith VA, Yancy WS, Jr., Weidenbacher HJ, et al. Bariatric Surgery and Long-term Durability of Weight Loss. JAMA surgery. 2016;151(11):1046-55.
4. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. Jama. 2004;291(16):2013-6.
5. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. Jama. 2000;284(23):3015-21.
6. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387-94.
7. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. The Cochrane database of systematic reviews. 2006(1):CD001106.
8. de Raaff CA, Pierik AS, Coblijn UK, de Vries N, Bonjer HJ, van Wagensveld BA. Value of routine polysomnography in bariatric surgery. Surgical endoscopy. 2017;31(1):245-8.
9. Peromaa-Haavisto P, Tuomilehto H, Kossi J, Virtanen J, Luostarinen M, Pihlajamaki J, et al. Prevalence of Obstructive Sleep Apnoea Among Patients Admitted for Bariatric Surgery. A Prospective Multicentre Trial. Obesity surgery. 2016;26(7):1384-90.
10. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. American journal of epidemiology. 2013;177(9):1006-14.
11. Hudgel DW, Patel SR, Ahasic AM, Bartlett SJ, Bessesen DH, Coaker MA, et al. The Role of Weight Management in the Treatment of Adult Obstructive Sleep Apnea. An Official American Thoracic Society Clinical Practice Guideline. American journal of respiratory and critical care medicine. 2018;198(6):e70-e87.
12. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. American journal of respiratory and critical care medicine. 2002;165(9):1217-39.
13. Sarkhosh K, Switzer NJ, El-Hadi M, Birch DW, Shi X, Karmali S. The impact of bariatric surgery on obstructive sleep apnea: a systematic review. Obesity surgery. 2013;23(3):414-23.
14. Ravesloot MJ, Hilgevoord AA, van Wagensveld BA, de Vries N. Assessment of the effect of bariatric surgery on obstructive sleep apnea at two postoperative intervals. Obesity surgery. 2014;24(1):22-31.
15. de Raaff CA, Coblijn UK, Ravesloot MJ, de Vries N, de Lange-de Klerk ES, van Wagensveld BA. Persistent moderate or severe obstructive sleep apnea after laparoscopic Roux-en-Y gastric bypass: which patients? Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2016;12(10):1866-72.
16. van Veldhuisen SL, Hazebroek EJ. Obstructive Sleep Apnea in Adults. The New England journal of medicine. 2019;381(3):e7.
17. Singh M, Liao P, Kobah S, Wijeysundera DN, Shapiro C, Chung F. Proportion of surgical patients with undiagnosed obstructive sleep apnoea. British journal of anaesthesia. 2013;110(4):629-36.

18. Kaw R, Michota F, Jaffer A, Ghamande S, Auckley D, Golish J. Unrecognized sleep apnea in the surgical patient: implications for the perioperative setting. Chest. 2006;129(1):198-205.
19. Kaw R, Chung F, Pasupuleti V, Mehta J, Gay PC, Hernandez AV. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. British journal of anaesthesia. 2012;109(6):897-906.
20. Flancbaum L, Belsley S. Factors affecting morbidity and mortality of Roux-en-Y gastric bypass for clinically severe obesity: an analysis of 1,000 consecutive open cases by a single surgeon. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007;11(4):500-7.
21. van Veldhuisen SL, Arslan I, Deden LN, Aarts EO, Hazebroek EJ. Safety of Continuous Postoperative Pulse Oximetry Monitoring Without Obstructive Sleep Apnea Screening in > 5000 Patients Undergoing Bariatric Surgery. Obesity surgery. 2019.
22. O'Reilly E, Doherty L, O'Boyle C. How Relevant Is Pre-operative Obstructive Sleep Apnoea in the Asymptomatic Bariatric Surgery Patient? Obesity surgery. 2019.
23. Meurgey JH, Brown R, Woroszyl-Chrusciel A, Steier J. Peri-operative treatment of sleep-disordered breathing and outcomes in bariatric patients. Journal of thoracic disease. 2018;10(Suppl 1):S144-S52.
24. de Raaff CAL, Gorter-Stam MAW, de Vries N, Sinha AC, Jaap Bonjer H, Chung F, et al. Perioperative management of obstructive sleep apnea in bariatric surgery: a consensus guideline. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2017;13(7):1095-109.
25. Chiu HY, Chen PY, Chuang LP, Chen NH, Tu YK, Hsieh YJ, et al. Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth sleepiness scale in detecting obstructive sleep apnea: A bivariate meta-analysis. Sleep medicine reviews. 2017;36:57-70.
26. Turnbull CD, Stradling JR. To screen or not to screen for obstructive sleep apnea, that is the question. Sleep medicine reviews. 2017;36:125-7.
27. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, Jr., et al. Screening for Obstructive Sleep Apnea in Adults: US Preventive Services Task Force Recommendation Statement. Jama. 2017;317(4):407-14.
28. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proceedings of the American Thoracic Society. 2008;5(2):173-8.
29. Tregear S, Reston J, Schoelles K, Phillips B. Continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea: systematic review and meta-analysis. Sleep. 2010;33(10):1373-80.
30. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. Journal of the American College of Cardiology. 2008;52(8):686-717.
31. Siccoli MM, Pepperell JC, Kohler M, Craig SE, Davies RJ, Stradling JR. Effects of continuous positive airway pressure on quality of life in patients with moderate to severe obstructive sleep apnea: data from a randomized controlled trial. Sleep. 2008;31(11):1551-8.

32. Jonas DE, Amick HR, Feltner C, Weber RP, Arvanitis M, Stine A, et al. Screening for Obstructive Sleep Apnea in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2017;317(4):415-33.
33. Fried M, Hainer V, Basdevant A, Buchwald H, Deitel M, Finer N, et al. Interdisciplinary European guidelines on surgery of severe obesity. Obesity facts. 2008;1(1):52-9.
34. Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2009;5(3):263-76.
35. Thorell A, MacCormick AD, Awad S, Reynolds N, Roulin D, Demartines N, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World journal of surgery. 2016;40(9):2065-83.
36. Brooks R. EuroQol: the current state of play. Health policy. 1996;37(1):53-72.
37. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015;18(6):753-8.
38. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205-13.
39. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of health economics. 2002;21(2):271-92.
40. Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the Functional Outcomes of Sleep Questionnaire. Sleep. 2009;32(7):915-9.
41. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep. 1997;20(10):835-43.
42. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.
43. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, Davies RJ, et al. Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): a 12-month, multicentre, randomised trial. The Lancet Respiratory medicine. 2014;2(10):804-12.
44. Zaremba S, Mojica JE, Eikermann M. Perioperative sleep apnea: a real problem or did we invent a new disease? F1000Research. 2016;5.
45. Nepomnayshy D, Hesham W, Erickson B, MacDonald J, Iorio R, Brams D. Sleep apnea: is routine preoperative screening necessary? Obesity surgery. 2013;23(3):287-91.
46. de Raaff CA, Coblijn UK, de Vries N, van Wagensveld BA. Is fear for postoperative cardiopulmonary complications after bariatric surgery in patients with obstructive sleep apnea justified? A systematic review. American journal of surgery. 2016;211(4):793-801.
47. George CF. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. Thorax. 2001;56(7):508-12.

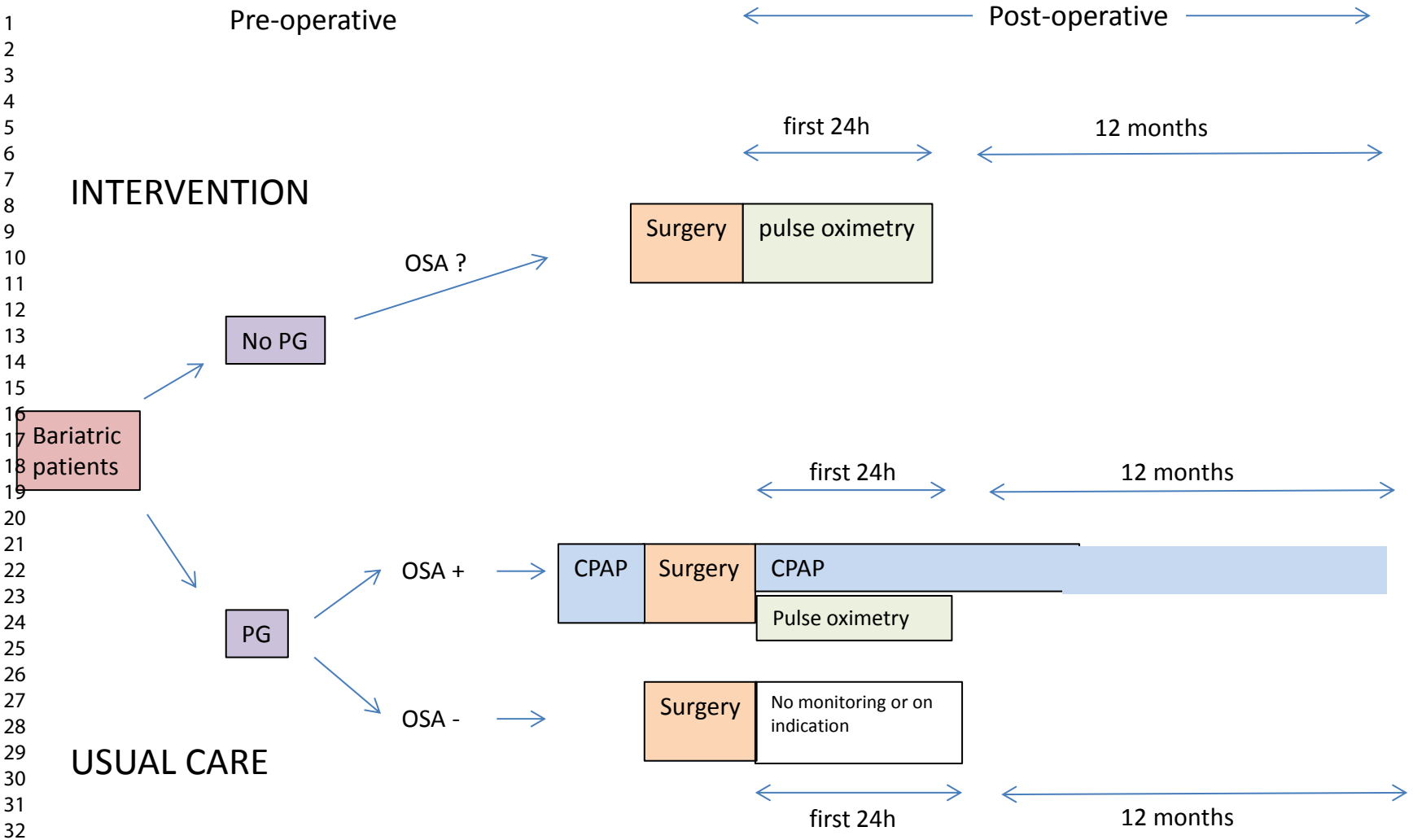

Figure 1. Flowchart of POPCORN study
PG polygraphy, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038830.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Jul-2020
Complete List of Authors:	van Veldhuisen, Sophie; Rijnstate Hospital, Department of Surgery / Vitalys Clinic Kuppens, Kim; St Antonius Hospital, Department of Pulmonary Medicine de Raaff, Christel; Albert Schweitzer Hospital, Department of Surgery Wiezer, René; Sint Antonius Hospital, Surgery de Castro, Steve; OLVG Locatie West, Surgery van Veen, Ruben; OLVG Locatie West, Surgery Swank, Dingeman; Nederlandse Obesitas Kliniek Demirkiran, Ahmet; Rode Kruis Ziekenhuis, Surgery Boerma, Evert-Jan; Zuyderland Medical Centre Heerlen, Surgery Greve, Jan-Willem; Zuyderland Medical Centre Heerlen, Surgery; Maastricht University, Surgery, Nutrim van Dielen, Francois; Maxima Medical Centre, Surgery Frederix, Geert; Universitair Medisch Centrum Utrecht, Department of Public Health, Julius Center Research Program Methodology Hazebroek, Eric; Rijnstate Hospital, Vitalys Clinic, Department of Surgery / Vitalys Clinic; Wageningen University and Research, Division of Human Nutrition and Health
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Respiratory medicine
Keywords:	Sleep medicine < ANAESTHETICS, SLEEP MEDICINE, Adult surgery < SURGERY, RESPIRATORY MEDICINE (see Thoracic Medicine)

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Authors

Sophie L. van Veldhuisen[1], Kim Kuppens[2], Christel A.L. de Raaff[3], Marinus J. Wiezer[2], Steve M.M. de Castro[4], Ruben N. van Veen[4], Dingeman J. Swank[5], Ahmet Demirkiran[6], Evert-Jan G. Boerma[7], Jan Willem M. Greve[7,8], Francois M.H. van Dielen[9], Geert W.J. Frederix[10], Eric J. Hazebroek[1,11]

Affiliations

[1] Department of Surgery / Vitalys Clinic, Rijnstate Hospital, Arnhem, the Netherlands

[2] Department of Pulmonary Medicine, St. Antonius Hospital, Utrecht, the Netherlands

[3] Department of Surgery, Albert Schweitzer Hospital, Dordrecht, the Netherlands

[4] Department of Surgery, OLVG, Amsterdam, the Netherlands

[5] Dutch Obesity Clinic, the Hague, the Netherlands

[6] Department of Surgery, Rode Kruis Hospital, Beverwijk, the Netherlands

[7] Department of Surgery, Zuyderland Hospital, Heerlen, the Netherlands

[8] Department of Surgery, Nutrim, Maastricht University, Maastricht, the Netherlands

[9] Department of Surgery, Máxima Medical Centre, Veldhoven, the Netherlands

[10] Department of Public Health, Julius Centre Research Program Methodology, University Medical Centre Utrecht, Utrecht, the Netherlands

[11] Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, the Netherlands

Corresponding author

Sophie L. van Veldhuisen, M.D.

Department of Bariatric Surgery

Rijnstate Hospital

Wagnerlaan 55, 6815 AD

Arnhem, the Netherlands

Phone: +31630705143

Email: svanveldhuisen@rijnstate.nl

Word count

4395

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.

Article summary

Strengths and limitations of this study

- This is the first prospective study to compare continuous postoperative pulse oximetry without preoperative OSA screening to routine OSA screening with consequent CPAP treatment as perioperative care for bariatric patients with potential OSA.

- The main outcome of this study is cost-effectiveness of these two perioperative care strategies in obese patients with no known OSA history.

- Results of this study will provide new insights in unknown aspects of perioperative interventions for undetected OSA, such as the impact on postoperative complications and general quality of life.

- Despite the non-randomized design, we hypothesize that the results are generalizable to most bariatric centres due to the large sample size and limited exclusion criteria.

- Our follow-up duration of one year enables analysis of long-term outcomes of perioperative interventions for OSA, such as influence on weight loss, sleepiness symptoms, quality of life with sleepiness and adherence to CPAP.

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).

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.

Funding

This work was supported by ZonMw, grant number '843004110'.

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.

References

1. WHO. Obesity and overweight; Fact sheet. . 2018.
2. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. Jama. 2004;292(14):1724-37.
3. Maciejewski ML, Arterburn DE, Van Scoyoc L, Smith VA, Yancy WS, Jr., Weidenbacher HJ, et al. Bariatric Surgery and Long-term Durability of Weight Loss. JAMA surgery. 2016;151(11):1046-55.
4. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. Jama. 2004;291(16):2013-6.
5. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. Jama. 2000;284(23):3015-21.
6. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387-94.
7. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. The Cochrane database of systematic reviews. 2006(1):CD001106.
8. de Raaff CA, Pierik AS, Coblijn UK, de Vries N, Bonjer HJ, van Wagensveld BA. Value of routine polysomnography in bariatric surgery. Surgical endoscopy. 2017;31(1):245-8.
9. Peromaa-Haavisto P, Tuomilehto H, Kossi J, Virtanen J, Luostarinen M, Pihlajamaki J, et al. Prevalence of Obstructive Sleep Apnoea Among Patients Admitted for Bariatric Surgery. A Prospective Multicentre Trial. Obesity surgery. 2016;26(7):1384-90.
10. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. American journal of epidemiology. 2013;177(9):1006-14.
11. Hudgel DW, Patel SR, Ahasic AM, Bartlett SJ, Bessesen DH, Coaker MA, et al. The Role of Weight Management in the Treatment of Adult Obstructive Sleep Apnea. An Official American Thoracic Society Clinical Practice Guideline. American journal of respiratory and critical care medicine. 2018;198(6):e70-e87.
12. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. American journal of respiratory and critical care medicine. 2002;165(9):1217-39.
13. Sarkhosh K, Switzer NJ, El-Hadi M, Birch DW, Shi X, Karmali S. The impact of bariatric surgery on obstructive sleep apnea: a systematic review. Obesity surgery. 2013;23(3):414-23.
14. Ravesloot MJ, Hilgevoord AA, van Wagensveld BA, de Vries N. Assessment of the effect of bariatric surgery on obstructive sleep apnea at two postoperative intervals. Obesity surgery. 2014;24(1):22-31.
15. de Raaff CA, Coblijn UK, Ravesloot MJ, de Vries N, de Lange-de Klerk ES, van Wagensveld BA. Persistent moderate or severe obstructive sleep apnea after laparoscopic Roux-en-Y gastric bypass: which patients? Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2016;12(10):1866-72.
16. van Veldhuisen SL, Hazebroek EJ. Obstructive Sleep Apnea in Adults. The New England journal of medicine. 2019;381(3):e7.
17. Singh M, Liao P, Kobah S, Wijeysundera DN, Shapiro C, Chung F. Proportion of surgical patients with undiagnosed obstructive sleep apnoea. British journal of anaesthesia. 2013;110(4):629-36.

18. Kaw R, Michota F, Jaffer A, Ghamande S, Auckley D, Golish J. Unrecognized sleep apnea in the surgical patient: implications for the perioperative setting. Chest. 2006;129(1):198-205.
19. Kaw R, Chung F, Pasupuleti V, Mehta J, Gay PC, Hernandez AV. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. British journal of anaesthesia. 2012;109(6):897-906.
20. Flancbaum L, Belsley S. Factors affecting morbidity and mortality of Roux-en-Y gastric bypass for clinically severe obesity: an analysis of 1,000 consecutive open cases by a single surgeon. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007;11(4):500-7.
21. van Veldhuisen SL, Arslan I, Deden LN, Aarts EO, Hazebroek EJ. Safety of Continuous Postoperative Pulse Oximetry Monitoring Without Obstructive Sleep Apnea Screening in > 5000 Patients Undergoing Bariatric Surgery. Obesity surgery. 2019.
22. O'Reilly E, Doherty L, O'Boyle C. How Relevant Is Pre-operative Obstructive Sleep Apnoea in the Asymptomatic Bariatric Surgery Patient? Obesity surgery. 2019.
23. Meurgey JH, Brown R, Woroszyl-Chrusciel A, Steier J. Peri-operative treatment of sleep-disordered breathing and outcomes in bariatric patients. Journal of thoracic disease. 2018;10(Suppl 1):S144-S52.
24. de Raaff CAL, Gorter-Stam MAW, de Vries N, Sinha AC, Jaap Bonjer H, Chung F, et al. Perioperative management of obstructive sleep apnea in bariatric surgery: a consensus guideline. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2017;13(7):1095-109.
25. Chiu HY, Chen PY, Chuang LP, Chen NH, Tu YK, Hsieh YJ, et al. Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth sleepiness scale in detecting obstructive sleep apnea: A bivariate meta-analysis. Sleep medicine reviews. 2017;36:57-70.
26. Turnbull CD, Stradling JR. To screen or not to screen for obstructive sleep apnea, that is the question. Sleep medicine reviews. 2017;36:125-7.
27. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, Jr., et al. Screening for Obstructive Sleep Apnea in Adults: US Preventive Services Task Force Recommendation Statement. Jama. 2017;317(4):407-14.
28. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proceedings of the American Thoracic Society. 2008;5(2):173-8.
29. Tregear S, Reston J, Schoelles K, Phillips B. Continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea: systematic review and meta-analysis. Sleep. 2010;33(10):1373-80.
30. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. Journal of the American College of Cardiology. 2008;52(8):686-717.
31. Siccoli MM, Pepperell JC, Kohler M, Craig SE, Davies RJ, Stradling JR. Effects of continuous positive airway pressure on quality of life in patients with moderate to severe obstructive sleep apnea: data from a randomized controlled trial. Sleep. 2008;31(11):1551-8.

32. Jonas DE, Amick HR, Feltner C, Weber RP, Arvanitis M, Stine A, et al. Screening for Obstructive Sleep Apnea in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2017;317(4):415-33.
33. Fried M, Hainer V, Basdevant A, Buchwald H, Deitel M, Finer N, et al. Interdisciplinary European guidelines on surgery of severe obesity. Obesity facts. 2008;1(1):52-9.
34. Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2009;5(3):263-76.
35. Thorell A, MacCormick AD, Awad S, Reynolds N, Roulin D, Demartines N, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World journal of surgery. 2016;40(9):2065-83.
36. Brooks R. EuroQol: the current state of play. Health policy. 1996;37(1):53-72.
37. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health economics. 2006;15(10):1121-32.
38. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015;18(6):753-8.
39. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205-13.
40. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of health economics. 2002;21(2):271-92.
41. Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the Functional Outcomes of Sleep Questionnaire. Sleep. 2009;32(7):915-9.
42. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep. 1997;20(10):835-43.
43. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.
44. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, Davies RJ, et al. Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): a 12-month, multicentre, randomised trial. The Lancet Respiratory medicine. 2014;2(10):804-12.
45. Versteegh M, Knies S, Brouwer W. From Good to Better: New Dutch Guidelines for Economic Evaluations in Healthcare. PharmacoEconomics. 2016;34(11):1071-4.
46. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Bmj. 2013;346:f1049.
47. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2014;17(1):5-14.

48. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, et al. Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. Journal of the American College of Cardiology. 2017;69(3):345-57.
49. Zaremba S, Mojica JE, Eikermann M. Perioperative sleep apnea: a real problem or did we invent a new disease? F1000Research. 2016;5.
50. Nepomnayshy D, Hesham W, Erickson B, MacDonald J, Iorio R, Brams D. Sleep apnea: is routine preoperative screening necessary? Obesity surgery. 2013;23(3):287-91.
51. de Raaff CA, Coblijn UK, de Vries N, van Wagensveld BA. Is fear for postoperative cardiopulmonary complications after bariatric surgery in patients with obstructive sleep apnea justified? A systematic review. American journal of surgery. 2016;211(4):793-801.
52. George CF. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. Thorax. 2001;56(7):508-12.

Legends

Figure 1 – Flowchart of the POPCORN study

PG Polygraphy, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure

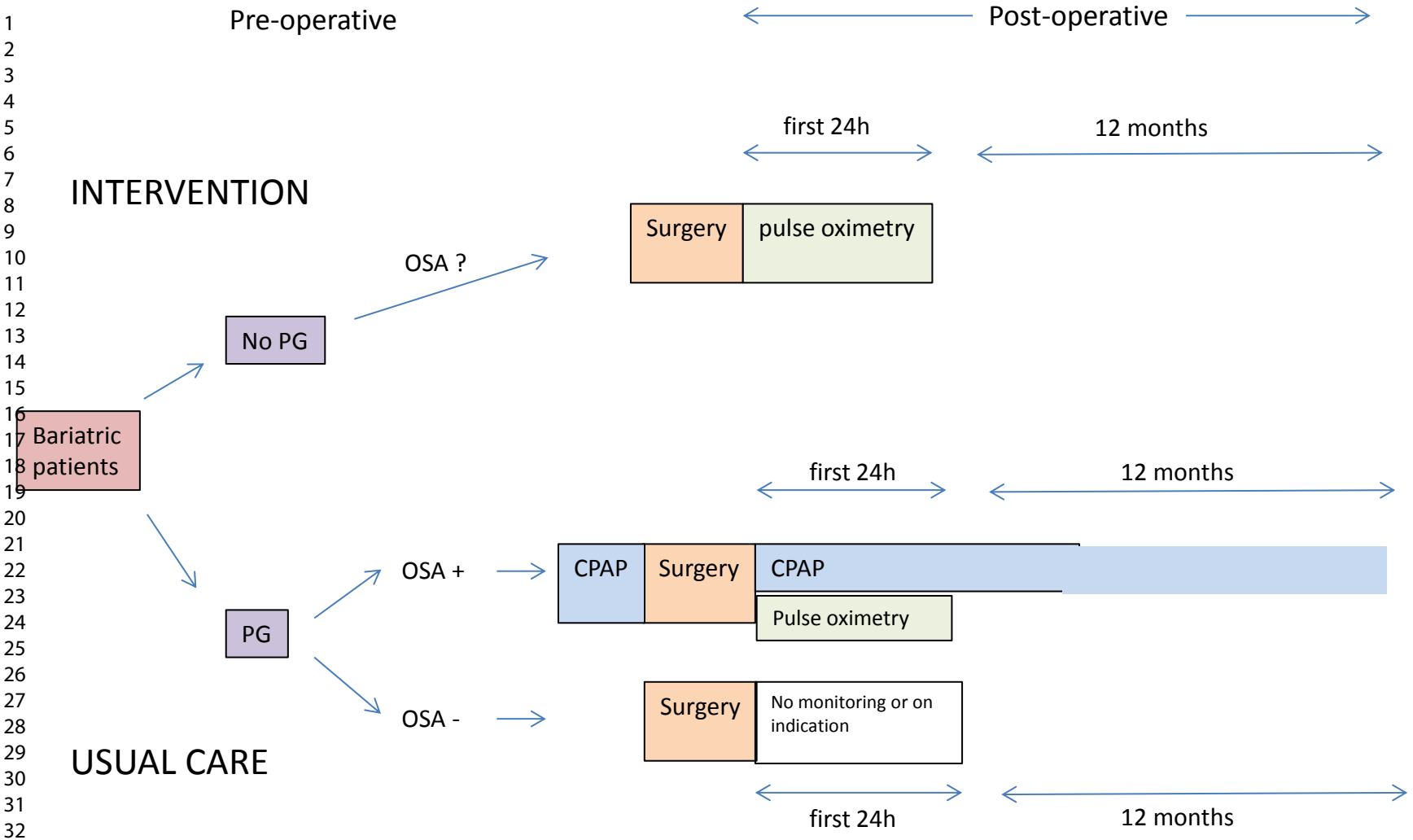

Figure 1. Flowchart of POPCORN study
PG polygraphy, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure