ADOLESCENTS LIVING WITH SEVERE OBESITY

A GROWING PROBLEM ASKING FOR DARING SOLUTIONS



YVONNE G.M. ROEBROEK

PROPOSITIONS

1. *The common opinion regarding bariatric surgery in adolescents has long been predominated by safety concerns, insufficient understanding of mechanisms and stigmatisation* – this thesis

2. *Increased BMI z-score and elevated triglyceride levels are associated with a higher apnea-hypopnea-index in adolescents living with severe obesity* – this thesis

3. *Laparoscopic adjustable gastric banding, as an additional treatment to multidisciplinary lifestyle interventions, results in significant weight loss after one year in adolescents living with severe obesity* – this thesis

4. *Laparoscopic adjustable gastric banding results in significant improvement of insulin sensitivity, serum triglycerides and apnea-hypopnea-index after one year* – this thesis

5. *While prevention remains the cornerstone of addressing the obesity pandemic, it is insufficient for adolescents living with severe obesity, making targeted treatment essential to improve outcomes and reduce future healthcare costs* – this thesis

6. *An ounce of prevention is worth a pound of cure* – attributed to Benjamin Franklin

7. *Het framen van obesitaschirurgie als 'laatste redmiddel' bij adolescenten is primair cultureel bepaald en niet evidence-based*

8. *He who desires to practice surgery must go to war* – Hippocrates

9. *Until the lion learns to write, every story will glorify the hunter* – African proverb

10. *Karakter is wat overblijft als niemand kijkt* – Ray Klaassens

11. *Your ordinary day is someone else's dream; be grateful for it*

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Aan mijn schoonvader Chiel,
die er in gedachten altijd bij is.

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GENERAL INTRODUCTION AND OUTLINE

HISTORICAL PERSPECTIVE

The noun 'obesity' originates from the Latin 'obesitas' (meaning 'overeaten') and is used in general to describe the condition of being fat or overweight [1]. The rising incidence and prevalence of overweight and obesity have gained much attention worldwide during the past decades, yet the condition is probably as old as human society itself: prehistoric statuettes of obese women have been preserved over time and date back to the Paleolithic era, their anatomical accuracy indicating that the statuettes give a truthful representation of prehistoric obesity [2, 3]. Documentation dating from the Ancient Greek era shows that Hippocrates already stated that "*Those who are constitutionally very fat are more apt to die quickly than those who are thin.*" [4]. Nevertheless, obesity was not a very common phenomenon during these ages, and populations thrived on an increasing body height and weight for centuries. It has only been since the 20th century that populations from the so-called high-income countries approached their genetic potential for longitudinal growth, while at the same time the increase in body weight persisted [5].

EPIDEMIOLOGY

Nowadays, we have reached the era in which excess weight is linked to more deaths worldwide than underweight [6]. The worldwide prevalence of obesity almost increased threefold during the past four decades, resulting in about 16% of the world's adult population suffering from obesity in 2022 [6, 7]. It is estimated that more than a billion adults suffer from obesity worldwide in 2025 [8]. The World Obesity Federation (WOF) stated in 2023: *No country has reported a decline in obesity prevalence across their entire population, and none are on track to meet the World Health Organization's (WHO) target of 'no increase on 2010 levels by 2025'* [9]. Despite numerous prevention strategies, the global number of people living with obesity keeps increasing. In the Netherlands, the prevalence of obesity in the adult population increased from 5.3% in 1981 to 15.6% in 2023 (Figure 0.1). The incidence of severe obesity (class 3, body mass index of 40 and higher) increased from 0.4% to 1.3% during that same period [10, 11].

Even more worrying is the fact that childhood obesity has also become a global epidemic. The World Health Organization considers childhood obesity as one of the most serious public health challenges of the 21st century [12, 13]. While only 2% of the worldwide childhood population (aged 5-19 years) was obese in 1990, a dramatic rise in prevalence resulted in 8% of children and adolescents being obese in 2022 [6, 7]. Data from three Dutch National Growth Studies show similar trends in the Netherlands [14, 15]. Based on databases from the USA, simulations predict that more than half of the current USA childhood population (aged 2-19 years) will be obese at the age of 35 years [16]. Recent

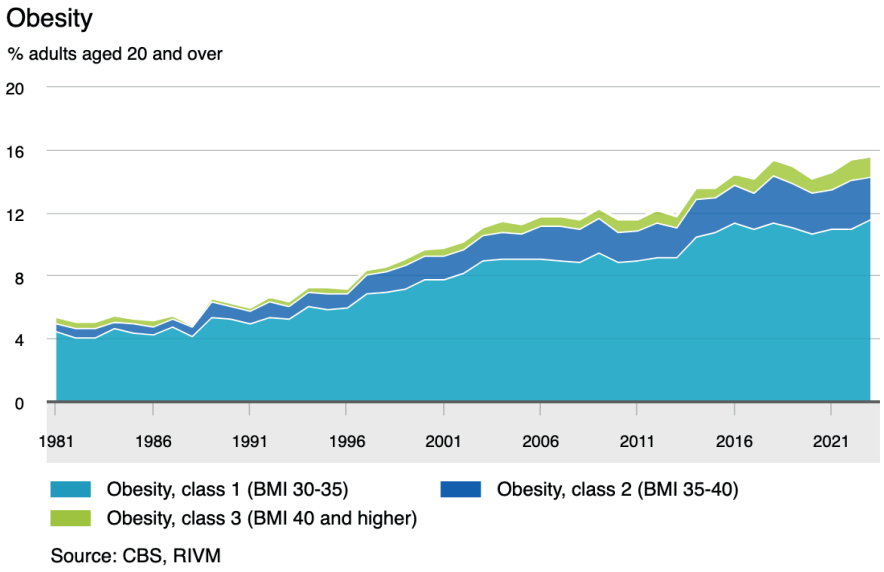


Figure 0.1: *Prevalence of obesity amongst Dutch adults aged 20 years and over. Source: Centraal Bureau voor de Statistiek, 2023.*

updates of national databases show that the rise in prevalence of childhood obesity of the past decades finally starts to level off, however at the same time a shift towards more severe degrees of obesity is observed [17, 18].

CATEGORIZATION AND DEFINITIONS

Several methods can be used to categorize terms like overweight, obesity and severe obesity; most of these methods are based on the commonly used Body Mass Index (BMI, see Table 0.1). Although the BMI cut-offs were initially based on life-expectancy data and accompanying risk calculations from life assurance companies, the cut-offs also match the increasing risks of obesity associated comorbidities [19]. Health risks accumulate with an increasing BMI: various studies show that each additional BMI-point is associated with an increased risk of diabetes mellitus, cardiovascular disease and osteoarthritis, amongst others [20, 21].

In children and adolescents, similar health risks will come at play with increasing BMI levels. However, the adult cut-off values for overweight and obesity cannot be used directly in the childhood population. In order to account for the growing and developing body of a child, the cut-off values need to be adjusted for sex and age [25, 26]. In addition,

Table 0.1: *Cut-off values for adults for being overweight or obese, according to the WHO [22-24].*

Classification	BMI cut-off points (kg/m^2)	Risk of comorbidities
Overweight	25.0 – 29.9	Increased
Obesity class I	30.0 – 34.9	Moderate
Obesity class II	35.0 – 39.9	Severe
Obesity class III	≥ 40.0	Very severe

the WOF (formerly called International Obesity Task Force (IOTF)) adjusted the childhood cut-off equivalent for grade III obesity (or severe / morbid obesity) from BMI ≥40.00 to BMI ≥35.00 kg/m ^{2} [26]. This leads to the BMI cut-off values in the childhood population as mentioned in Table 0.2 [27].

Table 0.2: *Childhood cut-off values for being overweight or obese at age 2-18 years, sex and age specific, according to the 1) World Health Organization (WHO), 2) Centers for Disease Control and Prevention (CDC), and 3) World Obesity Federation (WOF) [26, 28, 29].*

Classification	BMI cut-off values		
	WHO*	**CDC**	**WOF**
	[SDS]	[centiles]	[centile equivalents]
Underweight	≤ -2.00	< 5th percentile	< Ce-18.50
Normal range	-1.99 – 0.99	5th – 84th percentile	Ce-18.50 – Ce-24.99
Overweight	≥ +1.00	≥ 85th percentile	≥ Ce-25.00
Obese	≥ +2.00	≥ 95th percentile	≥ Ce-30.00
Morbid obese	≥ +3.00	≥ 99th percentile	≥ Ce-35.00

* WHO cut off values for children aged 5-19 years. SDS = standard deviation. Ce = centile equivalent.

PATHOPHYSIOLOGICAL CONSEQUENCES

With the rising incidence and prevalence of overweight and obesity, our knowledge of the disease and its associated comorbidities also improved. Susceptibility to obesity can be affected by multiple factors such as environmental issues and genetics, yet the actual fat accumulation is the result of a long-term disturbed energy balance [30]. Excessive fat accumulation can manifest both in subcutaneous adipose tissue and visceral adipose tissue and may lead to a broad spectrum of health-related consequences. Visceral

adipose tissue is regarded as a major contributor to metabolic diseases such as diabetes and atherosclerosis: it is hypothesized that both lipogenesis and lipolysis occur at high rates in visceral adipose tissue, disposing free fatty acids (FFAs) in the blood circulation leading to metabolic overload [31].

Various obesity-related comorbidities can occur via diverse and complex pathways. Interactions between comorbidities make it even more complicated to gain complete understanding of the pathophysiology of obesity related diseases. The major physical consequences of obesity are summarized below:

- *Disturbed glucose metabolism*: obesity itself is associated to insulin resistance, a pivotal factor in the development of type 2 diabetes mellitus (T2DM)[32]. Metabolic overload (via chronic nutritional excess, FFAs produced by adipose tissue, etc.) challenges the pancreas in keeping blood glucose levels within target values, the pancreas responds by increasing insulin production. Over time, the target cell's metabolic response to the high levels of insulin starts to decrease, resulting in even higher levels of insulin produced to maintain blood glucose stability. Eventually, blood glucose levels will rise and (pre)diabetes develops [33].
- *Dyslipidemia*: most commonly both elevated plasma triglycerides (TGs) and FFAs and lowered high-density lipoprotein cholesterol (HDL-cholesterol) [34]. It is hypothesized that the increased circulating FFAs (mainly from visceral adipose tissue) accumulate in lipid droplets as ectopic fat in non-adipose tissue; these ectopic fat depots lead to alterations in the trafficking of FFAs and TGs that govern obesity associated dyslipidemia [35, 36]. This atherogenic type of dyslipidemia is associated with increased cardiovascular risk [37, 38].
- *Hypertension*: one of the most common comorbidities in obesity. An increase in BMI is generally associated with a significant increase in prevalence of hypertension [20, 39]. It appears that an important mechanism in the pathophysiology of obesity-associated hypertension is an increase in sympathetic nervous system activity. Adipose tissue expresses and secretes angiotensin-converting enzyme (ACE) and angiotensinogen; these substances play a role in the sympathetic regulation of fluid retention and vasoconstriction, stimulating an increase in blood volume and blood pressure [40-42]. In addition, the excess body mass tissue itself creates an increased total peripheral vascular resistance, contributing to a further increase in blood pressure [43]. Other potential contributors are circulating adipokines, elevated FFAs and presence of sleep apnea [41, 44].
- *Inflammation*: metabolic overload can activate various inflammatory pathways. A positive association between obesity and inflammatory markers has been confirmed already a decade ago [45, 46]. In general, the body's homeostatic capacity can facilitate adipose tissue development with adipocyte hyperplasia in response to fat accommodation needs; however, this process has its limits and can turn into

adipocyte hypertrophy if limits are exceeded [47]. Adipocyte hypertrophy will lead to alterations in adipokine secretion, which may contribute to the development of metabolic diseases. In addition, ongoing hypertrophy will result in cell rupture, eventually leading to an inflammatory response [30]. Further, excessive feeding leads to oxidative stress, also leading to increased levels of inflammatory markers [47].

- *Nonalcoholic fatty liver disease (NAFLD)*: a condition resulting from the accumulation of excessive fat in the liver, which can lead to nonalcoholic steatohepatitis, cirrhosis and eventually liver cancer [48]. Metabolic overload, insulin resistance and inflammation can contribute to the development of NAFLD via elevated levels of circulating FFAs, which will be reabsorbed in liver tissue and accumulate under the form of triglycerides [49]. Triglyceride accumulation in the liver is hypothesized to be the first step in the pathophysiology of NAFLD.
- *Obstructive sleep apnea (OSA)*: obesity is one of the major risk factors for sleep apnea, while sleep apnea predisposes to weight gain and obesity [50]. The pathophysiology remains mainly unclear, however some associations have been discovered: two major mechanical contributors to sleep apnea in obesity are 1) pharyngeal anatomical imbalance, leading to narrowing of the airway and 2) central adiposity leading to decreased lung volume [51]. In addition, plasma leptin levels (an important adipokine) are modestly correlated to the apnea-hypopnea-index (AHI, as measure for severity of sleep apnea), independent of BMI or waist circumference [52, 53]. It is believed that increased leptin levels disrupt sleep architecture and ventilatory function via the carotid body chemoreflex [54].

Further, there is a psychosocial burden of overweight and obesity. Abundant evidence suggests that 20% to 60% of persons with obesity suffer from a psychiatric condition, mainly depressive or anxiety disorders or eating disorders [55-57]. Being overweight or obese at a young age already has a negative influence on aspects such as physical appearance self-esteem and body dissatisfaction [58, 59]. These negative influences are known to track into adolescence and adulthood [58].

PREVENTION AND TREATMENT

Prevention should be considered as the main goal in this era of 'globesity' yet is hampered by the multifactorial causation of obesity. Numerous prevention programs have been designed for local, national and global settings; however, the persistent rise in prevalence of obesity has not been turned yet. In addition, the currently obese children and adults will not be cured by prevention programs. Obviously, various treatment modalities have been developed over the past decades in order to treat the overweight and obese population.

In adults, the most commonly used treatment modalities can be subdivided roughly into lifestyle interventions, pharmacological treatments and surgical procedures. Lifestyle interventions, such as dietary counseling, behavioral therapy and sports and exercise, often appeal to healthcare professionals because they form a causative treatment idealistically focusing on sustainability throughout life. In addition, these interventions are non-invasive and often easily accessible. Evidence shows that combined lifestyle interventions can result in improved health status, yet the effect on body weight appears to be relatively small and difficult to maintain on the long term [60-64].
The pharmaceutical industry has developed several treatments for obesity, of which orlistat and sibutramine were commonly used in the past years. Sibutramine was developed to suppress appetite, where orlistat inhibits the digestive lipases in digestion and absorption of dietary fats. Metformin and the recently developed semaglutide (widely known as Ozempic®) are designed for treatment of diabetes mellitus type II and can induce weight loss as beneficial side effect. The effects of pharmacological treatments in terms of weight reduction are improving; structural use of semaglutide can result in up to 5-10% weight loss in one to two years [65, 66]. Counterarguments for the chronic use of these pharmaceuticals in the treatment of weight loss are also increasing: global supply shortages of the drugs in the field of diabetes care; the need for continued pharmaceutical treatment in order to maintain the effects; and last but not least potential gastrointestinal adverse events and lack of knowledge regarding long term side effects of the various types of medications [67, 68]. The Dutch National Health Care Institute recommends the use of semaglutide only for treatment of type 2 diabetes, and does not recommend orlistat as treatment of obesity because of lack of evidence regarding safety and effectiveness on the long term [69, 70]. Sibutramine has been withdrawn from the market in many countries because it has been associated with increased risk of cardiovascular events [71].

Weight loss surgery (known as bariatric surgery; BS) aims to establish structural changes of the gastrointestinal tract in order to decrease energy intake (restrictive surgery), energy uptake (malabsorptive surgery), or a combination of both. Commonly performed surgical procedures are the laparoscopic sleeve gastrectomy (LSG) and the laparoscopic Roux-and-Y gastric bypass (LRYGB), and in a far lesser extent the laparoscopic adjustable gastric band (LAGB); all summarized below [72]. All procedures have their own benefits and downsides; however, the sleeve gastrectomy and gastric bypass are often preferred because of their stronger effect on weight loss both on short- and long-term [73].

- *sleeve gastrectomy*: the greater curvature of the stomach is vertically resected and removed, resulting in a 'sleeve shaped' remaining stomach along the lesser curvature (see Figure 0.2A). The effects of a sleeve gastrectomy are believed to be caused by both restrictive and malabsorptive changes [74]. Reported effects range from 50-60% loss of excess weight up to ten years or more after surgery [75, 76]. Anastomotic

leakage forms a common complication on the short term, while anastomotic stricture or gastroesophageal reflux disease mostly occur later on.

- *Roux-and-Y gastric bypass*: the stomach is divided horizontally into an upper small pouch and a lower gastric remnant. A gastro-jejunal anastomosis is then created to allow ingested food to pass the pouch into the intestines, yet the food initially stays separated from all the digestive fluids. The dissected proximal jejunal part (transporting the gastric remnant's, pancreatic and hepatobiliary digestive enzymes) is connected to a more distal part of the jejunum via an entero-enterostomy, allowing the digestive enzymes to interact with the food eventually (see Figure 0.2B). The gastric bypass forms a combination of both restrictive and malabsorptive mechanisms of action [74]. A gastric bypass can result in approximately 80% excess weight loss, while 55-60% excess weight loss on average can be maintained up to ten years after surgery [75, 76]. Common complications are again anastomotic leakage on the short term, while long-term complications exist of internal herniation, anastomotic ulceration and/or nutritional deficiencies.
- *adjustable gastric banding*: a silicone band is placed around the upper part of the stomach, creating an upper pouch comparable to the pouch in LRYGB. The inner lining of the band is made of an inflatable silicone reservoir, connected to a subcutaneous port via a small tube, allowing physicians to adjust the degree of restrictiveness by injecting or retrieving saline via the subcutaneous port (see Figure 0.2C). The adjustable gastric band has merely restrictive effects, no parts of the digestive system are bypassed or removed [74]. On average, an excess weight loss of 40-45% can be achieved and maintained up to a decade after surgery [75, 76]. Reported complications consist of band slippage or erosion, and failure of the intervention on short- or long-term.

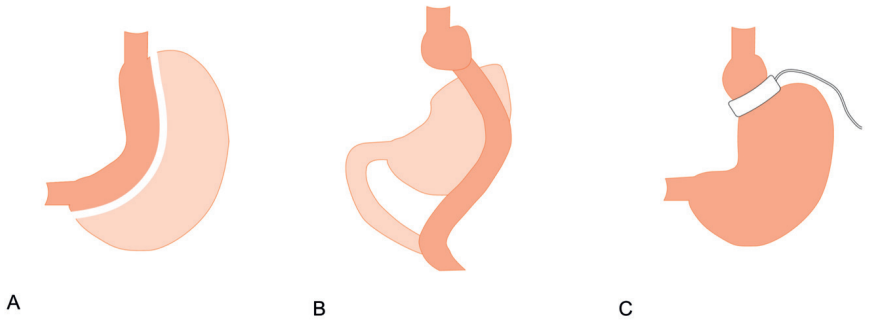


Figure 0.2: *Overview of commonly performed bariatric procedures: sleeve gastrectomy (A), Roux-and-Y gastric bypass (B) and adjustable gastric banding (C).*

Bariatric surgical procedures are thus accompanied by certain risks and complications, as is every surgical procedure. It was traditionally only recommended in morbid (or severe) obese adults, since the health-related consequences were then believed to outweigh the risks on damage or complications in or after surgery. Nowadays, a more liberal shift towards surgery for weight loss also in obese patients with obesity-associated metabolic comorbidity can be observed in certain areas [77]. In some countries, age restrictions are being extended to include youngsters and elderly as well, since morbid obesity itself is not limited to certain age groups [78-82]. However, randomized data as evidence on safety and efficacy of bariatric surgery in these specific subgroups remains scarce [83, 84].

TREATMENT OF SEVERE OBESITY IN CHILDREN AND ADOLESCENTS

Both national and international reports and guidelines suggest that the treatment of (morbid) obesity in children should follow a step-wise approach: lifestyle changes and structured weight management should be the first steps, followed by multidisciplinary lifestyle interventions or even more comprehensive tertiary care interventions [85-89].
Bariatric surgery can be performed as one of the tertiary care treatment modalities, only as last-resort treatment option in severe childhood obesity with failure of all the previous steps of the treatment plan. These pediatric patients living with severe obesity form the fastest growing subgroup within the pediatric obesity pandemic, suggesting there is an increasing need for efficient and persistent solutions such as bariatric surgery. Nevertheless, apart from multiple cohort series, not much high-level evidence has been reported regarding the safety and efficacy of bariatric surgery in children so far.

AIMS AND OUTLINE OF THIS THESIS

This thesis aims to contribute to a better understanding of the difficulties that adolescents with severe obesity encounter regarding access to specialized care and weight loss surgery, the physiological impact of obesity and the risks and challenges of (surgical) treatment in this specific age group. The studies presented in this thesis were conducted to answer the following questions:

1) *To what extent is specialized healthcare available and accessible for adolescents living with severe obesity and what is the role of different healthcare professionals in this landscape?*

2) *Is bariatric surgery in the form of laparoscopic adjustable gastric banding a safe and effective treatment option for adolescents?*

3) *To what extent will obesity-associated comorbidities improve in adolescents after weight loss due to bariatric surgery?*

Part I of this thesis focusses on access to specialized healthcare for adolescents living with severe obesity. **Chapter 1** describes the results of a survey amongst Dutch general practitioners regarding their attitudes towards treatment of childhood (severe) obesity. The differences in accessibility to specialized adolescent obesity care and national practices are further explored in **Chapter 2**. **Chapter 3** presents the design of the BAriatric Surgery In Children (BASIC) trial, a randomized controlled trial to investigate safety and efficacy of laparoscopic adjustable gastric banding as treatment of adolescents (14-16 years) living with severe obesity.

Part II explores the impact of severe obesity by evaluating different obesity associated comorbidities at baseline in the adolescents included in the BASIC trial. **Chapter 4** evaluates the presence of sleep abnormalities including OSA, while **chapter 5** focusses on the presence of left ventricular geometrical changes. The BASIC trial provides data on many more obesity associated comorbidities; however, those analyses fall beyond the scope of this thesis.

Part III of this thesis focusses on the results of the BASIC trial after one year of follow-up. **Chapter 6** provides the primary outcome measures of the trial: safety in terms of (serious) adverse events and efficacy measured in total weight loss and change in BMI z-score. In addition, changes in glycemic control are presented. **Chapter 7** evaluates the effects of LAGB on the presence and severity of OSA in comparison to the adolescents treated without surgery.

As the last part of this thesis, the Summary and Discussion will recapitulate the most important findings of the scientific research covered in this thesis and focus on the rationale of the BASIC trial and pros and cons of the trial. Opportunities for future clinical practice and research are presented regarding treatment modalities and prevention of severe obesity in adolescents.

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PART I:

ACCESS TO SPECIALIZED HEALTHCARE FOR ADOLESCENTS LIVING WITH SEVERE OBESITY



CHAPTER 1

Hurdles to take for adequate treatment of morbidly obese children and adolescents:

Attitudes of general practitioners towards conservative and surgical treatment of paediatric morbid obesity

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ABSTRACT

Background:

Bariatric surgery is regarded as the most effective treatment of morbid obesity in adults. Referral patterns for bariatric surgery in adults differ among general practitioners (GPs), partially due to restricted knowledge of the available treatment options. Reluctance in referral might be present even stronger in the treatment of morbidly obese children.

Objectives:

The aim of this study was to investigate the current practice of GPs regarding treatment of pediatric morbid obesity and their attitudes towards the emergent phenomenon of pediatric weight loss surgery.

Methods:

All GPs enlisted in the local registries of two medical centers were invited for a 15-question anonymous online survey.

Results:

Among 534 invited GPs, 184 (34.5%) completed the survey. Only 102 (55.4%) reported providing or referring morbidly obese children for combined lifestyle interventions. A majority (n = 175, 95.1%) estimated that conservative treatment is effective in a maximum of 50% of children. Although 123 (66.8%) expect that bariatric surgery may be effective in therapy-resistant morbid obesity, only 76 (41.3%) would consider referral for surgery. Important reasons for reluctance were uncertainty about long-term efficacy and safety. The opinion that surgery is only treatment of symptoms and therefore not appropriate was significantly more prevalent amongst GPs who would not refer (58.3% vs. 27.6%, $p < 0.001$).

Conclusion:

There is a potential for undertreatment of morbidly obese adolescents, due to suboptimal knowledge regarding guidelines and bariatric surgery, as well as negative attitudes towards surgery. This should be addressed by improving communication between surgeons and GPs and providing educational resources on bariatric surgery.

INTRODUCTION

The prevalence of morbid obesity in both adults and children has risen drastically worldwide over the past few decades, causing significant morbidity, mortality and financial costs for society [1-5]. In 2009, 2% and 0,5% of the children in the Netherlands were obese (BMI ≥ 30 kg/m^2) or morbidly obese (BMI ≥ 40 kg/m^2), respectively [5].

Combined lifestyle interventions (CLI) were developed as treatment for children and adolescents with (morbid) obesity. CLI should include at least dietary counselling, physical therapy and behavioural therapy, all provided by a specialized and dedicated multidisciplinary pediatric team [6, 7]. Although significant decrease of body mass index (BMI) has been reported in the short term, long-term benefits of CLI programs remain small [8, 9].

Consequently, several guidelines and position statements have been formulated to guide clinical decision-making which provide comparable indications, contra-indications and prerequisites for bariatric surgery in pediatric populations [10-15].

The Dutch Obesity Healthcare Standard (DOHS) advises pediatric bariatric surgery only in adolescents (i.e., age 16-17 years) who conform to a number of criteria, shown in Table 1.1 [14, 15]. In the Netherlands, pediatric bariatric surgery is exclusively performed in a clinical research setting.

Unfortunately, although bariatric surgery has been established as a highly effective treatment modality for a selected population of morbidly obese adults, a discrepancy has been noted between the number of patients eligible for bariatric surgery and the number of performed procedures [16-21]. This discrepancy has been attributed to several factors, such as knowledge of guidelines, knowledge of bariatric surgery and its outcomes, and referrer demographics [16-21]. The scarce literature available concerning referral patterns for children points towards an exceedingly conservative attitude, with a significant number of healthcare providers considering bariatric surgery in adolescents to be unacceptable and significant variations in opinions regarding prerequisites for surgery [22, 23].

To optimize pediatric obesity treatment, a potential discrepancy such as the aforementioned must be recognized and a possible educational gap filled. For this purpose, the practice, knowledge, and attitude of clinicians must be examined. In this light, GPs form an important group, as they are usually the first to encounter morbidly obese children and decide when to refer to a pediatrician. In addition, GPs play a crucial role in the follow-up of morbidly obese children, e.g., after (non-successful) combined lifestyle intervention (CLI) [14]. The aim of this study was to investigate the current

Table 1.1: *Criteria for pediatric bariatric surgery as defined by the DOHS [14, 15].*

Criteria for pediatric bariatric surgery
Adolescent (exact age not defined) with a BMI ≥ 40 or ≥ 35 with comorbidities
1-year treatment with CLI has provided insufficient weight loss (less than 10% of total body weight loss)
Bariatric surgery is combined with CLI
Attention is given to psychological multimorbidity
Adolescent must have grown fully physically and mentally
Family participation is essential
A motivation for long-term therapy and behavioural change must be present in adolescent and his/her family
The institution that performs the surgery must fulfill several predefined strict criteria

CLI = combined lifestyle intervention, at least consisting of dietary counseling, physical and behavioral therapy.

practice, knowledge, and attitude of Dutch GPs regarding conservative and surgical treatment of morbidly obese children.

METHODS

Questionnaire

An anonymous questionnaire was designed in an online platform for questionnaires and surveys (Survey Monkey Inc., San Mateo, California, USA) (Appendix 1.1). The questionnaire consisted of 15 questions covering demographics, current practice and attitudes towards bariatric surgery in children and adolescents (defined as youngsters aged 12-17 years). Conditional branching was used to create a respondent specific custom path based on the respondent's answers. Using this branching technique, the total amount of questions answered by a single respondent varied between 10 and 14 questions.

The fifteen items consisted of five dichotomous questions, one open question, five questions offered multiple choice with only one answer allowed, and four questions offered multiple choice allowing more than one answer. Of the latter, one question consisted of seven sub items, all to be scored on a Likert scale (range 1-5; never, seldom, sometimes, often, always). Some closed questions allowed textual remarks.

Participants

A sample size was determined using Cochran's formula for categorical data, using an alpha level of 0.05, a margin of error of 0.05 and an estimate of variance of 0.25 [24]. For

a representative sample of all the Dutch practice-based GPs (n = 9418; 7158 full-time equivalents), a minimum returned sample size of n = 364 was calculated. Consequently, a minimal sample size of n = 521 needs to be drawn from the population, assuming a response rate of 70%.

Selected for the online survey were all active GPs enlisted in the local registries of medical center A (n = 244) and medical center B (n = 290). Center A is a secondary and tertiary care hospital that holds the official Dutch training and education for GPs, and its local registry used for this survey consisted of only GPs affiliated to this official training. Center B is a secondary care hospital with bariatric surgery in adults as one of their main focuses; its local registry used for this survey consisted of all the GPs enlisted in their catchment area.

The GPs were invited for the online survey between July and September 2016. A single reminder was sent two to three weeks after the initial invitation.

Analysis

All completed surveys were used for analysis. Continuous data are presented as mean ± standard deviation. Categorical data are presented as number (percentage).
Categorical responses were compared using univariate analysis, χ^2 or Fischer's exact test where this was appropriate. Numerical responses were compared using independent samples t test. A significance level of $p < 0.05$ was used. The analyses were performed using IBM SPSS for Statistics (version 24.0.0.0).

RESULTS

Of the 534 invited GPs, 184 respondents completed the online survey (34.5%). All respondents were licensed and practicing GPs. The majority of respondents had less than 5 children on treatment for morbid obesity at the time of filling out the questionnaire (Table 1.2).

Lifestyle and dietary advices were reported to be provided often or always by at least 90% of the respondents in the case of childhood morbid obesity (Figure 1.1). Referral to sports or exercise programs was stated to be offered at least often by 70% of the respondents. The least frequent treatment modalities reported to be provided were cognitive behavioural therapy (CBT) and family treatment. When adequate GP treatment is defined as either referral to a pediatrician/specialized CLI team or self-provided high-intensity CLI including CBT and family treatment [6], only 55.4% (n = 102) of the respondents in this survey provides this adequate treatment.

Table 1.2: *Baseline characteristics of respondents and their practice.*

	Center A	Center B	p-value	Total
Number of respondents (n)	79	105		184
Years of working experience (mean ± SD)	19.6 ± 9.9	21.1 ± 10.0	0.308	20.4 ± 9.9
Children currently on treatment for morbid obesity, number (%)				
<5	68 (86.1)	89 (84.8)	0.803	157 (85.3)
5-15	9 (11.4)	16 (15.2)	0.451	25 (13.6)
16-30	2 (2.5)	0 (0)	0.183	2 (1.1)
>30	0 (0)	0 (0)		0 (0)

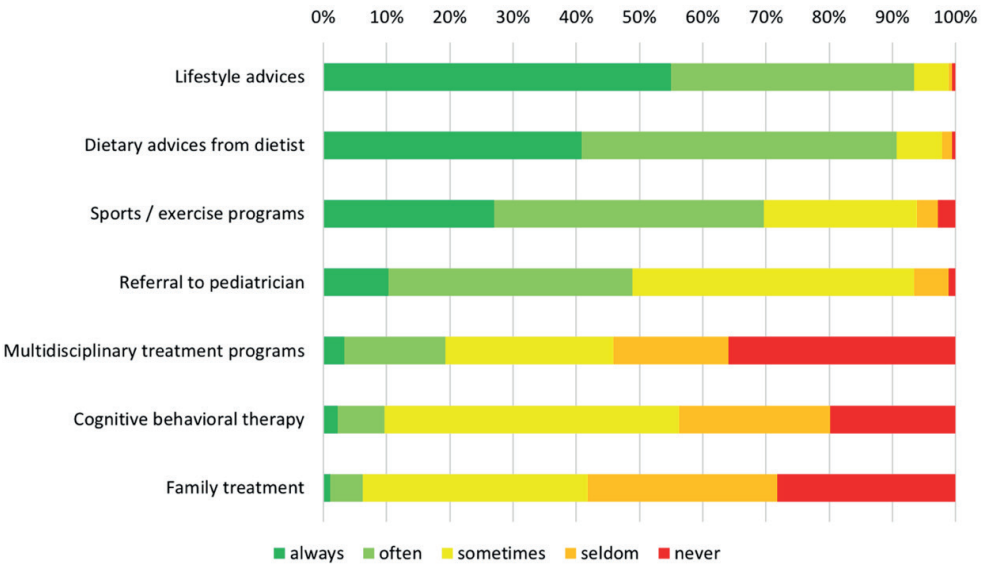


Figure 1.1: *Reported frequency of providing different treatment modalities.*

Different norms of treatment success were observed among respondents. Thirty-eight respondents (20.6%) considered weight stabilization after 6-12 months as treatment success. The majority reported that weight loss is necessary after 12 months of treatment to consider the treatment a success, varying from 5% weight loss or more (n = 34, 18.5%) to at least 10% (n = 60, 32.6%), being the DOHS definition for treatment success. Seventeen respondents (9.2%) noted to consider improvement of comorbidity as the parameter for treatment success. Thirty-five GPs (19.0%) stated they apply other (less objective) definitions, such as improvement of lifestyle or diet.

The vast majority (n = 175, 95.1%) estimated that the conservative treatment modalities offered are only effective in a maximum of 50% of the children. In general, 123 respondents (66.8%) answered they expect that bariatric surgery may be effective in children with therapy-resistant morbid obesity. Nevertheless, only 76 (41.3%) would consider referral for bariatric surgery in this population.

Different subgroups were analysed regarding both the expectation of effectiveness of bariatric surgery and the consideration for referral for surgery. Regarding the expectation of effectiveness, no differences were found in the following subgroups: different hospital regions (center A vs. center B, p = 0.707), years of working experience (<20 years vs. ≥20 years, p = 0.157), number of morbidly obese pediatric patients under treatment in practice (<5 vs. ≥5, p = 0.983). Willingness to refer for bariatric surgery did also not differ among the same subgroups: different hospital regions (p = 0.186), years of working experience (p = 0.291), number of morbidly obese pediatric patients under treatment in practice (p = 0.949).

The 76 respondents who would consider referral for bariatric surgery were asked additional questions regarding their attitudes towards specific aspects of bariatric surgery in children. Fifty-one GPs (67.1%) stated a lower threshold for age than 16 years old, proposing a mean minimum age of 14.1 years (range 10-16 years) [14]. The majority of the respondents (n = 42, 55.3%) would consider referral in case of a BMI ≥ 40 kg/m^2 (sex and age adjusted), while 20 respondents (26.3%) would already refer in case of a BMI ≥ 35 kg/m^2. Five respondents (6.6%) suggested a minimum BMI of 50 kg/m^2, nine (11.8%) could not suggest a specific BMI threshold.

The presence of obesity-related comorbidity would influence the minimum BMI threshold for 66 respondents (86.8%). Type II diabetes mellitus was answered most often as comorbidity of influence (n = 62, 93.9%), followed by obstructive sleep apnea (n = 49, 74.2%) and hypertension (n = 45, 68.2%). Dyslipidemia and non-alcoholic hepatic steatosis were relevant for 36 (54.5%) and 25 (37.9%) respondents, respectively. Presence of a depressive disorder was mentioned as relevant by 30 respondents (45.5%), arthropathies were mentioned by 23 (34.8%).
The 108 respondents who answered not to consider referral for bariatric surgery were asked if certain circumstances would alter their opinion. Twenty-two respondents (20.4%) reported to consider referral after all in case of severe and/or therapy-resistant comorbidity.

All 184 respondents were asked about possible reasons for reluctance towards bariatric surgery in children and adolescents with morbid obesity. Uncertainty regarding complications in the long term was mentioned most (n = 132, 71.7%), followed by

uncertainty regarding long-term efficacy (n = 119, 64.7%) and the notion that bariatric surgery only treats symptoms (n = 84, 45.6%) (Figure. 1.2).

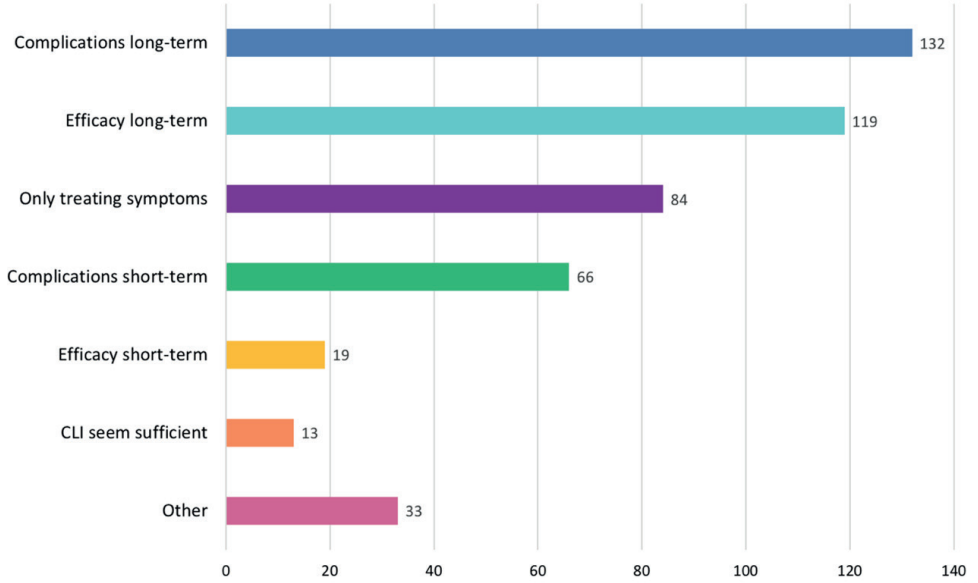


Figure 1.2: *Reported frequency of reasons mentioned for reluctance.*

There were no differences regarding uncertainty about complications or efficacy among the respondents who would refer for surgery compared to those who would not. However, the opinion that bariatric surgery is merely a treatment of symptoms as reason for reluctance was mentioned significantly more frequent by respondents who would not refer (n = 63, 58.3%) compared to the group that would refer (n = 21, 27.6%), $p < 0.001$. There were no differences in reasons for reluctance among the two hospital regions. Thirty-three respondents (17.9%) added other reasons to the list, varying from 'the expectancy that near future will bring other solutions to the problem' to 'supply creates demand'.

DISCUSSION

Main findings

The present study aimed to investigate the practice and attitudes of GPs regarding pediatric morbid obesity using a digital survey. In current treatment, lifestyle advices, dietary advices and sports or exercise programs (all provided by experts) are offered most often by the responding GPs. However, there is a significant discrepancy between the DOHS and reported GP practice, implicating a relevant knowledge gap (Table 1.3).

Table 1.3: *GPs answers in relation to position of DOHS [14, 15].*

Position of Dutch Obesity Healthcare Standard	Percentage of GPs adhering to/acknowledging guideline
An obese child should be treated via CLI (either by referral to a pediatrician/specialized CLI team or self-provided high-intensity CLI including CBT and family treatment)	55.4% (n = 102)
Treatment failure of CLI defined as less than 10% total body weight loss during 12 months, in outgrown children	32.6% (n = 60)
Bariatric surgery may be considered in children with therapy-resistant morbid obesity	66.8% (n = 123)
Minimum BMI for referral is ≥ 35-40 kg/m^2	81.6% (n = 62)*
The presence of comorbidity influences the minimum BMI threshold for referral	86.8% (n = 66)*

* Percentage of those who would refer

Ninety-five percent of GPs estimated that their treatment is only sufficient in <50% of the patients. Although the majority of respondents think that bariatric surgery may be an effective last-resort treatment option, only 41.3% of the respondents would consider referral for surgery in this childhood population. This discrepancy may be related to non-efficacy-related factors, such as matters of principle. For example, one GP noted that 'supply creates demand', another GP noted that 'the future will bring other solutions to the problem', and many GPs (45.6%), especially those who would not refer, stated the notion that surgery only treats symptoms as reasons for reluctance.

Remarkably, the average minimum age threshold of 14.1 years proposed by GPs that would consider referral was significantly lower than was found in a 2010 survey conducted amongst GPs and pediatricians in the United States, where physicians who would refer for bariatric surgery believed a minimum age of 16.9 years was necessary [23]. This might

indicate that the GPs open to referral for bariatric surgery are becoming more progressive in their attitudes, while the majority of GPs remain reluctant to refer morbidly obese children or adolescents for bariatric surgery.

Reasons for reluctance

Frequently mentioned reasons for reluctance were uncertainty regarding complications in the long term and uncertainty regarding long-term efficacy (71.7 and 64.7%, respectively). Although bariatric surgery is effective and safe both in the short and long term in an adult population [25-29], there indeed is a scarcity of long-term data in the pediatric population, which must be accommodated by future research [30]. On the other hand, a significant proportion of GPs reported reluctance due to the aforementioned personal notions, which should be addressed through educational means, to assure proper and uniform care for therapy-resistant morbid obese adolescents.

Strengths and limitations

One of the strengths of this study is that the population used for this survey is representative for the different Dutch GP practices, combining GPs affiliated with both secondary and tertiary medical centers. Since there are no Dutch tertiary centers practicing bariatric surgery on a regular base, the subgroup GPs affiliated to the tertiary center in the present study is assumed to be less experienced in bariatric care (but may be more updated on innovative treatments since they hold the GP training). Due to the design of this study, GPs affiliated to a secondary center without bariatric surgery have not been included, which may lead to a certain amount of bias. However, in a small country such as the Netherlands, most GPs are in close proximity to a bariatric center in daily practice.

Another strength of this survey is that reasons for reluctance were reported by all respondents, offering more insight in reasons why GPs would not refer.

Self-selection bias is one of the limitations of this study, accompanied by the fact that potential differences between responders and non-responders could not be assessed. Another important limitation to this survey is that the self-reported answers regarding current practice might not reflect the actual practice. This survey is based on estimations of GPs themselves and no verification of data has been carried out. In addition, the prevalence of childhood morbid obesity seems to be relatively low in most practices (85.3% treats less than 5 patients), which might hamper statements regarding current practice and could cause recall bias. Furthermore, the sample size of 184 respondents did not meet the desired minimum of the sample size calculation due to a lower than anticipated response rate. Although this must be kept in mind when interpreting the results, the current sample is the largest to date investigating this topic.

Interpretation of results in relation to existing literature

The reported absence of CLI treatment in many cases and poor compliance to the national guidelines when defining treatment success implies that there is a relevant knowledge gap that may lead to inadequate treatment of pediatric morbid obesity in primary care. This implication is further supported by several comparable studies in adults, where a majority of GPs reported feeling unconfident, insufficiently competent, and disempowered regarding treatment of obese patients [17, 19-21]. One study surveying knowledge on procedural aspects, efficacy, and safety of adult bariatric surgical procedures in primary care practitioners found that non-referrers had significantly less knowledge compared to those who do refer [16]. Additionally, in a recent study 92.5% of family physicians reported that they would like to receive more education about bariatric surgery [21]. Educational resources on the topic of bariatric surgery must be provided to GPs, to improve care for morbidly obese adolescents.

Only few surveys that have investigated attitudes of GPs towards bariatric surgery in youngsters have been published. Claridge et al. performed a qualitative study among 12 GPs [20], while Penna et al. surveyed a variety of health care professionals (of which only 30 were GPs) [22]. Woolford et al. performed a survey comparable to the current design; however, their survey has been conducted in 2007 while this relatively new field of treatment options is evolving rapidly [23].

Interestingly, the study of Penna et al. revealed that GPs prompted a higher minimum age for bariatric surgery than surgeons. By contrast, GPs were less likely to prerequire parental counselling and parental involvement in the child's weight management than surgeons. This discrepancy further supports the notion that education of GPs and communication between surgeons and GPs is necessary to offer a uniformly optimal quality of care for obese adolescents.

CONCLUSION

There may be a group of morbidly obese adolescents who would benefit from referral to bariatric surgery, but are instead treated sub-optimally. This could be the result of insufficient knowledge of clinical practice guidelines and bariatric surgery in general. Moreover, the fact that only half of the GPs would consider referral of selected adolescents, even though the majority considers bariatric surgery as an effective last-resort treatment option, may in part be based on opinions and matters of principle. These issues should be addressed by ameliorating communication and cooperation between surgeons and GPs as well as providing GPs with educational resources on bariatric surgery in adolescents and in general.

COMPLIANCE WITH ETHICAL STANDARDS

All authors declare that they have no conflict of interests.

APPENDIX 1.1:

Survey: attitudes towards bariatric surgery in children and adolescents

1. What is your current position?
    a. Registered General Practitioner (GP)
    b. General Practitioner in training (GP_{it})

2. How many years of experience do you have (including training)?

The next questions are asked to give us information about your experience and current practice regarding morbidly obese children (defined as BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with obesity-associated comorbidity; sex and age adjusted). Below you can find the Dutch sex and age adjusted thresholds for morbid obesity.

	Boys		Girls	
Age	**BMI 35**	**BMI 40**	**BMI 35**	**BMI 40**
12	30.2	34.8	31.2	38.0
13	31.8	36.9	32.6	38.9
14	32.9	38.4	33.3	39.4
15	33.7	39.1	33.9	39.7
16	34.2	39.5	34.3	39.9
17	34.6	39.8	34.7	39.9

3. How many morbidly obese children do you treat currently?
    a. <5
    b. 5-15
    c. 15-30
    d. >30

4. Which of the following treatment modalities or referrals do you offer to children with morbid obesity (never, seldom, sometimes, often, always)?
    a. Lifestyle advices
    b. Dietary advices (provided by dietician)
    c. Sports or exercise programs (provided by expert)
    d. Cognitive behavioural therapy (provided by behavioural therapist)
    e. Family treatment (provided by behavioural therapist)
    f. Multidisciplinary treatment programs
    g. Referral to pediatrician
    h. Other (please describe)

5. When do you consider the provided treatment as successful in full-grown morbidly obese children?
    a. Stabilization of weight after 6 months treatment
    b. Stabilization of weight after 12 months treatment
    c. Weight loss ≥ 5% after 12 months treatment
    d. Weight loss ≥ 10% after 12 months treatment
    e. Improvement of comorbidity, irrespective of weight changes
    f. Other (please describe)

6. In how many children with morbid obesity do you estimate that the provided therapy is effective?
    a. 0-25%
    b. 25-50%
    c. 50-75%
    d. 75-100%

7. Do you think that bariatric surgery can be an effective treatment modality in morbidly obese children who do not respond sufficiently to conservative treatment?
    a. Yes
    b. No

8. Would you consider referral of a child for bariatric surgery in case conservative treatment does not lead to sufficient improvement?
    a. Yes
    b. No (branching logic: respondent proceeds to question 14)

The following questions will be about your attitude towards bariatric surgery in morbidly obese children. For all questions, a stable and supportive home situation can be assumed. In addition, it can be assumed that combined lifestyle interventions have been provided for at least 1 year without success.

9. Should there be a minimum age threshold for childhood bariatric surgery?
    a. No, not necessary
    b. Yes, namely … (number in years)

10. In the case of no comorbidity, which BMI would you apply as a lower threshold when considering referral of a morbidly obese child for bariatric surgery?
    a. 30 kg/m^2
    b. 35 kg/m^2
    c. 40 kg/m^2
    d. 50 kg/m^2
    e. 60 kg/m^2
    f. Other (please describe)

11. Would the presence of comorbidity influence the answer given at question 10?
    a. Yes
    b. No (branching logic: respondent proceeds to question 13)

12. Presence of which of the following comorbidities would influence your attitude towards referral of morbidly obese children for bariatric surgery (as answered in question 10)?
    a. Type II diabetes mellitus
    b. Dyslipidemia
    c. Hypertension
    d. Obstructive sleep apnea
    e. Arthropathies
    f. Non-alcoholic hepatic steatosis
    g. Depressive disorder
    h. Other (please describe)

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CHAPTER 2

Current opinions and practices of bariatric surgery in adolescents:

A survey among pediatric surgeons

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ABSTRACT

Aim:

Bariatric surgery is performed at increasing rate in severely obese adolescents who do not respond to conservative treatment. In the United States of America (USA) this treatment is generally accepted, yet in Europe surgeons are more reluctant because of concerns regarding safety and (long-term) efficacy. We evaluated in which (European) countries bariatric surgery is allowed and performed, and the opinion of members of the European Paediatric Surgeons' Association (EUPSA) regarding bariatric surgery in adolescents.

Methods:

Information was obtained with an online questionnaire sent to all EUPSA members.

Results:

108 pediatric surgeons (PSs) from 33 countries (of which 25 European) completed the survey. Sixty-two PSs (57.4 %) from 22 countries stated that bariatric surgery in adolescents was allowed in their country. In only 14 countries, the costs were (partially) covered by healthcare insurances. Overall, 65.7 % of the surgeons (n=71) believed bariatric surgery may offer a valuable contribution to obtain substantial long-term weight loss in severely obese adolescents. Fifty-one (47.2 %) reported that these procedures should be performed by a combination of a bariatric and a pediatric surgeon, while 20 (18.5 %) and 16 (14.8 %) preferred that these procedures should be performed solely by a pediatric or bariatric surgeon respectively.

Conclusions:

Although allowed in most European countries, bariatric surgery in adolescents is only practiced on a small scale, and the treatment is often excluded from regular healthcare reimbursement. The majority of PSs acknowledge the value of bariatric surgery, which should be performed by a combination of pediatric and bariatric surgeons.

INTRODUCTION

In the past four decades the prevalence of childhood and adolescent obesity has risen tenfold, with currently 6% of girls (50 million) and nearly 8% of boys (74 million) being obese worldwide [1]. Although various registries show plateauing of the prevalence curves of pediatric obesity, the number of children with severe obesity (body mass index > 35kg/m2, BMI) is still increasing [2,3]. In consequence of this obesity pandemic, many efforts have been made to improve the treatment of obesity in the young age group [4,5]. Combined lifestyle interventions (CLI) were regarded as the most optimal treatment for obese and severely obese children and adolescents for a long time. Although significant short-time reduction of BMI can be obtained by conservative treatment, the long-term benefits of CLI programs remain small [5-7].

Because of the efficacy of bariatric surgery reported in adults, there is considerable interest to utilize this treatment modality in a younger population. Both among bariatric and pediatric surgeons, the trend of pediatric bariatric surgery is gaining attention and various bariatric procedures are already performed in adolescents with severe obesity not responding to conservative treatment [8]. Bariatric surgery is considered safe and effective by many to obtain substantial weight loss and resolution of associated comorbidities [9,10].

Despite the favorable results of bariatric surgery in the literature, implementation of this treatment shows a large variety worldwide. While numbers of severely obese adolescents undergoing bariatric surgery in the United States (US) are increasing, surgeons in Europe seem more reluctant to perform such procedures.

The aim of this study is to assess the opinion and practice of pediatric surgeons in different European countries to treat severe obesity in adolescents. Therefore, we conducted an online survey among European Paediatric Surgeons Association (EUPSA) members. We evaluated in which European countries bariatric surgery is allowed and performed, and the opinion of EUPSA members about bariatric surgery in adolescents.

MATERIAL AND METHODS

Questionnaire

A depersonalized questionnaire was designed using an online platform for questionnaires and surveys (Survey Monkey Inc., San Mateo, California, USA) (Appendix 1). The questionnaire consisted of 18 questions in total, obtaining information on national regulations and current national practice, and secondly, addressing the individual areas

of knowledge, current practice and attitudes towards bariatric surgery in adolescents. Except for two demographic questions, all questions were closed (one dichotomous, 15 multiple choice). Some closed questions did allow textual remarks. Conditional branching was used to create a customized path based on the respondent's answers. Using this branching technique, the number of questions answered by a single respondent varied between 11 and 18 questions.

Participants

All members of the European Paediatric Surgeons' Association (EUPSA) were invited for the online survey in October 2018. Responses received between October and November 2018 were eligible for inclusion. No reminders were sent to the invited surgeons.

Analysis

All completed surveys were used for analysis. Continuous data are presented as mean ± standard deviation. Categorical data are presented as number (percentage). If answers on questions about national practice and regulations from surgeons from one country were contradictory, the score for this country was classified as 'unknown'. For the question 'if bariatric surgery was performed or not', the answer was classified as 'yes' if one of the surgeons who answered ' yes' (a) also clarified that he himself performed bariatric surgery in adolescents or (b) if this 'yes' could be confirmed by international scientific publications about bariatric surgery in adolescents from this country.

RESULTS

Six-hundred eighty-six EUPSA members received an invitation for the survey in October 2018. Of the 118 responses, 8.5 % (n=10) were partially answered questionnaires and these were not included in the analyses. The 108 complete responses resulted in a response rate of 15.7 %.

Demographics

In total, 108 pediatric surgeons (PSs) from 25 European and 8 non-European countries completed the survey (Figure 2.1). The majority of respondents worked in a university hospital in a European country (Table 2.1). Twenty-eight PSs (25.9 %) reported no specialisation within pediatric surgery, while pediatric gastrointestinal surgery was reported by 47 (43.5 %). The mean working experience in pediatric surgery was 19.8 ± 12.9 years.

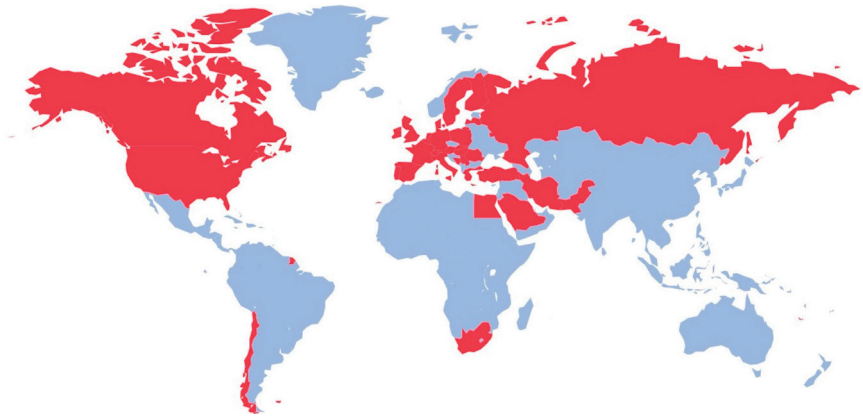


Figure 2.1: *Distribution of respondents (countries in red) around the world.*

Table 2.1: *Baseline characteristics of respondents.*

	Respondents (n=108)
Country of practice	
European	76.9 % (n=83)
Non-European	23.1 % (n=25)
Healthcare setting	
University hospital	80.6 % (n=87)
Regional hospital	11.1 % (n=12)
Private practice	5.6 % (n=6)
Other	2.8 % (n=3)
Current position	
Consultant	81.5 % (n=88)
Resident/Fellow (in training)	8.3 % (n=9)
Other	10.2 % (n=11)
Associate professor	2.8 % (n=3)
Professor	2.8 % (n=3)
Head of department	4.6 % (n=5)

National practice

In 22 countries, of which 16 European countries it was stated that bariatric surgery in adolescents was allowed or not forbidden. Unanimous standards for bariatric surgery in adolescents were, as reported, only present in three countries (Portugal, Saudi Arabia, USA)

Further differences among countries including the number of centers, the presence of separate pediatric bariatric surgical units, and differences in reimbursement of the costs are listed in Table 2.2.

The number of clinical practices in countries that perform such surgery is reportedly '1 – 2 centers', n=9; '1 – 5 centers', n=5; '3 – 5 centers', n=3; 'more than 5 centers', n=3; 'unknown' n=3. This includes one country in which bariatric surgery in adolescents is not allowed, apart from operations in a trial (The Netherlands). The costs for bariatric surgery are in most countries covered by the healthcare insurance.

Personal practice and opinion

Fifteen PSs (13.9 %) reported to personally perform bariatric surgery in children and/or adolescents. An additional 13 PSs (12.0 %) reported to work in a practice where bariatric surgery in adolescents was performed by colleagues; being either PSs (n=8, 7.4 %) or adult bariatric surgeons (n=5, 4.6 %).

The sleeve gastrectomy was the most commonly used operation (sleeve gastrectomy, n=21; gastric banding, n=10; Roux-and-Y gastric bypass, n=10; other procedures, n=3).

Overall, 65.7 % of the PSs (n=71) believed bariatric surgery may offer a valuable contribution to obtain substantial long-term weight loss in severely obese adolescents. Nine PSs (8.3 %) objected to bariatric surgery in adolescents, the rest of the respondents had no clear opinion. To who should do bariatric surgery in adolescents, fifty-one PSs (47.2 %) were in favour for a combination of both pediatric and bariatric surgeons, while 20 (18.5 %) and 16 (14.8 %) PSs preferred either a pediatric or a bariatric surgeon respectively.

Discussion

This survey aimed to assess the current national and personal practices of bariatric surgery in adolescents among PSs in Europe and other countries. Although there is plenty of literature assessing the feasibility and outcome of this treatment, data to assess the actual clinical practice of bariatric surgery in different countries is lacking.

Our findings demonstrate that most PSs believe that bariatric surgery offers a valuable treatment option for extreme obesity in adolescents who do not respond to conservative treatment. The majority of PSs stated that these procedures can be performed legally, however only few PSs were able to confirm the existence of national clinical standards and more than 20% of the respondents did not know if bariatric surgery was allowed in their country. There are specific guidelines for bariatric surgery in adolescents in several countries; only a limited number of the respondents of each of these countries was aware of its existence. The poor awareness of national guidelines implies a relevant

Table 2.2: *Practice and regulations for bariatric surgery in adolescents per country.*

Country	Number of respondents	Bariatric surgery in adolescents: allowed	Number of centers	Separate pediatric centers	Bariatric surgery in adolescents: reimbursement
Austria	2	Yes	1-2	Yes	HI
Belgium	4	Yes	3-5	Yes	Patient
Bosnia- Herzegovina	1	No	-	-	-
Canada	1	Yes	3-5	Yes	Hospital
Chile	2	Yes	1-2	No	Hospital
Denmark	3	No	-	-	-
Egypt	1	Yes	>5	Yes	Not stated
Finland	2	Yes	1-2	Unknown	HI
France	4	Yes	1-2/3-5	Yes	HI
Germany	6	Unknown	Unknown	-	HI, other (patient)
Greece	5	Yes	1-2	No	Patient
Hungary	3	No	-	-	-
Iran	1	Yes	Unknown	-	Combination
Ireland	1	Unknown	-	No	-
Italy	11	Yes	1-2/3-5	Yes/No	HI, patient
Latvia	1	No	-	-	-
Luxemburg	1	No	-	-	-
Netherlands	6	No*	1-2	Yes	HI
Pakistan	1	Unknown	1-2	Unknown	HI, patient
Poland	5	Yes	1-2/3-5	Yes	
Portugal	2	Yes	1-2	Yes	Hospital
Rumania	8	Yes	1-2/3-5	No	HI
Russia	1	No	-	-	-
Saudi Arabia	1	Yes	Unknown	No	HI
Serbia	1	Yes	1-2	No	HI
Slovakia	1	Yes	1-2	Yes	HI
South Africa	2	Unknown	Unknown	No	Unknown
Sweden	10	Yes	1-2	No	HI
Spain	8	Yes	1-2/3-5	Yes	HI
Switzerland	2	Yes	Unknown	Unknown	HI, combination
Turkey	13	Yes	3-5	Unknown	HI, combination
United Kingdom	6	Yes	>5	Yes	HI
United States	1	Yes	>5	Yes	HI

(HI: healthcare insurance, * only allowed in a clinical trial)

knowledge gap, possibly leading to a decreased access to this treatment for severely obese adolescents.

Based on this survey, we conclude that bariatric surgery in adolescents in Europe is only practiced on a small scale. A relatively small proportion of the respondents in our survey performs bariatric surgery themselves or works in an institution where adolescent

bariatric surgery is performed. We would expect that pediatric surgeons who actually do bariatric surgery in patients of this age group, would be more interested in this survey, and therefore have completed the survey more often. However, it is possible that bariatric surgeons do bariatric operations in this age group without pediatric surgeons knowing this and we have not sent the survey to bariatric surgeons to confirm our findings.

An important factor that may affect variation in bariatric surgical activity among countries is the reimbursement of the costs for bariatric operations in adolescents. This differs from reimbursement in adults as adolescent bariatric surgery is often not seen as a standard treatment for extreme obesity with supposedly inadequate evidence of its benefits. A study of Inge et al. demonstrated that age less than 18 years is by far the most common provided reason for denial in reimbursement of costs of adolescent bariatric surgery [11].

Information about bariatric surgery in adolescents has been collected from 33 different countries, including 25 European countries, so that a very good overview of adolescent bariatric surgical activity in Europe is obtained. As the epidemic of extreme obesity is also increasing in Europe, the conclusion that adolescent bariatric surgery in Europe will grow in the near future seems justified, although the percentage of severely obese youth in the US is still much higher than in Europe. Another interesting finding is that the vast majority of the pediatric surgeons who participated in the survey reported that there should be a role for the pediatric surgeon to do this type of surgery either together with a bariatric surgery or not. The special position of adolescents in whom behaviour is developing rapidly and in whom feeding and nutritional deficiencies including vitamins, minerals and trace elements, are vital for normal development, may necessitate a wide view on bariatric operations and an important role for the pediatric surgeon.

The majority of the respondents also recognizes a role for an adult bariatric surgeon in a future pediatric bariatric surgical team. This survey can act as an initiation for further assessment of various national practices and perhaps collaboration of both pediatric and bariatric surgeons in the different European countries.

CONCLUSION

Bariatric surgery in adolescents is allowed in most European countries, however only few countries have national clinical guidelines for this specific patient group. In most countries bariatric surgery in adolescents appears to be practiced only on a small scale, and patients may be excluded from regular healthcare reimbursement. The majority of PSs reported that bariatric surgery is a valuable treatment in adolescents with extreme obesity in whom other treatment has failed. It seems crucial that experiences both from

both adult bariatric surgeons and in pediatric surgeons are shared and consensus in treatment can be reached.

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CHAPTER 3

Bariatric surgery in adolescents:

A prospective randomized controlled trial comparing laparoscopic gastric banding to combined lifestyle interventions in adolescents with severe obesity (BASIC trial)

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ABSTRACT

Background:

Obesity in children and adolescents is an increasing problem associated with multiple comorbidities including metabolic and endocrine changes, cardiovascular abnormalities, and impaired quality of life. Combined lifestyle interventions are the current standard treatment for severe obesity in children. However, the medium- and long-term results of these interventions are relatively poor. Bariatric surgery shows substantial weight loss and health improvement in adults and retrospective studies in adolescents show similar outcomes. However, well-designed prospective studies in this young age group are rare. Our objectives are to determine whether combining surgery with lifestyle interventions in severely obese adolescents leads to a significant additional weight reduction compared to lifestyle interventions solely, and to assess its effect on obesity-associated comorbidities in a prospective randomized controlled setting.

Methods:

Patients aged 14-16 years with sex- and age-adjusted BMI ≥40 kg/m^2 (or ≥35 kg/m^2 with comorbidity) and failure to achieve weight reduction >5% during at least one year of combined lifestyle interventions are included in this trial. Randomization determines whether laparoscopic adjustable gastric banding will be added to combined lifestyle intervention throughout the trial period. Sixty children will be included in this trial. Follow-up visits are planned at 6 months, 1, 2 and 3 years. Primary endpoints are percentage of total weight loss, and change of BMI. Secondary endpoints include body composition, pubertal development, metabolic and endocrine changes, inflammatory status, cardiovascular abnormalities, non-alcoholic steatohepatitis, quality of life and changes in behaviour.

Discussion:

This randomized controlled trial is designed to provide important information about the safety and efficacy of laparoscopic adjustable gastric banding treatment in severely obese adolescents with unsuccessful combined lifestyle interventions. The reversibility of this surgical procedure forms a strong argument to decide for gastric banding over other surgical procedures, since bariatric surgery in adolescents is still in its infancy.

BACKGROUND

Overweight and obesity in children has become a global health problem during the past decades. It has already been designated as 'one of the most serious public health challenges of the 21st century' by the World Health Organization [1]. Obesity during childhood can have serious consequences for several organ systems including the cardiovascular and the endocrine, and can result in psychosocial comorbidity [2, 3]. Furthermore, children with overweight and obesity are prone to become obese adults, with an ongoing risk of comorbidities [4-6]. If obesity is more severe, or shows a greater variability or rapid increase, adolescents are less likely to grow out of their obesity [4, 7].

In accordance with treatment in adults, there are various treatment methods for overweight and obesity in children. Several interventions have been studied in childhood populations [8-11]. Lifestyle interventions are often based on physical activity, dietary and/or behavioural interventions. Combination of these non-pharmacological lifestyle components can result in a decrease in body mass index (BMI) up to twelve months after treatment, but effect sizes remain small [8]. Evidence for long-term weight control following these lifestyle interventions in children is scarce, but it should be noted that in adults the majority of these interventions have been proven to be ineffective in long-term weight control [12, 13]. Pharmacological treatment can enhance weight loss when prescribed as additional therapy next to lifestyle interventions [8]. Both orlistat and sibutramine seem to be effective in adolescents, but again the effects remain small and long-term data is limited [14-18].

Since the risk of associated comorbidity increases with an increasing BMI, the need for an effective and long-term solution to lose weight is even more urgent for children and adolescents with severe obesity [19, 20]. In the adult population, bariatric surgery is widely accepted as treatment for severe obesity. Bariatric surgery enables patients to lose more weight compared to non-surgical interventions, regardless of the type of surgery [21]. In addition, the effect of bariatric surgery has been proven to persist over many years, leading to reduction in mortality and obesity-associated comorbidity in the long-term [21-23]. Because of ethical considerations and the potential for serious complications, bariatric surgery is not generally accepted (yet) as a last-resort treatment option in therapy-resistant severely obese children. In order to substantiate the additional value of bariatric surgery compared to treatment with lifestyle interventions alone, more evidence on safety and effectiveness of childhood bariatric surgery is required. Few prospective cohort studies on childhood bariatric surgery have been published. The majority of these studies address one of the three common bariatric procedures: laparoscopic adjustable banding (LAGB), laparoscopic sleeve gastrectomy (LSG), and laparoscopic roux-and-y gastric bypass (LRYGB) [24, 25]. In general, these cohort studies suggest effective weight

loss up to 36 months (-10 to -15 BMI points depending on the procedure) [26]. However, only one randomized controlled trial has been carried out to compare bariatric surgery with conventional treatment in adolescents, resulting in -12.7 versus -1.3 BMI points after two years for intervention and control group respectively [27]. The present study differs from this previous study, as we include only patients who underwent lifestyle interventions in a multidisciplinary setting before for more than one year and nevertheless failed to lose weight [10, 11].

Despite the lack of the highest quality evidence that bariatric surgery in adolescents is safe and can be successfully done, this treatment has been popularised in certain countries to treat adolescents with severe obesity. In most countries in Europe, they are more reluctant to do an operation for severe obesity, or bariatric surgery in youngsters is not performed at all.

STUDY OBJECTIVES

Combined Lifestyle Interventions (CLI) are the current standard to obtain weight reduction in severely obese children and adolescents [10, 28, 29]. The main aim of the 'Bariatric Surgery in Children' (BASIC) randomized controlled trial is to investigate whether last-resort LAGB treatment in children and adolescents is safe and effective in terms of (excess) weight loss and loss of excess BMI. Secondary objectives in this trial focus on obesity associated comorbidity and include assessment of body composition, pubertal development, metabolic and endocrine changes, inflammatory status, cardiovascular abnormalities, non-alcoholic fatty liver disease, quality of life, general and food-specific cognitive processes, changes in behaviour and effects on sleep architecture.

METHODS

Study design

We will perform a prospective superiority trial by randomizing severely obese children and adolescents in a 1:1 ratio to receive LAGB on top of the CLI versus CLI treatment alone. The study protocol meets the criteria of the 'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT) Guidelines [30]. The trial will be carried out at the Maastricht University Medical Center in the Netherlands. Outcomes will be measured at six, 12, 24 and 36 months from randomisation and will be evaluated after 12 and 36 months.

Study population

Inclusion criteria: The study population includes severely obese children who underwent long-term multidisciplinary lifestyle interventions without the intended effect. All

children referred to our clinic for enrolment in the trial are screened for the following inclusion criteria: age 14, 15 or 16 years old; age- and sex-adjusted BMI ≥40 kg/m^2 or ≥35 kg/m^2 with obesity associated comorbidity (Table 3.1) [29, 31]; and participation in at least one multidisciplinary organized pediatric weight reduction program (as combined lifestyle interventions, CLI) for a minimum period of 12 months, without accomplishing the intended effect of 5% weight loss or more. The CLI should be coordinated and monitored by a pediatrician and include at least regular dietary advice and monitoring from a certified dietician, regular exercise training and behavioural therapy from a trained psychosocial worker.

Table 3.1: *Age- and sex-adjusted BMI cut-off points for severely obesity in the Dutch population [29].*

	Boys		Girls	
Age [years]	**BMI 35 [kg/m^2]**	**BMI 40 [kg/m^2]**	**BMI 35 [kg/m^2]**	**BMI 40 [kg/m^2]**
14	32.9	38.4	33.3	39.4
15	33.7	39.1	33.9	39.7
16	34.2	39.5	34.3	39.9

Obesity-associated comorbidity in this young population has been defined as one or more of the following: a) glucose intolerance (fasting glucose >6.1 mmol/L); type 2 diabetes mellitus (T2DM; fasting glucose >7.0 mmol/L and/or oral medication on prescription for known T2DM); b) hypertension (blood pressure >140 mmHg systolic and/or >90 mmHg diastolic, and/or oral medication on prescription for known hypertension); c) dyslipidemia (total cholesterol >6.5 mmol/l, low-density lipoprotein cholesterol >4.4 mmol/l, high-density lipoprotein cholesterol <0.9 mmol/l, triglycerides >1.94 mmol/l and/or oral medication on prescription for known dyslipidemia); d) obstructive sleep apnea (OSA; apnea-hypopnea index >5/hour, or continuous positive airway pressure treatment for known OSA)) non-alcoholic steatohepatitis (serum alanine aminotransferase >45 U/L for males and >35 U/L for females, or steatohepatitis proven by biopsy); f) depressive disorder (as diagnosed according to the DSM-IV or DSM-V)[32]; g) arthropathy; acanthosis nigricans; and/or idiopathic intracranial hypertension.

Only the comorbidities diagnosed and reported by the treating pediatrician and/or general practitioner of the patient are noted during assessment of inclusion criteria. The participation in one or more multidisciplinary weight reduction programs for a minimum period of 12 months needs to be confirmed by the referring physician.
In addition to the obesity-related inclusion criteria, patients will need to demonstrate an adequate level of decisional capacity, a sufficient level of Dutch language comprehension

and awareness of the randomization process with all its consequences; this will be assessed by an independent specialised youth psychologist during an intake session.

Exclusion criteria: The exclusion criteria for this trial are a) eating disorders ('binge eating', defined as compulsive overeating or consuming abnormal amounts of food while feeling unable to stop and at loss of control' and 'grazing', defined as repetitive periods of eating small amounts of food in an unplanned manner, at least twice daily); b) unrealistic expectations of weight loss; and inadequate social support of the family or caregivers, all to be assessed by the independent specialised youth psychologist and dietician. Dutch translations of validated questionnaires will be used for the assessment of the specific eating disorder exclusion criteria (i.e. the Eating Disorders Examination Questionnaire for Children, chEDE-Q); c) skeletal or developmental immaturity (premenarchal girls, boys with bone age younger than 15 years on X-ray of the hand); d) severe cardiorespiratory impairment (ASA class 3 or more); and e) syndromic disorders causing obesity (e.g. Prader-Willi syndrome). Other exclusion criteria are physical disorders with highly possible influence on weight, such as untreated hypothyroidism or prolactinoma; and unwillingness to adhere to the follow-up program.

Study outline

A pediatrician or general practitioner can refer adolescents to the BASIC trial research team at Maastricht University Medical Center. The referring physician will report general background of the patient, physical status and previous attempts to reduce weight including lifestyle interventions (among others). If the inclusion criteria on age, BMI and lifestyle interventions are met, the patient and his/her parents will be contacted and invited for an extensive intake at our medical center. The surgeon, pediatrician, bariatric dietician, pediatric psychologist and clinical investigator (MD) from the BASIC trial research group will carry out the intake session subsequently (Figure 3.1).

During the intake session, the patient and his/her parents or legal guardians will be extensively informed about the various aspects of the trial. A routine physical examination will be carried out to make sure all the inclusion criteria are met. Boys will undergo assessment of their bone age with an X-ray of their left hand; an experienced pediatric radiologist will assess the exact bone age. The bariatric dietician and the pediatrician will assess the quality of the attempts to lose weight and acquire possible contra-indications for enrolment in the trial. The patient will be asked about his or her motivation to enter the trial and the expectations of the surgical procedure and its consequences. The motivation, basic understanding of the possible operation and the expectations will be written down by the patient to verify if he or she has understood which decision is to be made. If patients continue to have too optimistic expectations about surgery, or do not understand the implications and consequences of the operation, they will not

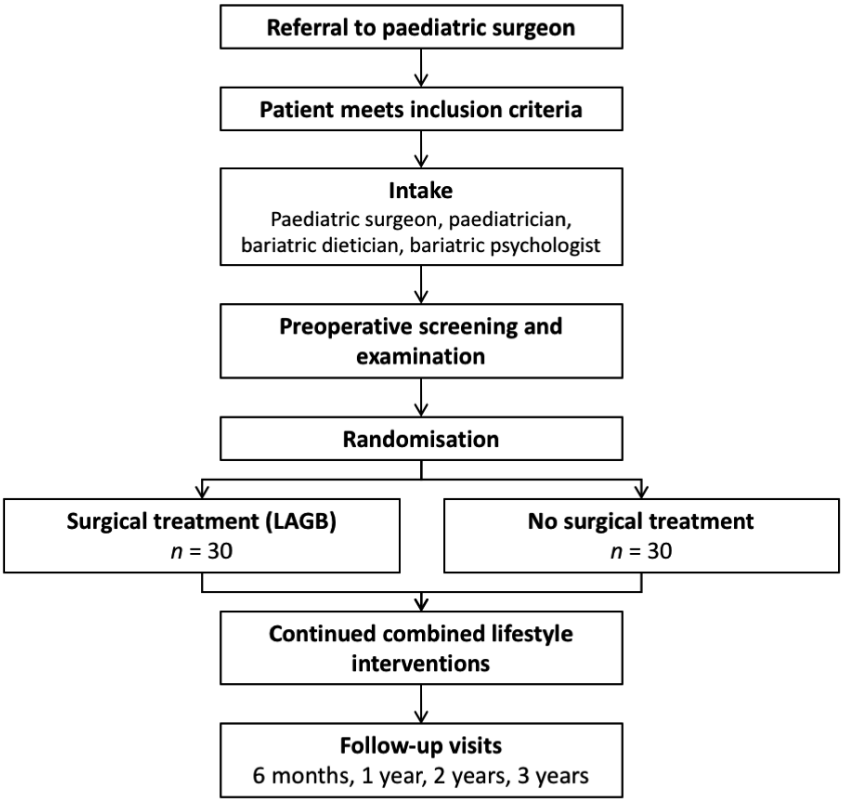


Figure 3.1: *Flowchart of the BASIC trial study design.*

be considered as suitable candidates to participate in the trial. The expert bariatric psychologist will advise both the patient and the parents. Afterwards, the patient will be discussed in a team meeting of pediatric and bariatric surgeons, bariatric dietician, pediatrician and pediatric psychologist. If one or more team members object to inclusion of patient, the patient will not be included in the trial and will be referred back to the referring pediatrician or general practitioner.

If the patient is considered suitable to participate in the trial, the investigator will obtain written consent from the patient and both parents / legal guardians for trial participation. The patient will then be admitted to the Maastricht University Medical Center for extensive physical screening. When a patient shows signs or symptoms of syndromic abnormalities or other disorders being a possible cause of obesity (e.g. hypothyroidism), further investigations will be carried out and treatment (other than being bariatric surgery) will be provided by the referring physician. If the physical screening shows no significant

abnormalities possibly causing obesity, the patient can proceed to randomization (Table 3.2).

The investigator will randomise all patients approved for inclusion in either the 'surgery and lifestyle group' (intervention group) or the 'lifestyle control group' (control group) at a 1:1 ratio by block randomization. A statistician affiliated with our medical center will create random blocks using a digital randomization program; the blocks can consist of two, four or six patients. This resulted in 60 sequentially numbered, opaque and sealed envelopes only accessible for principal investigator and pediatric surgeon LvH and for investigator YR. The investigator, bariatric surgeon, pediatric surgeon, patient and his/her parents will not be blinded for randomisation outcome, but will be blinded for the randomisation list. Other care providers from the Maastricht University Medical Center will be blinded, as will be the data analysts and outcome assessors other than the investigators. Referring pediatricians and general practitioners will not be blinded, to assure adequate care and awareness for potential complications throughout follow-up.

The patients in the intervention group will be readmitted to the surgical center within 6 weeks after randomisation for routine preoperative evaluation. The dedicated bariatric dietician from the research team will visit the patient and accompanying parents on the ward and provides them with extensive dietary advice and guidelines for the home-based setting. A booklet with summary of the advice will be handed over in duplicate, to make sure the dietician in the CLI treatment team at center of referral will be provided with the same information. The bariatric surgeon and pediatric surgeon will visit the patient and parents that same day, to reconfirm informed consent for surgery and provide all the information about the surgical procedure, postoperative phase and follow-up. The next day the patient will be operated on under general anesthesia and receives a LAGB (LAP-BAND AP® Adjustable Gastric Banding System, Allergan Inc., Dublin, Republic of Ireland) using the pars flaccida technique [33]. The expected postoperative hospital stay is one or two days. After six weeks, the gastric band can be insufflated gradually if necessary. Adjustments to the volume of the gastric band will be performed at our medical center and include X-ray control to evaluate the effect of any adjustment, all adjustments will be registered in a standardized file. Afterwards the patient receives yearly routine surgical follow-up, or more often if medically necessary.

All patients participating in the trial (both intervention group and control group) will receive lifestyle interventions and follow-up throughout the entire trial period. All patients will return to the pediatrician, dietician and psychologist of the referring obesity clinic for continuation of the lifestyle program. The multidisciplinary follow-up of the previous life style interventions will be continued in both groups after randomisation to guarantee the best achievable weight loss in both study groups.

Table 2: *Schedule of enrolment, interventions and assessments of the BASIC trial.*

	STUDY PERIOD						
	Enrolment	**Allocation**	**Post-allocation**				**Close-out**
TIMEPOINT*	$-t_1$	0	t_6	t_{12}	t_{24}	t_{36}	t_x
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
CLI		X	←	—	—	→	
LAGB + CLI		X	←	—	—	→	
ASSESSMENTS:							
Body composition	X		X	X	X	X	
Metabolic status	X		X	X	X	X	
Endocrine status	X		X	X	X	X	
Inflammatory status	X		X	X	X	X	
Non-alcoholic fatty liver disease	X			X	X	X	
Cardiac pathology	X			X	X	X	
Sleep abnormalities	X			X	X	X	
Microvascular status	X			X	X	X	
Macrovascular status	X			X	X	X	
Behavioral changes	X		X	X	X	X	
Health-related Quality of Life	X		X	X	X	X	
Physical activity	X		X	X	X	X	

* Time points noted in months. CLI: combined lifestyle interventions. LAGB: Laparoscopic adjustable gastric banding.

The investigator will monitor the post-inclusion care by a telephone follow-up call once every three months. All patients will be subjected to an extensive clinical review at the surgical center at 6 months, 12 months, 2 years and 3 years after inclusion. Adherence to the routine follow-up visits will be registered.

To date, bariatric surgery in children and adolescents is prohibited in The Netherlands for all clinical settings except for this trial. Patients from the control group who turn 18 years during the trial period are offered to crossover to the intervention group and receive surgical treatment. If the patient decides for any other type of weight loss surgery after turning 18, this event will be registered yet the patient will still be invited for follow-up visits and be part in the 3-year follow-up analyses. If this trial will provide sufficient data proving that surgical treatment in adolescents is safe and effective, the Dutch Health Care Inspectorate will evaluate and decide whether the remaining patients from the control group can be offered to crossover to the intervention group.

Patients who withdraw from the trial prematurely will receive their regular follow-up from the referring pediatrician. If patients have been operated upon, they will receive their regular surgical follow-up and treatment, but additional trial related investigations will be discontinued.

Outcomes

Primary outcome measures:

These are defined as percentage total weight loss (%TWL) and change in BMI. Height will be noted to the nearest 0.1 cm and body weight to the nearest 0.1 kg, measured with a stadiometer and digital scale respectively with children dressed in underwear. Self-reported weight data will never be used. BMI will be calculated by dividing weight in kilograms by height in meters squared; excess BMI and excess weight will be calculated according to the cut-off points as shown in Table 3.1.

Secondary outcome measures:

In addition to height and weight, other anthropometric measurements will be used to assess body composition, including neck, waist and hip circumferences, and skinfold thickness at standardised anatomical points. Dual energy X-ray absorptiometry (DXA) will be used to assess bone density and calculate fat and lean tissue mass. More specific measurement of weight distribution over the different body compartments will be carried out by total body water (TBW) measurement using deuterium dilution [34].

Metabolic and endocrine changes in body homeostasis will be assessed by biochemical analysis of glucose metabolism parameters (both fasting and during oral glucose tolerance test), lipid metabolism parameters (cholesterol, free fatty acids, and triglycerides), thyroid function parameters (thyroid stimulating hormone, free T4, parathyroid hormone) and gonadotropins. Decreased insulin sensitivity (insulin resistance) will be measured using the homeostatic model assessment of insulin resistance (HOMA-IR), while glucose intolerance and diabetes will be defined according to the American Diabetes Association [35-37]. Daytime blood pressure will be measured while resting during a period of 60 to

90 minutes (intervals of 3 minutes between measurements) using the Mobil-O-Graph® NG (I.E.M. GmbH, Stolberg, Germany). Hypertension and prehypertension will be defined according to the National High Blood Pressure Education Program update on American guidelines [38]. Inflammatory status will be assessed by biochemical analysis of inflammatory variables.

Liver functioning and potential non-alcoholic hepatitis steatosis will be monitored by testing biochemical liver function variables. Furthermore, a specialised pediatric radiologist will carry out a standardised ultrasound investigation of the liver to screen patients for structural liver abnormalities, monitor liver dimensions and obtain a rough estimate of hepatic steatosis.

Cardiac functioning will be investigated by a specialised pediatric cardiologist, who will perform Doppler echocardiography in each patient yearly, assessing the cardiac dimensions and potential left ventricle hypertrophy. Macrovascular changes will be monitored throughout the trial by measurement of the carotid intima-media thickness, carotid-femoral pulse wave velocity, pulse waveform analysis and flow mediated dilation of the brachial artery [39-41]. Microvascular changes will be measured by testing nailfold capillary density and post occlusive nailfold capillary recruitment [42]. Vasomotion of the microcirculation in the skin will be measured at wrist level during the oral glucose tolerance test using laser Doppler flowmetry [43, 44].

Quality and architecture of sleep and potential obstructive sleep apnea will be analysed objectively with an annual polysomnography.

Patients will be asked to carry an accelerometer at standardised time points during follow-up. The meter will then be carried for seven days while performing regular activities. A diary will be kept during these seven days to gain more insight in the activities. At the same standardised time points patients will be asked to fill out a Baecke questionnaire (adapted for children) evaluating work activity, sports activity and non-sports leisure activity [45].

Eating behaviour and response to food stimuli will be assessed with Dutch translations of validated self-report questionnaires, including the Eating Disorders Examination Questionnaire for Children (chEDE-Q), the Three Factor Eating Questionnaire (TFEQ) and the Power of Food Scale (PFS) [46-48]. A computerized version of the Iowa Gambling Task (IGT) will be used to investigate decision making and reward dominance of the study participants [49, 50]. The Stop Signal Test (SST) will be used to measure response inhibition and monitor potential changes throughout the study [51]. In order to study

the rewarding value of food items, the patients will play a Wanting and Liking Test (WLT) before and after a standardised meal [52].

Psychosocial status and functioning will be assessed both at the beginning and throughout the trial. Health-related quality of life (HRQOL) will be monitored with use of the Dutch translation of the Pediatric Quality of Life Inventory (PedsQL) for children aged 13 to 18 years [53]. In addition, the Beck Depression Inventory (BDI)-II will be used to gain more insights in psychosocial functioning [54].

All outcome variables will be measured at baseline, 12 months, 24 months and 36 months. At six months, all examinations will be carried out except for DXA, liver and cardiac ultrasound, microvascular and macrovascular changes and the polysomnography.

Sample size

The total number of needed study participants was calculated for the primary outcome measure weight loss and is based on the following assumptions: (1) the expected weight loss after 1 and 3 years in the surgery group is 25%; (2) the expected weight change in the control group is 0%, as the patients in the control group have previously been unsuccessfully treated with combined lifestyle interventions; (3) the expected standard deviation is 10% for both groups [55]. To assess a difference in weight loss of 10% or more (7% weight loss is considered to be relevant as it results in a significant improvement in risk and comorbidity in severely obese adolescents), 44 patients have to be included ($\alpha = 0.05$, $\beta = 0.10$) [56]. Based on previous studies in adults at our institution, we assume that approximately 20% of the patients will not finish the one-year follow-up period, 60 patients need to be included into the study to preserve results on 44 patients treated per protocol. The number of patients necessary to show significant relative excess weight loss or loss of relative excess BMI is smaller. The sample size needed to detect significant and relevant weight loss after surgery compared to conservative treatment will also be sufficient to assess significant differences in insulin resistance and hypertension between both groups. The expected resolution of both insulin resistance or diabetes, and hypertension after surgery is 70%-90%, while no effect of continuing life style interventions can be expected [55, 57]. For most of the other variables the currently available information about the expected outcome is not sufficient for a reliable power analysis.

Data collection and management

Standardized case report forms will be used for source data during the trial and stored by the investigator in a locked, fireproof place. To ensure privacy of the participants, identifying data will be stored in coded form secured by a password only known to the investigator and principal investigator. Tissue and plasma samples will be stored in coded form and stored in a locked freezer at the surgical laboratory of the principal investigator.

Data and human material will be kept for 15 years. Statistical analyses are done by the professional statistician participating in the research staff of the study. (Appendix 3.1).

In order to ensure data quality, both the cardiac and liver ultrasound will be carried out by clinical experts and measurements are repeated at least twice per participant per examination. The DXA outcome variables will be evaluated by two specialised nuclear physicians. Anthropometric measurements and microvascular and macrovascular investigations will be performed by a trained laboratory technician; duplicate measurements will be carried out for all of these specific outcomes.

The results of the study will be presented at scientific meetings and published in peer-reviewed medical journals.

Safety

Serious adverse events and adverse events will be registered in accordance to the standards of Good Clinical Practice. The Dutch Health Care Inspectorate will supervise this clinical trial independently and performs unannounced audits. All early and late operative complications such as wound site infections, slippage of the gastric band, and pouch dilatation of the created gastric pouch will be monitored throughout the entire duration of the trial according to the Clavien-Dindo scoring system [58]. Puberty development will be monitored with growth (body height) and plasma levels of gonadotropins and sex hormones. Nutritional status will be assessed to prevent malnutrition.

The study will be terminated prematurely in case of serious and unexpected complications of surgery, if the complication rate of surgery exceeds the 95% confidence interval of the 10% complication rate considered as normal and in case of serious adverse events that are directly related to the diagnostic procedures performed in this study.

Monitoring

To monitor the safety of all patients included in the trial, a Data Safety Monitoring Board (DSMB) will be installed. The board will consist of three independent physicians from the departments of General Surgery and Pediatrics of the Maastricht University Medical Center. The progress of the trial will be reported to the DSMB after every tenth inclusion in the trial. The report will contain data on all complications of surgery, all adverse events, major protocol deviations and other relevant information per coded participant. The opinion of the DSMB and consequent binding (dis)approval of continuation of the trial will be written down and stored in the trial master file. The medical ethics committee of Maastricht University Medical Center will be informed about the DSMB opinions.

DISCUSSION

The BASIC trial is designed to provide high-quality data on the safety and efficacy of LAGB treatment in severely obese children and adolescents. Lack of available long-term data on safety and efficacy of bariatric surgery in youngsters advocates an extremely cautious approach and intensive monitoring of growth and development in these specific patients. Nevertheless, severe obesity has already proven to impair children and adolescents in their pubertal and psychosocial development and significantly increases risks for development of cardiovascular diseases amongst others [2-6]. The BASIC trial will provide tertiary and multidisciplinary care for its participants: comprehensive health examinations will be carried out throughout the trial and results will be discussed in a multidisciplinary setting to guarantee optimal care for this vulnerable population. This is the first randomized controlled trial investigating bariatric surgery as a complementary treatment in adolescents with failed combined lifestyle interventions. Outcome measurement will focus primarily on percentages of total weight loss and excess weight loss, yet a comprehensive set of secondary outcome measures will be provided as well.

A potential limitation of this study includes the choice of LAGB treatment over other bariatric procedures as investigational intervention. Laparoscopic adjustable gastric banding is a restrictive bariatric procedure that can be reversed easily and enables weight loss without altering absorptive processes. The reversibility of the LAGB procedure formed an important argument in this study design of this experimental trial, since the study population is very young and patients might want to make use of possible new and innovative treatment options in the future. Other bariatric procedures have proven to be more effective in terms of excess weight loss and improvement of comorbidity in adults, though these results do not necessarily apply to children and adolescents in the same extent [21, 25].

Secondly, this study may be at risk for relative high loss-to-follow up rates throughout the study period. Because of the comprehensive attempts to lose weight (without intended effect) prior to enrolment in this study, patients may have developed a certain attitude towards healthcare systems and providers negatively affecting their compliance and their stamina. Allocation to the control group might amplify these developments, resulting in high risks for getting loss-to-follow up. The coordinating investigator of the BASIC trial will be aware of these risks and attempt to keep the patients involved with their own health status and potential beneficial treatment methods. Patients and their parents will be informed of the results of their annual comprehensive medical examination and will be involved in the possible adjustments that have to be made to the combined lifestyle interventions and/or gastric band care if applicable.

In summary, this randomized controlled trial will provide important information on the safety and efficacy of LAGB surgery in severely obese adolescents with unsuccessful CLI. The unique control group will provide a necessary framework of data regarding physiological changes throughout adolescence and pathophysiological effects of persistent childhood severe obesity. The results of this study may steer the international opinion regarding treatment options of severely obese adolescents who still have most of their lives ahead of them.

ETHICS APPROVAL

The study is conducted in accordance to the standards of Good Clinical Practice, in agreement with the Declaration of Helsinki and with Dutch law in general and with the Act Medical Research Involving Human Subjects in particular. This study was approved by the medical ethics committee of Maastricht University Medical Center (NL26279.068.09 / METC 09-2-024). A written informed consent was signed by all patients included in this trial and their parents / legal guardians.

COMPETING INTERESTS

All authors declare that they have no conflict of interest.

APPENDIX 3.1

Statistical analysis plan for outcome measurements

Descriptive statistics

Numerical data will be tested for normality with the Kolmogorov-Smirnov statistics and will be presented as mean ± standard deviation if there is a normal distribution, otherwise as median [range]. Categorical data will be presented as number (percentage).

Longitudinal treatment effect

Linear and logistic mixed models will be used to assess the longitudinal treatment effect for numerical and categorical outcome variables, respectively. This analysis method accounts for the correlation between repeated measures, uses all available data, and uses a likelihood approach for missing outcome data, which are assumed to be missing at random (MAR). Group, time and group*time will be included as fixed factors to assess the treatment effect at different time points. Variables related to missing outcome data, based on logistic regression analyses, will be included to the fixed part of the model to ensure MAR. As for the random part, random intercept and/or slope will be considered, where the best option will be selected based on Bayesian Information Criterion (BIC). As sensitivity analysis, baseline characteristics that substantially differ between groups are then also included in the model.

Interim analysis (if applicable)

Not applicable.

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PART II:

COMORBIDITIES IN ADOLESCENTS LIVING WITH SEVERE OBESITY



CHAPTER 4

Obstructive sleep apnea in obese adolescents referred for bariatric surgery:

Association with metabolic and cardiovascular variables

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ABSTRACT

Background:

obstructive sleep apnea (OSA) is a well-described disease entity in adults, with a higher prevalence in severely obese individuals, while at the same time associated with several comorbidities independently of BMI. Literature regarding OSA in severely obese adolescents is qualitatively and quantitatively limited, possibly resulting in suboptimal diagnosis and treatment.

Methods:

polysomnographic, demographic, anthropometric, and comorbidity-related data were prospectively collected in 56 adolescents with morbid obesity refractory to conservative treatment who presented for surgical therapy. Differences between adolescents with no/mild (apnea-hypopnea index (AHI) 0 - 4.9) and moderate/severe OSA (AHI ≥ 5.0) were evaluated using independent-samples t, chi-square or Fisher's exact tests. Multivariable linear regression analysis was performed to evaluate the association of several variables with AHI, corrected for BMI z-score.

Results:

of the 53 included subjects, 48 (90.6%) showed some degree of sleep disordered breathing and 20 (37.7%) had moderate/severe OSA. Patients with moderate/severe OSA had on average a higher neck circumference (42.4 versus 40.1 cm, $p = 0.008$), higher BMI z-score (3.7 versus 3.4, $p = 0.003$), higher plasma triglyceride level (2.2 versus 1.5 mmol/L, $p = 0.012$), and lower insulin like growth factor (IGF; 29.6 versus 40.2 mmol/L, $p = 0.010$) than those with no/mild OSA. BMI z-score and plasma triglyceride levels were independently related to AHI.

Conclusion:

OSA is highly prevalent amongst morbidly obese adolescents and is strongly associated with BMI z-score. Elevated plasma triglyceride levels are associated with AHI, independent of BMI z-score.

INTRODUCTION

Obesity forms a global public health issue since its prevalence has increased dramatically over the past few decades, both in adult and pediatric populations [1-4]. In 2013, the combined prevalence of pediatric overweight (sex- and age-adjusted BMI 25-30 kg/m^2) and obesity (sex- and age-adjusted BMI ≥30 kg/m^2) in developed countries was 23.8% and 22.6% for boys and girls, respectively [5]. A large number of conditions have been associated with obesity, such as type 2 diabetes, cardiovascular disease, and obstructive sleep apnea (OSA) [6].

OSA, defined in adults as an apnea-hypopnea index (AHI) ≥ 5 with specific symptoms, has been extensively studied and its reported prevalence varies between 5 and 38% in the general adult population [7,8]. By contrast, OSA prevalence can increase to over 75% in subgroups of severely obese patients undergoing bariatric surgery [9]. This high prevalence is alarming as a vast body of evidence suggests an association of OSA, independent of BMI, with dyslipidemia, type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), hypertension, and other endocrine deregulation (e.g. elevated insulin like growth factor (IGF)) [10-16]. For screening purposes, several adult prediction models for OSA have been formulated, which include basic demographic and anthropometric measures, providing sensitivities ranging from 76 to 96% and specificities from 13 to 54% [17-19].

There is a relatively limited number of studies in obese children and adolescents with sleep disordered breathing which address associated metabolic and cardiovascular variables and many of these are retrospective with a heterogeneous study population with regard to pubertal status [20]. A retrospective chart review of morbidly obese adolescents who had undergone bariatric surgery by Koeck et al. showed OSA (defined as obstructive AHI ≥ 5) in 21 out of 49 adolescents (42.9%) [21]. They found that patients with OSA had a higher BMI, were more frequently male and more frequently hypertensive. A relatively limited number of retrospectively collected clinical variables were used to assess correlations with OSA and these correlations were not corrected for BMI or BMI z-score. Kalra et al. retrospectively reported OSA prevalence (defined as AHI ≥ 5) of all morbidly obese adolescents who received Roux-en-Y gastric bypass during a specified timeframe, yielding 34 subjects with an OSA prevalence of 55% [22]. Kalra et al. did not evaluate clinical correlates of OSA with comorbidities. Watson et al. retrospectively evaluated 96 obese patients aged 12-16 years and found an independent positive association between AHI and fasting insulin, HOMA-IR and triglyceride levels [23]. Other studies have found associations between pediatric obesity and an adverse metabolic profile, but these studies also evaluated non-morbidly obese individuals and included an even broader age range [24,25]. The main purpose of the current study was to assess the prevalence of OSA in severely obese adolescents and correlations between OSA and an extensive number

of potentially relevant clinical variables, including demographic, anthropometric and comorbid factors. Thus, we aim to shed a light on the burden of OSA in this population and evaluate its predictors.

METHODS

This study was conducted as part of a prospective study in adolescents eligible for bariatric surgery (BASIC trial, NCT01172899) [26]. The study population consists of morbidly obese adolescents who all had been treated before with extensive combined lifestyle interventions for at least twelve months without effect. The current study was based on the baseline measurements of this trial before interventions took place.

Participants

All patients included in the BASIC trial who received a baseline polysomnographic evaluation of sufficient quality were used for this baseline analysis. Detailed information regarding the BASIC trial study design, in- and exclusion criteria, and randomization process were published previously. In summary, inclusion criteria were: age 14-16 years; sex- and age-adjusted BMI ≥40 kg/m^2 (or ≥35 kg/m^2 combined with presence of obesity-associated co- morbidity); participation in combined lifestyle interventions during at least 12 months without expected weight loss (defined as 5% total body weight loss). Girls were excluded if they were premenarchal, boys if their bone age was <15 years.

All participants were subjected to standardized comprehensive baseline measurements and investigations in order to confirm physical fitness for possible surgery and absence of (subclinical) conditions causing obesity.

Measurements

All measurements within one patient were carried out during a single visit. Body height and weight were measured using a stadiometer and digital scale respectively, with patients dressed in underwear. A tape measure was used for standardized measurement of body circumferences at neck level, abdominal level and hip level. BMI was calculated as [body weight]/[body height*body height] in kg/m^2, BMI z-scores were calculated using Cole's LMS method [27]. Daytime blood pressure was measured while the patient was resting, during a period of 60-90 minutes with intervals of 3 min between measurements, using the Mobil-O-Graph® NG (I.E.M. GmbH, Stolberg, Germany). Prehypertension and hypertension were defined according to the fourth report from the National High Blood Pressure Education Program, blood pressure z-scores were calculated according to the method described in that same report [28]. Video-assisted 12 channel polysomnography (PSG) (Brain RT, OSG, Rumst, Belgium) was performed at the pediatrics department of Maastricht University

Medical Center. The following parameters were assessed: electrocardiography, oxygen saturation (pulse oximeter), nasal airflow (nasal pressure transducer system and nasal end-tidal pCO2 measurement), chest and abdominal motion (inductive plethysmographic belts), EEG, EOG and EMG (submental muscles and anterior tibialis muscles), digital video (infrared camera synchronized with the polysomnography data), snoring sounds and body position. The scoring of sleep stages and respiratory related events were performed by a single specialized analyst (CvdG) using the American Academy of Sleep Medicine (AASM) 2012 updated guidance for scoring pediatric respiratory events [29].

OSA was defined as mild (AHI 1 - 4.9/h), moderate (AHI 5.0 - 9.9/h), or severe (AHI ≥ 10/h), following the guideline of the American Academy of Pediatrics [30]. Since OSA is often defined as an AHI ≥ 5.0 in comparable studies on adolescents, patients were grouped as either no/mild OSA (AHI 0 - 4.9/h) or moderate/severe OSA (AHI ≥ 5.0/h) [21,22]. Snoring was assessed with the use of a questionnaire. If they answered 'sometimes' or 'always', this was considered as snoring.

With a fasting laboratory evaluation serum glucose, insulin, cholesterol, triglycerides, free fatty acids, glycated hemoglobin (HbA1C), alanine transaminase (ALT), aspartate aminotransferase (AST), cortisol, insulin-like growth factor (IGF), and c-reactive protein (CRP) were assessed.

Statistical analysis

Numerical data are presented as mean ± standard deviation or median [range] where appropriate. Categorical data are presented as number (percentage). Demographic and clinical variables were compared between patients with no or mild OSA and patients with moderate to severe OSA, using an independent-samples t-test for numerical variables and chi-square or Fisher's exact test for categorical variables. Multivariable linear regression analysis was used to evaluate the association between several relevant demographic, anthropometric and comorbid endpoints and AHI. Due to sample size, these variables were assessed separately with correction for BMI z-score, as this is a known variable related to AHI. All assumptions were checked using plots (scatterplots for linearity, Q-Q-plots and histograms for normality, residual plots for homoscedasticity), where Cook's distance was used to detect influential outliers. In case normality was violated, a log or square root transformation was considered to achieve normality. For comparison, a similar multivariable linear regression was performed with a direct marker of oxygenation, namely the 3% oxygen desaturation index (ODI-3%). IBM SPSS Statistics for Windows (version 24.0; Armonk, NY, USA) was used for the aforementioned statistical analysis. Two-sided p-value ≤ 0.05 was considered statistically significant.

Results

Of the 60 adolescents included in the BASIC trial, 56 subjects received a polysomnographic evaluation. The four last subjects did not receive a polysomnographic evaluation, due to unforeseen practical circumstances not related to the study. One subject was excluded from analysis due to a newly diagnosed prolactinoma. Furthermore, poor registration quality was observed in two polysomnographies due to device malfunction, which were therefore excluded from analysis.

The baseline characteristics of the remaining 53 adolescents are presented in Tables 4.1 and 4.2. None of the adolescents had a prior diagnosis of OSA or received treatment for OSA. The majority (79.2%) was female, the mean age was 15.7 ± 1.0 years, and the mean BMI was 44.1 ± 5.2 kg/m^2. Forty-eight patients (90.6%) had some degree of sleep disordered breathing (AHI ≥ 1.0) and 20 (37.7%) had moderate/severe OSA (AHI ≥ 5.0). The median AHI was 3.7 (range 0.0-26.0).

Table 4.1*: Patient characteristics of total group and according to no/mild OSA and moderate/ severe OSA. Data are described as 'mean ± SD' or 'number of patients (%)'.*

Baseline parameter	Total (n = 53)	Group 1: no/mild OSA (n = 33)	Group 2: moderate/ severe OSA (n = 20)	p-value
Gender female	42 (79.2%)	26 (78.8%)	16 (80.0%)	1.000*
Age – yr	15.7 ± 1.00	15.4 ± 1.0	16.1 ± 1.0	**0.032**
Smoking – n	11 (20.8%)	6 (18.0%)	5 (25.0%)	0.728*
Snoring positive – n	25 (47.2%)	15 (45.5%)	10 (50%)	0.531
Weight – kg	128.9 ± 19.5	123.5 ± 14.3	137.9 ± 23.7	**0.008**
Length – cm	1.71 ± 0.1	170.7 ± 7.8	171.1 ± 10.2	0.856
BMI – kg/m^2	44.1 ± 5.2	42.4 ± 4.3	46.9 ± 5.5	**0.002**
BMI z-score	3.5 ± 0.3	3.4 ± 0.3	3.7 ± 0.3	**0.003**
Neck circumference – cm	41.0 ± 3.1	40.1 ± 2.9	42.4 ± 3.0	**0.008**
Abdominal circumference – cm	128.2 ± 12.5	125.9 ± 10.2	131.9 ± 15.0	0.090
Hip circumference – cm	130.3 ± 10.3	128.1 ± 8.7	133.8 ± 11.9	0.054
Waist-hip ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.335

* Fischer's exact test applied.

Bold p-values denote statistical significance.

Table 4.2: *Polysomnographic variables in this population. Where applicable, data are described as 'mean (± SD)', median [range], or 'number of patients (%)'.*

Variable	Total sample (n = 53)
Level of sleep disordered breathing - n	
No OSA (AHI < 1)	5 (9.4%)
Mild OSA (AHI 1 – 4.9)	28 (52.8%)
Moderate OSA (AHI 5 – 9.9)	10 (18.9%)
Severe OSA (AHI ≥ 10)	10 (18.9%)
AHI	3.7 [0.0 – 26.0]
Average O_2 dip (%)	3.0 ± 0.5
Maximum O_2 dip (%)	6.4 ± 2.7
Lowest O_2-sat. (%)	89.4 ± 3.5
Wake O_2-sat. (%)	96.7 ± 0.8
Time O_2-Sat. under 90% (min.)	1.3 ± 6.3
ODI > 3% per hour	6.5 ± 5.9

In comparison to subjects with no or mild OSA, adolescents with moderate/severe OSA were on average older (16.1 ± 1.0 versus 15.7 ± 1.0 years, p 0.032), more overweighed (137.9 ± 23.7 versus 123.5 ± 14.3 kg, p 0.008), and had a higher BMI (46.9 ± 5.5 versus 42.4 ± 4.3 kg/m2, p 0.002) and BMI z-score (3.7 ± 0.3 versus 3.4 ± 0.3, p 0.003). Moreover, adolescents with moderate/severe OSA had larger neck circumferences (42.4 ± 3.0 versus 40.1 ± 2.9 cm, p 0.008). Snoring percentages were similar in the groups with no/mild OSA and moderate/severe OSA (45.5% versus 50.0%, p 0.531).

A comparison of several endpoints of comorbidity between patients with no/mild OSA and moderate/severe OSA is presented in Table 4.3. In the latter group, plasma triglyceride levels were higher (2.2 ± 1.0 versus 1.5 ± 0.7 mmol/L, p 0.012), whereas IGF levels were lower (29.6 ± 8.7 versus 40.2 ± 15.8 nmol/L, p 0.010). No statistically significant differences were observed in glycemic, vascular and hepatic endpoints.

The results of multivariable linear regression analysis of the association between several clinical variables and AHI, correcting for BMI z-score is shown in Table 4.4. BMI z-score was significantly related to AHI (unstandardized β = 6.685, 95% CI = 1.701-11.669). Additionally, higher plasma triglyceride levels (unstandardized β = 1.655 mmol/L, 95% CI = 0.071-3.239) were associated with a higher AHI, independently of BMI z-score. Since AHI was slightly skewed to the right, a sensitivity analysis using square-root transformed AHI as the dependent variable was performed, revealing no differences in statistically significant outcomes to the original analysis. Multivariable linear regression with ODI-3% showed

that ODI-3% predicted triglyceride levels with comparable strength (unstandardized β = 0.057, 95% CI = 0.013-0.101).

***Table 4.3**: Comparison between no/mild OSA and moderate/severe OSA with regard to dyslipidemia, insulin resistance, cardiovascular disease risk, NAFLD risk, and other variables. Data described as mean ± SD.*

Variable	Total sample n = 53	Group 1: no/mild OSA n = 33	Group 2: moderate/ severe OSA n = 20	p-value
Triglycerides - mmol/L	1.8 ± 0.9	1.5 ± 0.7	2.2 ± 1.0	**0.012**
Free fatty acids - mmol/L	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.435
Total cholesterol - mmol/L	4.6 ± 0.8	4.6 ± 0.8	4.8 ± 0.9	0.315
HDL - mmol/L	1.1 ± 0.4	1.1 ± 0.3	1.0 ± 0.4	0.298
LDL - mmol/L	2.8 ± 0.8	2.7 ± 0.9	2.9 ± 0.8	0.552
TC/HDL-ratio	4.6 ± 1.6	4.4 ± 1.7	5.0 ± 1.6	0.192
HbA1cRel - %	5.6 ± 1.3	5.6 ± 1.6	5.5 ± 0.4	0.917
Fasting glucose - mmol/L	5.4 ± 1.8	5.5 ± 2.2	5.4 ± 0.6	0.780
Fasting insulin - pmol/L	211.0 ± 118.3	208.7 ± 123.1	215.7 ± 113.4	0.859
HOMA-IR	7.4 ± 4.9	7.3 ± 5.2	7.5 ± 4.6	0.860
RR systolic - mmHg	121.8 ± 10.6	121.7 ± 10.5	122.0 ± 11.2	0.915
Z-score RR systolic	0.8 ± 1.1	0.8 ± 1.0	1.0 ± 1.3	0.468
RR diastolic - mmHg	69.7 ± 8.8	70.1 ± 9.0	68.9 ± 8.5	0.656
Z-score RR diastolic	0.5 ± 0.9	0.4 ± 0.8	0.6 ± 1.1	0.471
ALAT - U/L	31.2 ± 16.0	28.5 ± 12.7	35.7 ± 19.9	0.167
ASAT - U/L	25.4 ± 9.4	23.7 ± 6.7	28.2 ± 12.4	0.153
CRP - mg/L	6.8 ± 6.8	5.9 ± 7.0	8.4 ± 6.4	0.233
Cortisol - nmol/L	340.3 ± 156.3	322.5 ± 129.1	370.3 ± 194.0	0.295
IGF - nmol/L	36.1 ± 14.4	40.2 ± 15.8	29.6 ± 8.7	**0.010**

Bold p-values denote statistical significance.

***Table 4.4**: Results of multivariable linear regression analysis for the predictive value of several variables regarding AHI, correcting for BMI z-score.*

Variable	Unstandardized β	95%-CI
BMI z-score *	6.685	**1.701 – 11.669**
BMI (kg/m^2) *	0.399	**0.128 – 0.669**
Neck circumference (cm)	0.087	- 0.477 to 0.651
Abdominal circumference (cm)	-0.049	- 0.218 to 0.120
Hip circumference (cm)	0.006	- 0.197 to 0.209
Waist-hip ratio	-4.533	- 22.641 to 13.575
Triglycerides (mmol/L)	1.655	**0.071 – 3.239**
Free fatty acids (mmol/L)	3.430	- 2.634 to 9.495
Total cholesterol (mmol/L)	1.109	- 0.592 to 2.811
HDL (mmol/L)	-0.700	- 5.022 to 3.622
LDL (mmol/L)	0.544	- 1.192 to 2.279
TC/HDL-ratio	0.326	- 0.580 to 1.232
HbA1cRel (%)	-0.159	- 1.305 to 0.987
Fasting glucose (mmol/L)	-0.164	- 0.987 to 0.660
Fasting insulin (pmol/L)	0.002	- 0.011 to 0.014
HOMA-IR	0.008	- 0.291 to 0.306
RR systolic (mmHg)	-0.033	- 0.175 to 0.108
Z-score RR systolic	0.158	- 1.190 to 1.506
RR diastolic (mmHg)	0.008	- 0.160 to 0.176
Z-score RR diastolic	0.603	- 0.987 to 2.192
ALAT (U/L)	-0.001	- 0.099 to 0.096
ASAT (U/L)	-0.006	- 0.169 to 0.157
CRP (mg/L)	-0.033	- 0.255 to 0.189
Cortisol (nmol/L)	0.002	- 0.007 to 0.012
IGF (nmol/L)	-0.090	- 0.194 to 0.014

* Variable not corrected.

Bold 95%-CIs denote statistical significance.

DISCUSSION

This is the first prospective study that systematically evaluates clinical correlates of OSA in severely obese adolescents. The main unique feature of our study population is the narrow age range, which represents adolescents in their late puberty and thus contributes

to the internal validity of our findings. Moreover, our population specifically concerns those morbidly obese adolescents who were referred for bariatric surgery and consists mostly of females. In addition to polysomnography, we have prospectively collected extensive data of a wide range of comorbidities. Among the 53 analyzed severely obese adolescents, sleep disordered breathing was seen in 48 (90.6%), of whom 20 (37.7%) suffered from moderate/severe OSA. We found that elevated plasma triglyceride levels is independently associated with higher AHI.

Comparable studies in severely obese adolescents are limited to retrospective studies including patients with a wide BMI and age range, as detailed in the introduction [21-24]. Koeck et al., to a lesser extent and partially via retrospective chart review of adolescent bariatric surgery patients who had undergone PSG, compared characteristics of severely obese adolescents with no/mild and moderate/severe OSA. They reported a prevalence of moderate/severe OSA of 42.9%, which is equivalent to our study [21]. This suggests that OSA is highly prevalent amongst severely obese adolescents and raises the suspicion that OSA is underdiagnosed and/or undertreated in this population, as is also likely the case amongst severely obese adults [31]. Possible contributing factors to under-recognition of OSA are lack of symptoms or awareness of symptoms, suboptimal screening tools and an expensive and time-consuming diagnostic tool in the form of polysomnography.

Importantly, we found that the typical adult predictors of OSA, such as neck circumference and blood pressure, did not independently predict AHI in our population. Moreover, although self-reported snoring was common in our population (47.2%), there was no significant difference in the prevalence of self-reported snoring between those with no/mild OSA and moderate/severe OSA. This is consistent with the literature, which reports a weak relationship between self-reported snoring and AHI [32]. Based on our findings, a statistically significant association existed between AHI and BMI z-score. In addition, higher plasma triglyceride levels were associated with a higher AHI and a higher ODI-3%, independently of BMI z-score. This positive association between plasma triglyceride levels and AHI and ODI-3% is concordant with recent evidence that suggests that OSA independently predicts adverse lipid profiles in adults [33-36]. Drager et al. showed that the fractional clearance rate of plasma triglycerides is lower in adults with OSA, compared to controls, and that 3-month treatment with continuous positive airway pressure (CPAP) resulted in a five-fold increase in fractional triglyceride clearance rate [35]. These findings suggest that early recognition and proactive treatment of OSA results in better metabolic outcomes.

OSA, if left untreated, is independently associated with several comorbidities and thus early recognition is crucial [10-16]. These findings in this study may help in clinical decision making to detect OSA in severely obese adolescents; since (severe) obesity becomes more

common, assessing every obese child for OSA would be challenging when the limited resources and infrastructure are taken into account. Approximately 40% of the severely obese adolescents suffer from moderate/severe OSA, and therefore severe obesity on its own seems to provide suboptimal guidance in the decision whether to assess possible OSA by resource-intensive polysomnography (as gold-standard diagnostic tool) or not. Routine laboratory testing, e.g. plasma triglycerides levels may be used as an additional measure to justify polysomnography to diagnose OSA in morbidly obese adolescents. Larger studies need to be performed to further evaluate these associations.

Contrasting to the study by Koeck et al., where 80% of the male and 33.3% of the female morbidly obese adolescents had moderate/ severe OSA, in our study this was the case for 30.0% of the male and 42.5% of the female subjects, respectively. In the adult population, a higher prevalence of OSA has been reported in men [37]. Our contrasting findings imply that the gender differences found in adolescent literature may be due to chance. Further studies are necessary to elucidate the role of gender predisposition to OSA in adolescent populations.

There are a number of limitations to this study. Though a relatively large sample was used compared to other studies, the sample size may have limited the statistical power to prove some of our findings. Moreover, the small proportion of male inclusions made it impossible to reliably determine gender specific differences in implications and predictors of OSA. In addition, our analysis did not take into consideration the presence of anatomical factors which influence the risk of OSA, such as tonsil, uvula and tongue size.

CONCLUSION

Our data show that OSA is highly prevalent among severely obese adolescents and is significantly associated with BMI z-score. Elevated plasma triglyceride levels were also associated with OSA, independent of BMI z-score. We advise high clinical suspicion of OSA and low threshold utilization of polysomnographic studies in this population, especially when these associated factors are present. Further research should evaluate the influence of weight loss intervention on the prevalence of OSA in this population, as well as the influence of OSA on success of weight loss intervention.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.02.026.

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CHAPTER 5

Left ventricular geometrical changes in severely obese adolescents:

Prevalence, determinants, and clinical implications

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ABSTRACT

Left ventricular hypertrophy (LVH) is independently associated with a higher risk of cardiovascular morbidity and mortality in adults. Adiposity is a risk factor for LVH, independent of blood pressure. Potential causes of this nonhemodynamic pathogenesis identified in adults include adverse body fat distribution, insulin resistance, dyslipidemia, and obstructive sleep apnea syndrome (OSA). In severely obese adolescents, the determinants of obesity-induced changes in left ventricular structure are poorly characterized. Cardiac ultrasonographic, demographic, anthropometric, and comorbidity-related data were prospectively collected in adolescents with severe obesity refractory to conservative treatment who presented for surgical therapy. Differences between adolescents with LVH and without LVH were evaluated using independent samples t, chi-square, or Fisher's exact test. Multivariable linear regression analysis was performed to evaluate associations with left ventricular structural changes, corrected for body mass index (BMI) z score. Forty-three patients entered analysis, of whom 24 (55.8%) showed LVH. The most common geometrical change was eccentric LVH (eLVH), occurring in 21 subjects (48.8%). Demographic and anthropometric variables did not differ between patients with and without LVH. Independent of BMI z score, left ventricular mass index was significantly associated with apnea–hypopnea index (AHI) (regression parameter $\beta = 0.8$; 95% CI 0.3 to 1.2). Interventricular septum thickness (IVST) was significantly associated with HOMA-IR values ($\beta = 0.1$; 95% CI 0.04 to 0.2), HDL-cholesterol ($\beta = -1.2$; 95% CI − 2.2 to 0.1), and triglyceride levels ($\beta = 0.5$; 95% CI 0.001 to 0.9). LVH, especially eLVH, is highly prevalent amongst severely obese adolescents. Adverse changes in cardiac structure, increased IVST in particular, are independently associated with several nonhemodynamic comorbidities that are common in this population, namely OSA, insulin resistance, and dyslipidemia.

INTRODUCTION

Pediatric obesity is associated with adverse changes in left ventricular geometry, especially left ventricular hypertrophy (LVH) [1–6]. In adults, LVH increases the risk of ventricular arrhythmias and decompensation, and poses a fourfold increased risk of cardiovascular morbidity and mortality [7]. In hypertensive patients, the presence of LVH increases the risk of cardiovascular events by a factor 20 [8].

The reported prevalence of LVH in obese children, adolescents, and young adults between the ages of 3 and 22 years old ranges from 10 to 46% [1–6]. Although LVH is normally asymptomatic in children, multiple prospective longitudinal studies have established that several risk factors for adverse cardiovascular events persist into adulthood [9,10]. Interestingly, on long-term follow-up of patients with essential hypertension, (partial) reversal of LVH by antihypertensive treatment has been found to reduce the risk of cardiovascular morbidity and mortality to the same level as those who did not have LVH at the beginning of follow-up [11]. This provides an argument for early detection of LVH in obese individuals and treatment of causative factors.

Adiposity is a predictor of LVH in both hypertensive and nonhypertensive children, independent of age [12–15]. The mechanisms underlying obesity-induced changes in left ventricular geometry are diverse and include hemodynamic factors (hypertension, increased intravascular volume), metabolic factors, hormonal factors, and factors related to OSA [16]. In the Bogalusa Heart study, it was found that young adults (aged 24–44 years) were more likely to suffer from LVH if they were exposed to risk factors of LVH in childhood, including obesity, diabetes, increased waist circumference, elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP), insulin resistance, and dyslipidemia [17].

The aim of our research is to improve understanding of the prevalence and determinants of left ventricular geometrical changes in a homogeneous and well-characterized population of severely obese adolescents. We hypothesize that LVH, especially eccentric LVH, is highly prevalent in our population, that BMI is the most important anthropometric predictor of LVH, and that LVH is independently associated with several pathogenic factors, including blood pressure and variables related to insulin sensitivity, lipid profile, hormonal aberrancies, and OSA.

METHODS

This study was conducted as part of a randomized controlled trial for adolescents eligible for bariatric surgery (BASIC trial, NCT01172899) [18]. The study population of the BASIC trial consists of severely obese adolescents who all have been treated extensively for their severe obesity by conservative methods during at least 12 months without effect. The current study was based on the baseline measurements of this trial, before randomization took place.

Participants

All patients included in the BASIC trial who received a baseline cardiac ultrasound examination were used for this baseline analysis. Detailed information regarding the BASIC trial study design, in- and exclusion criteria, and randomization process was published previously [18]. In summary, inclusion criteria were age 14–16 years; sex- and age-adjusted BMI ≥ 40 kg/m2 (or ≥ 35 kg/m2 combined with presence of obesity-associated comorbidity); and participation in combined lifestyle interventions during at least 12 months without adequate weight loss (defined as 5% total body weight loss). In order to maintain a homogenous study population with regard to pubertal status, girls were excluded if they were premenarchal, boys if their bone age was < 15 years.
All participants were subjected to standardized comprehensive baseline measurements and investigations in order to exclude (subclinical) conditions causing obesity.

Measurements

All measurements within one patient were carried out during a single visit. Body height and weight were measured using a stadiometer and digital scale, respectively, with patients dressed in underwear. A tape measure was used for standardized measurement of body circumferences at neck level, abdominal level, and hip level. BMI was calculated as [body weight]/[body height*body height] in kg/m^2, and BMI z scores were calculated using Cole's LMS method [19]. Daytime blood pressure was measured while the patient was resting, during a period of 60 to 90 minutes with intervals of 3 min between measurements, using the Mobil-O-Graph® NG (I.E.M. GmbH, Stolberg, Germany). Prehypertension and hypertension were defined according to the fourth report from the National High Blood Pressure Education Program, and blood pressure z scores were calculated according to the method described in that same report [20].

A fasting blood draw was performed to measure serum glucose, insulin, cholesterol, triglycerides, free fatty acids, glycated hemoglobin (HbA1C), and leptin. HOMA-IR was calculated according to the method described by Mathews et al., i.e., ((fasting insulin (microU/l)/(fasting glucose (mmol/l))/22.5, where insulin was converted from pmol/l to microU/l by dividing by 6.945 [21].

Video-assisted 12 channel polysomnography (PSG) (Brain RT, OSG, Rumst, Belgium) was performed at the pediatrics department of Maastricht University Medical Center. The scoring of sleep stages and respiratory-related events were performed by a single specialized analyst using the American Academy of Sleep Medicine (AASM) 2012 updated guidance for scoring pediatric respiratory events [22].

All cardiac ultrasounds were planned with a single pediatric cardiologist, who reported interventricular septal thickness (IVST), left ventricular end-diastolic posterior wall thickness (LVPWT), left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimension (LVESD). In the absence of this pediatric cardiologist, another experienced pediatric cardiologist was consulted to perform the ultrasound examination.

Left ventricular mass (LVM) was calculated using the Devereux formula, where left ventricular mass (in grams) is equal to 0.8(1.04((LVEDD + IVST + LPWT)3−LVEDD3)) + 0.6 [23]. Left ventricular mass was subsequently indexed by dividing it by height to the power of 2.7, which was previously described as the optimal height exponent between children and adults for indexing LVM [24, 25]. Thus, left ventricular mass index (LVMI) is equal to LVM divided by $height^{2.7}$ (height in meters). LVH was defined as a LVMI ≥ 38.6 g/m2.7, in accordance with the 95th percentile of LVM in a cohort of 192 healthy children of 6 to 17 years old [25].

Cardiac geometry was further specified using the relative wall thickness (RWT) and LVMI, according to the method of Ganau et al., where RWT was calculated as 2*LVPWT/LVEDD [26]. In children, an RWT > 0.41, corresponding to the 95th percentile of RWT in children and adolescents, corresponds to concentric changes, and an RWT ≤ 0.41 corresponds to normal geometry or eccentric changes [27]. We defined normal geometry and concentric left ventricular remodeling (cLVR) as a normal LVMI (< 38.6 g/m2.7) with an RWT that is ≤ 0.41 or > 0.41, respectively. We defined left ventricular hypertrophy as a LVMI ≥ 38.6 g/m2.7 and further specified this as eccentric left ventricular hypertrophy (eLVH) if RWT was ≤ 0.41 and concentric left ventricular hypertrophy when RWT was > 0.41.

Statistical analysis

Numerical data are presented as mean ± standard deviation and range where appropriate. Categorical data are presented as number (percentage). Demographic and clinical variables were compared between patients with no LVH and patients with LVH, using an independent samples t test for numerical variables and $\chi 2$ or Fisher's exact test for categorical variables. Multivariable linear regression analysis was used to evaluate the association between several relevant demographic, anthropometric, and comorbidity endpoints and LVMI, correcting for BMI z score. As sensitivity analysis, these analyses were repeated, where we additionally corrected for age and gender. The associations

between the dependent and independent variables were assessed separately as the sample size was too small to include all independent variables in one regression model. All assumptions were checked using plots (scatterplots for linearity, Q–Q-plots and histograms for normality, residual plots for homoscedasticity), where Cook's distance > 1 was used to define an influential outlier. In case normality was violated, a log or square-root transformation was considered to achieve normality. IBM SPSS Statistics for Windows (version 24.0; Armonk, NY, USA) was used for the aforementioned statistical analyses. Two-sided p-value ≤ 0.05 was considered statistically significant.

RESULTS

Of the 60 adolescents included in the BASIC trial, 43 subjects received a baseline cardiac ultrasound, of whom 42 were performed by CvL. Seventeen patients did not receive an ultrasound due to logistic circumstances, mainly unavailability of a pediatric cardiologist. The baseline characteristics of the 43 remaining adolescents are presented in Table 5.1. The majority (79.0%) was female; mean (± SD) age was 15.7 ± 1.0 years; and BMI was on average 44.2 ± 5.5 kg/m2, with a mean BMI z score of 3.5 ± 0.3.

The mean values measured with cardiac ultrasonography in our study population were: LVM of 170.4 g (± 42.3), LVMI of 40.4 g/$m^{2.7}$ (± 8.3), IVST of 9.6 mm (± 1.3), LVPWT of 9.1 mm (± 1.0), and LVEDD of 50.3 mm (± 4.7). The average RWT was 0.37 (± 0.05). Twenty-four patients (55.8%) had a LVMI of ≥ 38.6 g/$m^{2.7}$, corresponding to LVH according to the pediatric definition [25]. Figure 5.1 shows the geometrical distribution in our study population. eLVH, cLVH, and cLVR occurred in 21 (48.8%), three (7.0%), and two (4.7%) patients, respectively.

Differences in demographic, anthropometric, and potentially pathogenic factors between patients with LVH and without LVH are shown in Tables 5.1 and 5.2. We did not observe any statistically significant differences in these factors between patients with LVH and patients without LVH. As a sensitivity analysis, we further analyzed our data using the adult cut-off for LVH (≥ 51.0 g/$m^{2.7}$), upon which only six patients (14.0%) would have LVH with no statistically significant differences between the group with LVH and without LVH.

Table 5.1: *Demographic and anthropometric characteristics for overall population and patients with LVH.*

Variable	Overall (n = 43)	No LVH (n = 19)	LVH (n = 24)	p-value
Demographic variables				
Age – yr	15.7 ± 1.0	15.8 ± 1.0	15.6 ± 0.9	0.657
Gender female - %	34 (79.0%)	17 (89.4%)	17 (70.8%)	0.257*
Anthropometric variables				
BMI – kg/m^2	44.2 ± 5.5	45.2 ± 5.5	43.5 ± 5.5	0.330
BMI z-score	3.5 ± 0.3	3.6 ± 0.3	3.5 ± 0.3	0.420
Neck circumference – cm	40.9 ± 3.5	41.4 ± 3.2	40.6 ± 3.7	0.423
Abdominal circumference – cm	126.5 ± 13.7	127.8 ± 15.6	125.6 ± 12.4	0.625
Hip circumference – cm	131.7 ± 10.3	132.5 ± 9.2	131.2 ± 11.2	0.674
Waist-length ratio	0.7 ± 0.2	0.7 ± 0.3	0.7 ± 0.1	0.466
Waist-hip ratio	1.0 ± 0.9	1.0 ± 0.1	1.0 ± 0.1	0.835
Fat free mass - %	66.2 ± 11.1	69.6 ± 15.0	66.1 ± 7.6	0.336

* Fischer's exact test performed

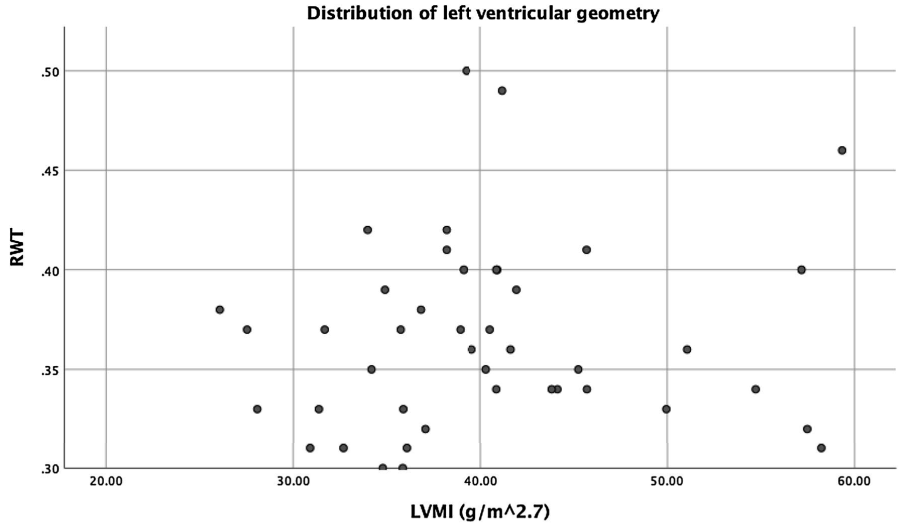


Figure 5.1: *Distribution of left ventricular geometry in morbidly obese adolescents. RWT: relative wall thickness; LVMI: left ventricular mass index. A LVMI of > 38.6 g/m$^{2.7}$ was considered as hypertrophy. A RWT > 0.41 was regarded as concentric LVH or concentric remodeling, depending on the LVMI. A RWT ≤ 0.41 was regarded as eccentric LVH or normal geometry, depending on the LVMI.*

Table 5.2: *Potentially pathogenic characteristics for overall population and patients with LVH.*

Variable	Overall (n = 43)	No LVH (n = 19)	LVH (n = 24)	p-value
Blood pressure related				
SBP - mmHg	121.4 ± 11.3	118.7 ± 11.4	123.3 ± 11.0	0.221
DBP - mmHg	69.5 ± 9.1	68.0 ± 9.5	70.5 ± 9.0	0.417
Z score SBP	0.7 ± 1.0	0.4 ± 1.1	0.9 ± 1.0	0.134
Z score DBP	0.3 ± 0.8	0.2 ± 0.9	0.4 ± 0.7	0.485
Glycemic control				
Fasting glucose - mmol/l	5.4 ± 1.8	5.6 ± 2.7	5.2 ± 0.5	0.451
Fasting insulin - pmol/l	208.1 ± 126.0	210.6 ± 144.0	207.2 ± 113.8	0.933
HbA1c - %	5.5 ± 1.3	5.6 ± 2.0	5.4 ± 0.3	0.663
HOMA-IR	7.3 ± 4.9	7.6 ± 5.5	7.1 ± 4.5	0.705
Lipid profile				
TC – mmol/l	4.7 ± 0.9	4.7 ± 0.9	4.6 ± 0.9	0.705
HDL-c – mmol/l	1.1 ± 0.4	1.1 ± 0.5	1.1 ± 0.3	0.477
Ratio TC-HDL-c	4.7 ± 1.7	4.7 ± 2.1	4.7 ± 1.4	0.801
LDL-c – mmol/l	2.7 ± 0.9	2.8 ± 1.0	2.7 ± 0.8	0.590
FFA – mmol/l	0.8 ± 0.3	0.8 ± 0.3	0.9 ± 0.2	0.599
Triglycerides – mmol/l	1.9 ± 0.9	1.8 ± 1.0	1.9 ± 0.8	0.855
OSA-related				
AHI	5.8 ± 5.2	4.3 ± 3.6	7.0 ± 6.1	0.119
Average O_2-dip - %	3.0 ± 0.5	3.0 ± 0.7	2.9 ± 0.3	0.385

By contrast, multivariable linear regression analysis, correcting for BMI z score, showed that increased LVMI was associated with higher AHI (see Table 5.3). In our study population, 38 patients received polysomnographic evaluation (88.4%). The mean AHI was 5.8 (± 5.2), ranging from 0 to 20.1. For purpose of this analysis, we square-root transformed AHI, which had a right-skewed distribution, to sqrtAHI, upon which normal distribution was achieved. We found that higher LVMI was associated with higher AHI (regression coefficient β = 0.8; 95% CI 0.3 to 1.2) as well as sqrtAHI (β = 3.6; 95% CI 1.3 to 5.9) after correction for BMI z score. The association of AHI and sqrtAHI with LVMI persisted after further correcting for age and sex in addition to BMI z score (β = 0.8; 95% CI 0.3 to 1.3, and β = 3.7; 95% CI 1.3 to 6.1).

Furthermore, we found that higher IVST was associated with a number of cosevere risk factors, namely higher fasting insulin (β = 0.005; 95% CI 0.002 to 0.007), higher HOMA-IR (β = 0.1; 95% CI 0.04 to 0.2), lower HDL-c (β = −1.2; 95% CI − 2.2 to 0.1), higher triglyceride

levels (β = 0.5; 95% CI 0.001 to 0.9), and higher AHI (β = 0.1; 95% CI 0.01 to 0.2), independent of BMI z score. After further correcting for age and gender, significance persisted for AHI, HOMA-IR, and fasting insulin levels.

DISCUSSION

The major findings from our study population of severely obese adolescents are as follows: (1) LVH is highly prevalent and is mostly of the eccentric type; (2) higher LVMI is not significantly associated with anthropometric measures but is independently associated with male gender and higher AHI, the latter implying a pathophysiological relationship between nocturnal hypoxemia and LVH; (3) higher IVST is associated with male gender, lower insulin sensitivity, adverse lipid profile, and higher AHI, independent of BMI z score, which suggests that IVST is associated with an adverse metabolic profile in severely obese adolescents.

Multiple studies describing geometrical changes in obese children have been performed, though they are limited by a high level of intra- and interstudy variability in population characteristics (e.g., a wide range of age, BMI, and ethnicity) and methodology (e.g., different definitions of geometrical aberration), resulting in a reported prevalence of LVH ranging from 10 to 46% [1–6]. Additionally, some studies report that the most common change is eLVH [1,2], while others report a higher prevalence of cLVR [3] or cLVH [4]. Moreover, data regarding severely obese adolescent patients is scarce, and recent literature is limited to a single study by Ippisch et al. [4]. In our study population of 43 severely obese adolescents aged 14–16 years old (average 15.7 ± 1.0 years), we found that 60.5% suffered from abnormal left ventricular geometry overall, with eLVH in 48.8% and cLVH in 4.6%. Ippisch et al. describe a similar prevalence of abnormal left ventricular geometry of 64% in their population of 13–19-year-old patients with a mean BMI of 60 ± 9 kg/m2, though they used the adult cut-off of the LVMI of 51 g/m2.7 [4].

When applying the same cut-off of LVMI in our population, only six patients (14.0%) would suffer from LVH, possibly because the population in the study of Ippisch et al. had on average an even higher BMI than our population (15.8 kg/m^2 difference). We recommend that future studies evaluate more specifically defined populations and determine left ventricular geometry by utilization of LVMI (g/m$^{2.7}$) and RWT, using the pediatric 95th percentile cut-off values of 38.6 g/m$^{2.7}$ and 0.41 cm, respectively, or reporting results using both the pediatric and adult cut-off values [24, 25, 27].

The association between anthropometric measures, in particular BMI and abdominal circumference, with metabolic syndrome is well established [28]. Similarly, several

Table 5.3: *Unstandardized regression coefficients B and 95% confidence intervals, indicating associations of various variables with left ventricular geometrical indices, corrected for BMI z score. Statistically significant differences emphasized with a bold font.*

	LVMI (g/m^{27})	**LVM (g)**	**IVST (mm)**	**LPWT (mm)**	**LVEDD (mm)**
Demographic variables					
Age - yr	0.6 (-2.2 to 3.4)	4.6 (-9.4 to 18.6)	0.06 (-0.3 to 0.5)	-0.1 (-0.5 to 0.2)	0.9 (-0.6 to 2.5)
Gender female	-4.3 (-11.0 to 2.4)	**-68.1 (-95.3 to 40.9)**	**-1.9 (-2.7 to 1.1)**	-0.4 (-1.2 to 0.4)	**-6.6 (-9.8 to 3.3)**
Anthropometric variables					
BMI – kg/m^2 *	-0.1 (-0.6 to 0.3)	-0.8 (-3.3 to 1.6)	-0.006 (-0.08 to 0.07)	-0.004 (-0.06 to 0.05)	-0.1 (-0.4 to 0.1)
BMI z score *	-1.5 (-9.9 to 6.9)	5.7 (-37.3 to 48.7)	0.2 (-1.0 to 1.5)	-0.2 (-0.8 to 1.2)	-0.3 (-5.2 to 4.5)
Neck circumference - cm	-0.5 (-1.5 to 0.5)	3.2 (-1.7 to 8.1)	0.1 (-0.006 to 0.3)	-0.02 (-0.1 to 0.1)	0.2 (-0.4 to 0.7)
Abdominal circumference - cm	-0.01 (-0.3 to 0.3)	1.0 (-0.5 to 2.5)	0.03 (-0.02 to 0.07)	-0.002 (-0.04 to 0.03)	0.1 (-0.03 to 0.3)
Hip circumference - cm	-0.1 (-0.6 to 0.3)	-0.9 (-3.0 to 1.1)	-0.006 (-0.07 to 0.06)	0.01 (-0.04 to 0.06)	-0.2 (-0.4 to 0.07)
Waist-length ratio	4.1 (-9.0 to 17.2)	-5.7 (-73.0 to 61.6)	0.2 (-1.8 to 2.1)	-0.6 (-1.0 to 2.1)	-2.6 (-10.1 to 4.8)
Waist-hip ratio	9.7 (-23.2 to 42.7)	144.2 (-18.4 to 306.9)	3.2 (-1.6 to 8.1)	0.8 (-4.7 to 3.2)	**21.5 (3.9 to 39.1)**
Fat free mass - %	-0.2 (-0.4 to 0.1)	-0.6 (-0.8 to 0.7)	-0.01 (-0.05 to 0.02)	-0.005 (-0.04 to 0.02)	-0.07 (-0.2 to 0.07)
Blood pressure related					
SBP – mmHg	0.2 (-0.1 to 0.4)	0.9 (-0.3 to 2.2)	0.03 (-0.006 to 0.07)	0.02 (-0.01 to 0.04)	0.07 (-0.8 to 0.2)
DBP – mmHg	0.1 (-0.2 to 0.4)	0.6 (-0.9 to 2.1)	0.03 (-0.02 to 0.08)	0.02 (-0.02 to 0.05)	0.002 (-0.2 to 0.2)
Z score SBP	1.7 (-0.8 to 4.2)	0.1 (-13.2 to 13.4)	0.1 (-0.3 to 0.5)	0.1 (-0.2 to 0.4)	-0.3 (-1.8 to 1.1)
Z score DBP	1.9 (-1.5 to 5.2)	0.2 (-17.0 to 17.4)	0.2 (-0.3 to 0.7)	0.2 (-0.2 to 0.6)	-0.8 (-2.7 to 1.1)
Glycemic control					
Fasting glucose – mmol/l	-1.2 (-2.6 to 0.2)	-3.1 (-10.4 to 4.3)	-0.01 (-0.2 to 0.2)	-0.05 (-0.2 to 0.1)	-0.5 (-1.3 to 0.3)

Fasting insulin – pmol/l	-0.001 (-0.02 to 0.02)	-0.04 (0.07 to 0.2)	**0.005 (0.002 to 0.007)**	0.001 (-0.002 to 0.003)	-0.002 (-0.02 to 0.01)
HbA1c - %	-1.7 (-3.6 to 0.3)	-5.5 (-15.6 to 4.6)	-0.03 (-0.3 to 0.3)	-0.08 (-0.3 to 0.2)	-0.8 (-1.9 to 0.3)
HOMA-IR	-0.2 (-0.8 to 0.4)	0.6 (-2.3 to 3.6)	**0.1 (0.04 to 0.2)**	0.005 (-0.06 to 0.07)	-0.1 (-0.5 to 0.)
Lipid profile					
TC – mmol/l	-1.6 (-4.6 to 1.3)	-6.0 (-21.2 to 9.1)	0.01 (-0.4 to 0.5)	-0.05 (-0.4 to 0.3)	-1.2 (-2.8 to 0.5)
HDL-c – mmol/l	-4.8 (-12.3 to 2.6)	-32.8 (-70.3 to 4.7)	**-1.2 (-2.2 to 0.1)**	-0.7 (-1.5 to 0.2)	-1.6 (-5.9 to 2.7)
Ratio TC/HDL-c	0.1 (-1.5 to 1.7)	2.4 (-5.6 to 10.4)	0.2 (-0.07 to 0.4)	0.05 (-0.1 to 0.2)	-0.1 (-1.0 to 0.8)
LDL-c – mmol/l	-1.6 (-4.6 to 1.4)	-6.1 (-21.6 to 9.3)	-0.04 (-0.5 to 0.4)	-0.04 (-0.4 to 0.3)	-1.1 (-2.8 to 0.6)
FFA – mmol/l	-3.5 (-13.7 to 6.7)	-32.9 (-85.0 to 19.2)	-0.2 (-1.8 to 1.4)	-0.2 (-1.5 to 1.0)	**-5.7 (-11.2 to 0.2)**
Triglycerides – mmol/l	-0.3 (-3.5 to 2.8)	7.2 (-8.8 to 23.1)	**0.5 (0.008 to 0.9)**	0.1 (-0.3 to 0.5)	-0.2 (-2.0 to 1.6)
OSA-related					
AHI	**0.8 (0.3 to 1.2)**	2.5 (-0.03 to 5.1)	**0.1 (0.01 to 0.2)**	**0.1 (0.02 to 0.1)**	0.06 (-0.3 to 0.4)
sqrtAHI	**3.6 (1.3 to 5.9)**	**13.2 (1.1 to 25.2)**	**0.5 (0.1 to 0.8)**	**0.4 (0.08 to 0.6)**	0.4 (-1.1 to 2.0)
Average O_2-dip - %	-1.9 (-7.2 to 3.5)	-18.0 (-44.0 to 8.0)	-0.2 (-1.0 to 0.6)	-0.3 (-0.9 to 0.3)	-2.3 (-5.4 to 0.8)

* not corrected

anthropometric variables, including BMI, waist circumference, waist-hip ratio, and waist-length ratios are associated with LVM in adults [29–34]. The pediatric literature relating anthropometric measures with LVM is limited [5]. Daniels et al. described a significant association between LVM and body fat percentage [5]. Within our homogeneous study population of severely obese adolescents with a BMI of 44.2 kg/m^2 (± 5.5), we did not find an association between LVH and any anthropometric variable, such as BMI, neck circumference, and abdominal circumference. Our findings by them self could suggest that in this population at high risk for LVH, additional anthropometric measurements are not valuable to stratify risk. However, the findings by Ippisch et al. raise the question whether further increases in BMI are associated with an increased severity of left ventricular hypertrophy [4].

Our hypothesis that higher LVM could be independently associated with an adverse metabolic profile was based on the adult literature that shows an independent association between higher LVM, insulin resistance, and dyslipidemia [35–39]. We did not find any such association with LVM or LVMI. By contrast, we found that IVST is associated with several variables related to comorbidity, namely HOMA-IR, HDL-c, triglyceride levels, and AHI, independent of BMI z score. After further correction for age and gender, associations remain significant for insulin levels, HOMA-IR, and AHI. Previously, multiple studies established that increased IVST is associated with an adverse metabolic profile [40–42], higher blood pressure in young healthy adults [43, 44], and higher all-cause mortality in adults with cardiovascular disease [45, 46]. Our findings support the hypothesis that hyperinsulinemia plays a role in the nonhemodynamic pathogenesis of cardiac hypertrophy, albeit limited to the ventricular septum. Multiple pathogenic mechanisms by which insulin resistance contributes to altered left ventricular geometry are proposed in the literature, including increased fatty acid oxidation with accumulation of cardiotoxic metabolic intermediates and direct binding of insulin to insulin-like growth factor 1 receptors, resulting in cardiomyocyte proliferation [47–51].

We did not find an association between blood pressure and any parameter of left ventricular geometry (LVMI, LVM, IVST, LPWT, or LVEDD), possibly because the levels of systolic and diastolic blood pressure in our population were relatively normal, with z scores of 0.7 (± 1.0) and 0.3 (± 0.8), respectively. These findings are in conjunction with the observations of the Bogalusa heart study, which found that increased left ventricular mass in obese children and young adults preceded the development of increases in systolic and diastolic blood pressure [14]. This further emphasizes the importance of considering obesity as an independent modifiable risk factor for cardiac geometrical changes.

OSA is a well-established independent risk factor for LVH in adults, both through hemodynamic and nonhemodynamic mechanisms [52]. Cloward et al. demonstrated that treatment of OSA in adults resulted in a reduction in interventricular septal thickness [53]. Amin et al. found that in children and adolescents, an AHI > 10 was associated with a significantly higher risk of LVH when compared to primary snorers (odds ratio 11.2, 95% confidence interval 1.9–64) [54]. Chan et al. evaluated children between 6 and 13 years old with or without OSA and found that higher AHI values were associated with increased IVST and RWT [55]. Furthermore, they found that improvement of OSA resulted in improvement of these variables [55]. Recently, Hanlon et al. compared the prevalence of LVH in 61 subjects with or without OSA, with a mean age of 13.1 years and a median BMI of 36.3 kg/m^2 [6]. They found that OSA was an independent risk factor of LVH and that the risk of LVH increased with the severity of OSA. In our study, we found that square-root-transformed AHIs were associated with LVMI, LVM, IVST, and LVPWT, independent of BMI z score. Regression coefficients remained significant, also after further correction for

age and gender. Importantly, OSA is highly prevalent in severely obese adolescents, with 86.9% of our patients having an AHI ≥ 1 and 39.5% having an AHI ≥ 5, corresponding to mild and moderate-severe OSA, respectively [56]. Our findings support the notion that OSA is an important pathogenic factor in obesity-related LVH and indicate the importance of early recognition and treatment of this serious comorbidity.

The main strengths of our study are a high level of methodological standardization and extensive evaluation across several relevant clinical domains. Our study population consists of well-defined prospectively recruited severely obese adolescents aged 14–16 years, allowing adequate characterization of this specific population. We were able to evaluate multiple hypotheses related to the determinants of LVH in severely obese adolescents, owing to the extensive data we have on the overall condition of our study population, including hemodynamic factors, metabolic aberrations, and polysomnographic characteristics.

Our study has a number of limitations. A significant number of patients did not receive cardiac ultrasound due to logistic reasons, resulting in a limited sample size. This may have hampered the statistical significance of certain findings and did not allow us to investigate all risk factors in one model, i.e., correcting for the influence of these factors on each other. Moreover, our population concerns mainly females, and therefore, the applicability of these findings to male severely obese adolescents cannot be guaranteed. We conclude that LVH, especially eLVH, occurs in the majority of severely obese adolescents and that adverse geometrical changes, in particular increased IVST, are independently associated with multiple commonly occurring nonhemodynamic risk factors, including OSA, dyslipidemia, and insulin resistance. We recommend low threshold of suspicion of these risk factors and proactive treatment, in order to potentially improve cardiovascular prognosis. Future research should focus on the effect of reversal of these risk factors on cardiac geometry.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: None of the authors have a disclosure to declare.

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PART III:

WEIGHT LOSS AND IMPROVEMENT OF COMORBIDITIES AFTER BARIATRIC SURGERY:

RESULTS OF THE BASIC TRIAL



CHAPTER 6

Weight loss and glycemic control after bariatric surgery in adolescents with severe obesity:

A randomized controlled trial

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ABSTRACT

Background:

Bariatric surgery is regarded as a valuable treatment option for adolescents with severe obesity. However, high-quality evidence of its superiority over prolonged conservative treatment with multidisciplinary lifestyle intervention (MLI) is limited.

Objective:

This study investigated the efficacy and safety of bariatric surgery in adolescents without sufficient weight loss after MLI for severe obesity.

Methods:

A two-group randomized controlled trial was designed to assess one-year health effects of bariatric surgery in adolescents with severe obesity. The participants were referred by pediatricians after completing MLI without sufficient effects. Eligible for participation were adolescents aged 14 to 16 years with severe obesity (age- and sex-adjusted body mass index (BMI) using the International Obesity Task Force (IOTF) cut-offs: BMI ≥40 kg/m^2, or ≥35 kg/m^2 in combination with comorbidity). Participants were assigned to MLI combined with laparoscopic adjustable gastric banding (n = 29) versus only MLI (n = 30). Participants were included from 2011 to 2019. Main outcomes were weight change and sex- and age-specific BMI loss. Additionally, glucose metabolism, blood pressure and lipid profile were analysed.

Results:

Fifty-three patients completed the 12-months follow-up (89·8%). Mean (± SD) weight loss in the surgery group was 11·2 ± 7·8 % after 12 months, compared to a weight gain of 1·7 ± 8·1 % in the control group. The fasting insulin, insulin resistance score and lipid profile improved significantly in the surgery group.

Conclusions:

Bariatric surgery was associated with substantial weight loss and improvements in glucose and lipid metabolism after 12 months compared to conservative treatment in adolescents with severe obesity.

Implications and contributions:

This randomized controlled trial was designed to assess health effects of bariatric surgery in adolescents with severe obesity. Bariatric surgery was associated with substantial weight loss and improvements in glucose and lipid metabolism after 12 months in these adolescents who already participated in multidisciplinary lifestyle interventions.

BACKGROUND

Over the past decades, the prevalence of obesity in childhood and adolescence has increased substantially in both the western world and developing countries [1]. In particular the subgroup of children and adolescents with severe obesity (International Obesity Task Fore (IOTF) body mass index (BMI) 35 or higher) is found to be growing at an alarming pace [2-4].Obesity at a young age increases the risk of the early development of non-communicable disorders such as type 2 diabetes [5], hypertension, other cardiovascular diseases [6, 7], and depression [8, 9]. Adults living with obesity have worse medical outcomes if they are already obese during adolescence, and obesity-related health risks do not persist if an adolescent becomes nonobese again [10, 11]. The severity of obesity is found to be directly correlated to an increased risk of developing these non-communicable disorders [12-14].

The standard treatment of childhood obesity consists of a stepped care approach. Well-structured and family-based multidisciplinary lifestyle intervention (MLI) is the first treatment of choice [15, 16]. Although MLI can result in significant weight loss in adolescents living with severe obesity, a substantial part of this specific population experiences insufficient treatment effects. For those who not respond to MLI, more intensive levels of intervention may be required [14, 16] [17, 18]. Bariatric surgery has demonstrated significant weight reduction and improved obesity-associated health conditions in adults, both in short and long-term evaluations [19, 20]. There is increasing evidence of the efficacy of bariatric surgery in adolescents [21-25].

This study was designed to investigate the efficacy and safety of bariatric surgery to achieve weight loss in young adolescents living with severe obesity, in whom multidisciplinary lifestyle interventions in a stepped-care approach were inadequate. Although the widely used laparoscopic Roux-en-Y Gastric Bypass (LRYGB) and laparoscopic Sleeve Gastrectomy (LSG) are safe and effective procedures in adults, long-term follow-up of the side effects in adolescents are lacking. Laparoscopic Adjustable Gastric Banding (LAGB) was chosen as surgical procedure in this current trial because it is relatively easy to reverse. In addition, the study also analyzed the improvement of obesity-related comorbidities due to surgical intervention.

METHODS

Study design and overview

The Bariatric Surgery in Children (BASIC) trial is a single centered, randomized controlled trial comparing LAGB combined with multidisciplinary lifestyle intervention to

multidisciplinary lifestyle intervention alone for treating severe obesity in adolescents. The study's rationale, design, and applied methodology were previously reported in the study protocol [26]. The Medical Research Ethics Committee of the Maastricht University Medical Centre approved the protocol for this study.

Study setting

The study was conducted in the Maastricht University Medical Center. In the Netherlands, weight loss surgery in children and adolescents was only allowed in a research setting, under surveillance of the Dutch Health and Youth Care Inspectorate.

Patient selection and randomization

Eligibility screening for this study was conducted by a team of pediatric surgeons, pediatricians, bariatric dieticians, and bariatric psychologists. Adolescents (14 to 16 years) living with severe obesity and inadequately responding to multidisciplinary lifestyle intervention for a minimum of 12 months were eligible for trial participation. Severe obesity was defined as IOTF age- and sex-adjusted BMI (the weight in kilograms divided by square of height in meters) to be ≥ 40 kg/m^2, or ≥ 35 kg/m^2 if obesity-mediated comorbidities were present [4]. Previous participation in a multidisciplinary combined lifestyle intervention for a minimum period of 12 months without at least 5% of total weight loss was one of the mandatory criteria for eligibility. Contraindications for surgery included eating disorders, lack of understanding of the surgical treatment and its risks and/or effects, inadequate social support by family or guardians, skeletal or developmental immaturity, severe cardiorespiratory impairment, and/or syndromic disorders causing obesity, or unwillingness to adhere to the trial follow-up program [26].

Participant inclusion started in December 2011 and continued till April 2019. Written informed consent was obtained from all participants and parents or guardians. Block randomization with a 1:1 ratio in blocks sized 2 to 6 participants was set up by the participating statistician using a digital randomization program [26]. The participants were treated with either bariatric surgery combined with multidisciplinary lifestyle intervention (surgery group) or multidisciplinary lifestyle intervention alone (control group).

Interventions

Participants in the surgery group received a laparoscopic placement of an adjustable gastric band (LAP-BAND AP ® Adjustable Gastric Banding System with OMNIFORM TM Design; Allergan, Santa Barbara, CA USA). The surgical procedures were performed by two surgeons; one leading bariatric surgeon and a second surgeon trained by the leading surgeon; both using the same surgical protocol (pars flaccida technique). Extensive dietary instructions were given both before and after the surgical procedure [26]. Participants in both groups continued multidisciplinary lifestyle intervention at their referring pediatric

obesity clinic. The investigators monitored the patient's adherence to the multidisciplinary lifestyle intervention and its progress during the follow-up.

Measurements and patient follow-up

All participants were subjected to an extensive clinical assessment at the investigation site at baseline, after which they were randomized to either the intervention or the control group. Subsequent follow-up assessments were performed at 6 and 12 months and included measurement of body weight, height, and blood pressure (blood pressure was not measured at 6 months). Blood was sampled to measure the metabolic and endocrine status. A detailed overview of all the clinical investigations and measurements conducted at each follow-up visit has been reported previously in the published study protocol [26]. In between the clinical assessments, at 3 and 9 months, participants were contacted by phone to motivate them, evaluate the progress, and assess the possible complications. Adjustments to the volume of the gastric band were performed by increasing meal sizes, decreasing satiety sensation, or dysphagia at the investigation site when indicated.

Study outcome measures

The study's primary outcome involved the assessment of total weight change (in percentage) from baseline. Secondary outcomes included changes in BMI, glucose metabolism, blood pressure, lipid profile, and any adverse events or complications. Change in BMI was reported in z-scores to consider the changing body composition during pubertal development. Z-scores were calculated according to sex- and age-specific reference values using the modified LMS (Lambda-Mu-Sigma) method [4].

Daytime blood pressure was measured using the Mobil-O-Graph® NG (I.E.M. GmbH, 291 Stolberg, Germany). Fasting glucose, fasting insulin, and insulin resistance score (HOMA-IR index) were used to assess glucose metabolism. Diabetes was defined as fasting glucose levels of ≥126 mg per deciliter (7.0 mmol/L) or if the participant was using diabetes medication, including metformin or insulin. The lipid profile was assessed by estimating serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and free fatty acids [26, 27]. Also, early and late postoperative complications were monitored to investigate the safety of the intervention.

Statistical analysis

A sample size of 22 participants per study arm was estimated to provide a statistical power of 90% and to detect a difference of 10% total body weight changes between groups (standard deviation [SD] was assumed to be 10% within a group). Taking 20% as the loss to follow-up ratio, a total of 60 participants were targeted to be included in the present study [26]. Numerical data are presented as mean ± SD or median (interquartile range) wherever appropriate. Categorical data are presented as numbers (or percentages).

Linear mixed models were used to assess the longitudinal treatment effect for numerical outcome variables. This analysis method accounts for the correlation between repeated measures, uses all available data, and uses a likelihood approach for missing outcome data, which are assumed to be missing at random (MAR). Group, time and group*time were included as fixed factors to assess the treatment effect at different time points. Variables related to missing outcome data were included in the fixed part of the model to ensure MAR. Random intercept and/or slope were considered for the random part, where the best option was selected based on Bayesian Information Criterion (BIC). All the analyses were performed using IBM SPSS Statistics for Windows (version 24, Armonk NY, IBM Corp.). Two-sided p-values of ≤ 0·05 were considered statistically significant.

RESULTS

Patient enrollment and follow-up

In total, 132 adolescents were referred to our research team for trial participation. The details of the participant inclusion are depicted in Figure 6.1. Sixty adolescents were considered eligible for trial participation and underwent the physical examination. One participant was excluded before randomization due to newly diagnosed prolactinoma. Thus, 59 patients were randomized to surgery and control group based on age, sex, weight, and BMI. The baseline characteristics before randomization of the 59 patients are presented in Table 6.1 and Figure 6.2 and 6.3.

Trial treatments, adherence and surgery complications

Twenty-nine patients were allocated to the surgery group and received a laparoscopically placed adjustable gastric band. All the patients were followed up at the investigation site after a mean (± SD) period of 6·5 ± 1·1 months and 12·0 ± 0·8 months. There were no cross-overs between the two study groups. Six patients (10·2%) from the control group withdrew shortly after randomization. However, their baseline characteristics were comparable to the ones remaining in the control group. Further, the primary outcome measure (change in body weight) was missing for two patients at 6 months and once at 12 months within the control group since the patients could not visit the investigation site due to personal reasons.

All gastric bands remained in situ throughout the 12 months follow-up in the surgery patients. Gastric band adjustments were not performed within 6 weeks after surgery. No fixed schedule was used for adjustments, all adjustments were either on request of the patient or in case weight loss came to a standstill. All adjustments were preceded by fluoroscopy combined with contrast swallow in order to detect complications such as malpositioning and to confirm room for further adjustments. Gastric band adjustments

were performed in 22 patients during these 12 months (once in 9 patients, twice in 9 patients, and thrice in 4 patients).

Three patients from the surgery group reported heartburn or peptic complaints and were treated successfully with proton pump inhibitors for a short period (Clavien Dindo Grade I surgical complication) [28]. The access port of the gastric band was dislocated in one patient and was refixed under local anesthesia (Clavien Dindo Grade III-a surgical complication). One patient developed symptomatic cholecystolithiasis, for which a laparoscopic cholecystectomy was performed (Clavien Dindo Grade III-b surgical complication).

Trial Outcomes

Participants with a gastric band exhibited a mean (±SD) bodyweight reduction of 11·2% (±7·8) at the end of the first year after surgery, compared to a mean (±SD) weight gain of 1.7% (±8·1) in the control group. This resulted in a treatment effect of 13.1% change in total body weight favouring the surgical option of adjustable gastric banding in addition to lifestyle interventions. Treatment with a gastric band resulted in significant weight loss compared to the control group as observed in BMI z-score ($p<0·001$) as well as absolute weight ($p<0·001$) (Table 6.2, Figure 6.4). Additionally, surgery combined with multidisciplinary lifestyle intervention resulted in a significant improvement in fasting insulin, HOMA-IR index, and lipid profile compared to the control group (Table 6.2).

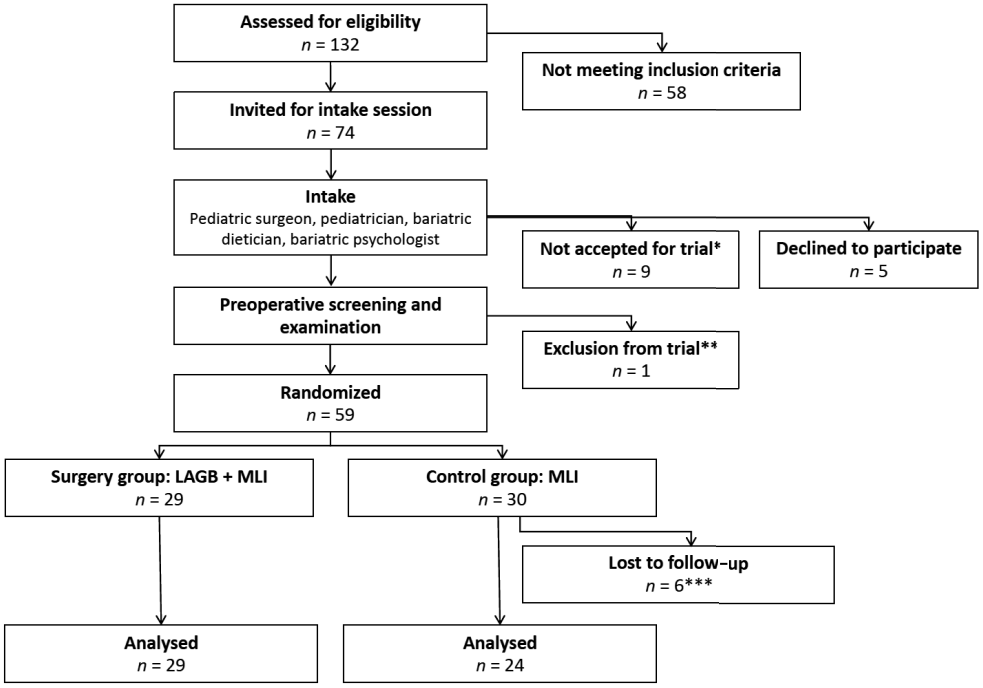


Figure 6.1: *CONSORT flow-diagram of the participant enrollment in the study.*

LAGB: laparoscopic adjustable gastric banding. MLI: multidisciplinary lifestyle intervention.

* lifestyle intervention in the past turned out not to be multidisciplinary (n=4), psychological problems not adequately treated (n=1), not able to oversee consequences and risks of trial participation (n=1), BMI below the threshold (n=1), bone age younger than 15 years in a boy (n=1), suffering from therapy-resistant binge eating behavior (n=1).

** exclusion based on diagnosis of a prolactinoma as cause of the severe obesity.

*** not willing to proceed with multidisciplinary lifestyle intervention during the trial period (n=6).

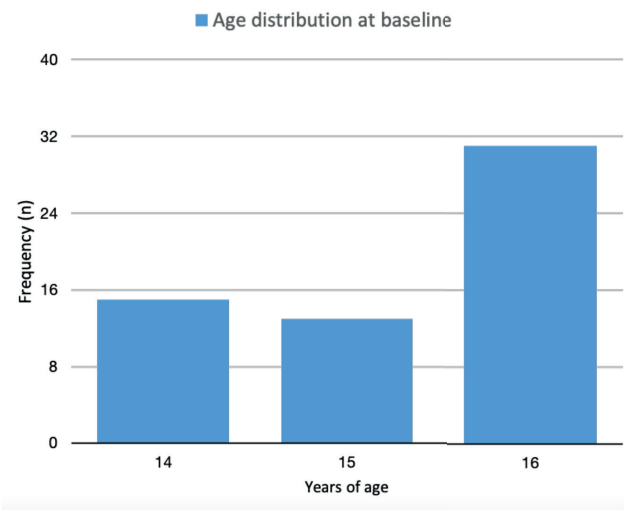


Figure 6.2: *Distribution of age at baseline.*

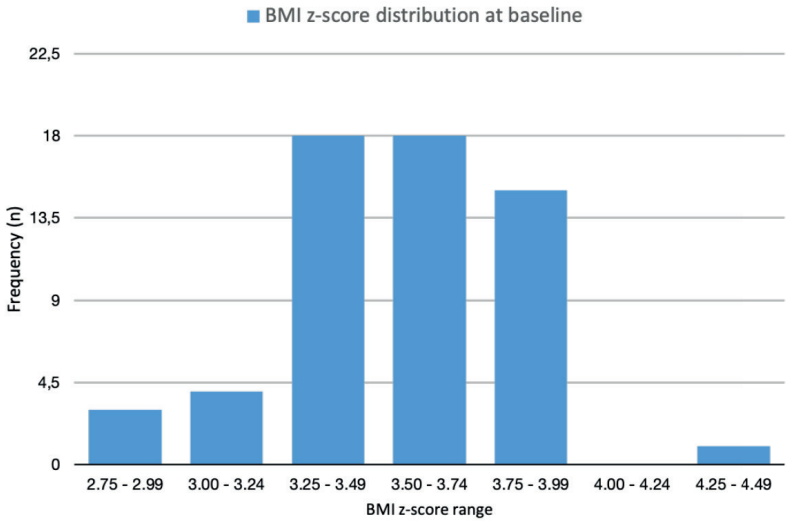


Figure 6.3: *Distribution of BMI z-scores at baseline.*

Table 6.1: *Baseline characteristics of the study participants.*

Characteristic	Total (n=59)	Surgery Group (n=29)	Control Group (n=30)
Age – yr	15·8 ± 1·0	15·9 ± 1·0	15·6 ± 1·0
Male/female – no.	12 / 47	6 / 23	6 / 24
Weight – kg	128·8 ± 19·8	129·0 ± 18·5	128·6 ± 21·3
BMI[#] – kg/m^2	44·1 ± 5·6	43·9 ± 5·6	44·3 ± 5·6
BMI z-score*	3·54 ± 0·29	3·54 ± 0·28	3·54 ± 0·31

Values are presented as mean ± SD.

[#] BMI- Body mass index is the weight in kilograms divided by the square of the height in meters.

* Calculated according to gender- and age-specific reference values using the LMS method[4]

Table 6.2: *Study outcome results during the 6-month and 12-month follow-up of the participants.*

	Observed data		**Treatment effect (95% CI)**	**p-value**
	Surgery Group	**Control Group**		
Weight loss - %				
6 months	-8·83 ± 5·18 (29)	-0·27 ± 5·49 (22)	-8·73 (-11·70, -5·77)	<0·001
12 months	-11·23 ± 7·76 (29)	1·74 ± 8·05 (23)	-13·10 (-17·49, -8·72)	<0·001
BMI z-score				
Baseline	3·54 ± 0·28 (29)	3·54 ± 0·31 (30)	-	
6 months	3·24 ± 0·44 (29)	3·49 ± 0·36 (22)	-0·25 (-0·38, -0·12)	<0·001
12 months	3·11 ± 0·56 (29)	3·58 ± 0·36 (23)	-0·43 (-0·59, -0·26)	<0·001
Total body weight - kg				
Baseline	129·0 ± 18·5 (29)	128·6 ± 21·3 (30)	-	
6 months	117·7 ± 18·8 (29)	130·1 ± 27·3 (22)	-11·5 (-15·6, -7·4)	<0·001
12 months	114·7 ± 20·3 (29)	134·0 ± 26·5 (23)	-16·9 (-22·9, -11·0)	<0·001
Systolic blood pressure – mmHg				
Baseline	125 ± 13 (29)	120 ± 11 (30)		
12 months	125 ± 16 (27)	123 ± 10 (21)	-2 (-9, 5)	0·56
Diastolic blood pressure – mmHg				
Baseline	74 ± 11 (29)	68 ± 8 (30)		
12 months	72 ± 29 (27)	68 ± 9 (21)	-2 (-7, 2)	0·34
Fasting glucose – mg/dL				
Baseline	91·4 ± 9·2 (29)	102·0 ± 40·9 (30)		
6 months	84·8 ± 6·1 (29)	100·2 ± 44·5 (20)	-10·5 (-19·0, -1·9)	0·02
12 months	89·7 ± 6·9 (29)	107·5 ± 53·0 (23)	-4·0 (-12·3, 4·3)	0·34
Glycated hemoglobin - %				
Baseline	5·3 ± 0·4 (29)	5·7 ± 1·6 (30)		
6 months	5·2 ± 0·3 (29)	5·5 ± 1·1 (20)	-0·1 (-0·3, 0·1)	0·37
12 months	5·2 ± 0·3 (29)	5·7 ± 1·6 (23)	-0·1 (-0·3, 0·1)	0·45
Fasting insulin – µU/L				
Baseline	27·7 [21·2-47·3] (28)	27·8 [22·0-39·7] (30)		
6 months	17·7 [13·2-25·3] (29)	24·8 [18·0-41·9] (20)	†	0·008
12 months	22·8 [15·0-28·2] (28)	28·2 [18·7-45·7] (23)	†	0·003

HOMA-IR index				
Baseline	5·2 [4·0-8·8] (28)	5·5 [4·3-8·6] (30)		
6 months	3·1 [2·4-4·6] (29)	4·7 [3·2-10·0] (20)	†	0·002
12 months	4·2 [2·9-5·4] (28)	5·9 [3·7-10·2] (23)	†	0·002
Total cholesterol – mg/dL				
Baseline	174·4 ± 29·0 (29)	182·9 ± 37·0 (30)		
6 months	160·5 ± 27·5 (29)	174·6 ± 28·7 (20)	-8·4 (-21·5, 4·6)	0·20
12 months	163·9 ± 27·7 (29)	179·6 ± 34·1 (23)	-7·9 (-20·65, 4·8)	0·22
HDL cholesterol – mg/dL				
Baseline	43·5 ± 15·0 (29)	42·0 ± 11·0 (30)		
6 months	44·0 ± 11·2 (29)	43·3 ± 8·0 (20)	-0·2 (-4·9, 4·4)	0·92
12 months	43·6 ± 12·4 (29)	40·5 ± 9·4 (23)	0·9 (-3·6, 5·5)	0·69
Total/HDL cholesterol ratio				
Baseline	4·4 ± 1·6 (29)	4·7 ± 1·5 (30)		
6 months	3·8 ± 1·3 (29)	4·2 ± 1·0 (20)	-0·3 (-0·8, 0·2)	0·22
12 months	3·9 ± 1·4 (29)	4·6 ± 1·4 (23)	-0·5 (-1·0, 0·0)	0·05
Triglycerides – mg/dL				
Baseline	165·8 ± 81·3 (29)	148·8 ± 72·6 (30)		
6 months	113·5 ± 47·1 (29)	116·6 ± 54·6 (20)	-25·8 (-56·6, 4·9)	0·10
12 months	126·0 ± 38·9 (29)	143·0 ± 63·3 (23)	-33·3 (-64·3, -2·4)	0·04
Free fatty acids– mg/dL				
Baseline	24·1 ± 7·4 (27)	23·9 ± 7·8 (28)		
6 months	26·8 ± 12·3 (28)	25·5 ± 7·2 (18)	-0·0 (-5·7, 5·7)	1·00
12 months	23·8 ± 9·8 (25)	25·4 ± 10·6 (22)	-1·6 (-7·2, 4·0)	0·58

Plus-minus values are mean ± standard deviation (total no. of patients evaluated) or median (interquartile range). p≤0·05 was considered significant.

† Statistics performed after log transformation due to skewness of the parameter outcomes. Thus, treatment effect not given.

The HOMA-IR (Homeostatis model assessment for insulin resistance) index was estimated for assessment of insulin sensitivity.

At baseline, 6 participants (3 in the surgery group and 3 in the control group) were diagnosed with type 2 diabetes and were treated with metformin (3 in the surgery group and 2 in the control group) or insulin (1 in the control group). One participant in the surgery group achieved normal fasting glucose without using any medication at the end of 12 months while the other 5 patients showed no improvement in the diabetic status. There were no patients who developed type 2 diabetes during the follow-up period in either group.

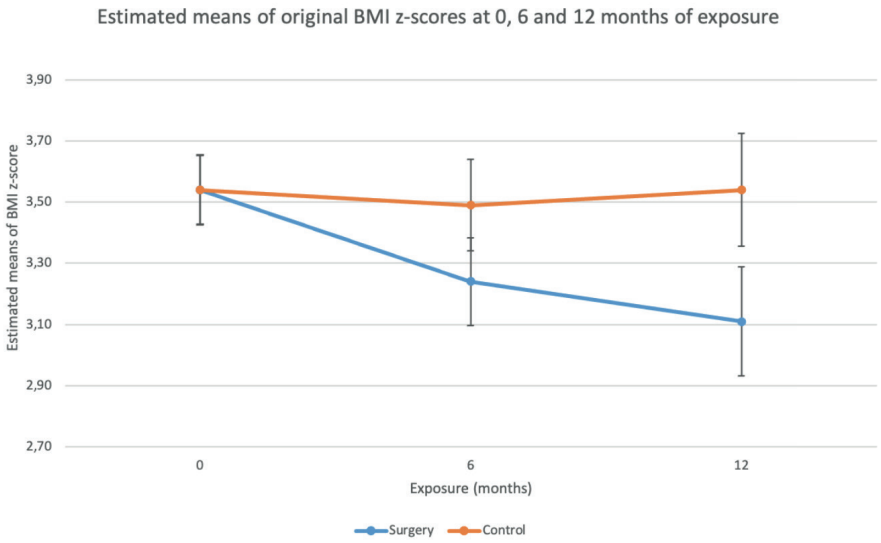


Figure 6.4: *Estimated means of original BMI z-scores during follow-up.*

DISCUSSION

The results of this randomized controlled trial confirm that adding adjustable gastric banding to the treatment of severe obesity in adolescents can lead to significant weight loss and improvement of insulin sensitivity. In our group of patients there was a reduction of mean total bodyweight of 11% one year after surgery, while the body weight in the control group increased with 2% after one year. The patients in the surgery group showed a significant improvement in fasting insulin, insulin sensitivity (HOMA-IR index), and serum triglycerides levels after one year compared to the control patients. Furthermore, the surgery led to only a relatively small percentage of minor complications.

Recent studies show comparable effects of chronic medical treatment on weight loss in adolescents living with severe obesity [29, 30]. Although higher percentages of weight loss have been reported after adjustable gastric banding, the current study included only adolescents living with severe obesity and without sufficient weight loss after participating in well-structured multidisciplinary lifestyle interventions for one year or longer. The importance of this lies in the stepped care approach in adolescent obesity healthcare: the risks of surgery for severe obesity should be restricted only to those adolescents who do not benefit from all the other non-surgical treatment steps. Therefore, we researched the efficacy of surgery in a selected group of non-repsonders to MLI. This aim was reflected in our data; continuation of MLI in the control group had no effect and the patients in the

control group gained weight, which suggests that the health benefits in the intervention group (by randomization equal to the control group) are specifically achieved by adding surgery to MLI.

Several studies have reported good outcomes of bariatric and/or metabolic surgery in adolescents, but the results are more heterogenous in adolescents compared to adults [22, 24]. Large cohorts have been reported comparing different types of bariatric surgery to one another, but comparison to MLI treatment in a randomized setting is rare [21-24]. Yet especially in adolescence, the physiology of the developing adolescent body on i.e. body weight and insulin resistance must be taken into account in researching this age group and interpreting results [31]. In the current study among a relatively young group of adolescents (aged 14 to 16 years) living with severe obesity, we used randomization to take into account general effects of the developing body while assessing the benefits and risks of bariatric surgery in this age group.

Concerns regarding weight loss surgery in adolescents remain among many pediatricians and other physicians. These concerns include interference with normal growth and development, safety in adolescents, and the risks on serious adverse events in the long term [22-24]. Laparoscopic gastric banding was chosen as surgical treatment in the present study because of its acceptable perioperative complication rate and negligible risk of malabsorption of vitamins and micronutrients since the procedure does not structurally affect the anatomy.

The laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass have gained popularity in the past decade and are the present surgical procedures of choice to obtain substantial weight loss in adolescents living with severe obesity [32-34]. The gastric banding procedure is often regarded as outdated due to the lack of efficacy and relatively high revision and band removal rates [35, 36]. Jarvholm et al. recently published the 2-year results of an RCT comparing the commonly used surgical procedures (mostly laparoscopic gastric bypass) to non-surgical treatment in adolescents, showing promising results regarding efficacy and safety [25].

The current study reports the short-term results of this clinical trial, the long-term efficacy and the long-term complication rate were not addressed. This limits the applicability of our findings since long-term results may be more relevant. The percentage of patients in the control group who finished the study was high with 80% follow-up after one year. Bariatric surgery in minors has no part in the regular Dutch healthcare, therefore our patients could not undergo bariatric surgery in other hospitals. This limited the option of crossover for patients who participated in this trial.

An inclusion period of more than 7 years was one of the limitations of this study. Inclusion in the trial was prolonged as the pediatricians were reluctant to refer adolescents, especially in the beginning of the trial, since bariatric surgery as obesity treatment was hardly accepted in this age group [37, 38]. Strict inclusion criteria of age and the required quality of MLIs prior to surgery also limited the number of eligible adolescents. Furthermore, the Dutch Health and Youth Care Inspectorate paused the trial for almost six months to evaluate the study design and implementation (no violations of the protocol were ascertained). The impact of the long inclusion period on the results was limited by the use of block randomization.

Another limitation of the study is the definition of severe obesity in our inclusion criteria, since the international cut-off for severe adolescent obesity from an adult equivalent BMI of 40 kg/m2 was lowered to to 35 kg/m2 (irrespective of the obesity-associated comorbidities) during the inclusion phase of this trial [4]. The inclusion criteria for the BASIC trial have not been adjusted to the revised cut-off criteria in order to maintain homogeneity in the study population.

In conclusion, the current study provides evidence on safety and efficacy of adjustable gastric banding in addition to well-structured multidisciplinary lifestyle intervention in the treatment of severe obesity in adolescence. Early surgery in adolescents living with severe obesity who inadequately respond to well-structured MLI is recommended.

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CONTRIBUTORS

BW and YGMR performed all the statistical and modelling analysis, and verified the underlying data. Additional authors contributing to the formal analysis included GFP, AT and NDB, and these authors had full access to the data. YGMR and LWEvH wrote the first draft of the manuscript. GFP, AT, EGAHvM, ACEV, BW, CDAS, JWMG, ND and the members

of the BASIC trial consortium commented on the manuscript. LWEvH, YGMR, and NDB had final responsibility for the decision to submit to publication.

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APPENDIX 6.1: BASIC TRIAL CONSORTIUM

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CHAPTER 7

The effect of bariatric surgery on obstructive sleep apnea in adolescents;

A randomized controlled trial

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Submitted

ABSTRACT

Aim:

Obstructive sleep apnea (OSA) is highly prevalent among patients eligible for bariatric surgery (BS). OSA is known to decrease after BS in adults, but literature in adolescents is scant and limited to mainly retrospective studies. Therefore, we aimed to investigate the impact of BS on OSA in adolescents with severe obesity, using data from a randomized controlled trial.

Methods:

We conducted a randomized controlled trial, including adolescents (14-16 years) with severe obesity. Participants were randomized into the intervention group (multidisciplinary lifestyle intervention and laparoscopic adjustable gastric banding) or the control group (multidisciplinary lifestyle intervention alone). Anthropometric measurements and polysomnography (PSG) were performed at baseline and one year follow-up.

Results:

Participants were mainly female (79%) and the mean (±SD) age was 15.8 ± 1.0, mean BMI-z score was 3.5 ±0.3, and mean AHI 6.9 ± 6.1 events per hour. After one year, significant differences in PSG variables between the study groups were found, including AHI (mean difference -4.37, 95%CI -7.52 to -1.22), independently of BMI-z score. The remission rate of OSA was 31.3% and patients with remission were all from the intervention group. We did not find significant associations between change in AHI and change in BMI, leptin, or insulin resistance.

Discussion:

Independent of BMI-z score, the intervention group had significantly more reduction in OSA than the control group. Not all patients with weight loss achieved complete remission of OSA, suggesting that other factors may influence remission in adolescents.

INTRODUCTION

Childhood obesity is a concerning public health problem. According to the World Health Organization 206 million children aged between 5 and 19 years old are currently obese. Global estimates predict that the prevalence will increase to 254 million children by 2030 [1]. Of major concern is the simultaneous rise of obesity-associated comorbidities, such as obstructive sleep apnea (OSA). OSA is prevalent in 38 -78% of adolescents with obesity, compared to 15-37% in their non-obese peers [2]. Independent of obesity, OSA is associated with components of the metabolic syndrome, including insulin resistance, hypertension, and a pro-inflammatory state [3].

First line treatment of OSA in adolescents consists of continuous positive airway pressure (CPAP) therapy and adenotonsillectomy, but in individuals with obesity weight loss may be the key factor to decrease OSA severity [4]. Bariatric surgery (BS) is an effective therapeutic option for weight loss and can reduce the severity of OSA in adults [5-7]. Similar to adult studies, research in adolescents found significant improvements in OSA severity after BS [8-10]. However, not all patients have remission of OSA after BS. Although it can be hypothesized that those who have persistent OSA after BS have limited weight loss, this relationship between weight loss and OSA is not established in adolescents. Amin et al. observed improvements in OSA shortly after BS (3 weeks), even without substantial weight loss [11]. This raises the question of whether weight-independent factors may contribute to the improvement of OSA following BS. Understanding the mechanisms underlying this change in OSA after BS in adolescents is essential for the enhancement of patient selection for BS.

Research on this topic is scant and limited to mainly retrospective observational study designs. Moreover, few studies measured OSA objectively with PSG before and after surgery and most studies lack a control group. Therefore, this randomized controlled trial aims to investigate the efficacy of BS with multidisciplinary lifestyle intervention (MLI) on the improvement of OSA, comparing them to the control group that receives MLI alone. Additionally, we assess the influence of weight-independent factors, such as leptin and insulin resistance, on OSA post-BS.

METHODS

This randomized controlled trial included adolescents eligible for BS. The study's rationale, design, and applied methodology were previously reported in the study protocol; the Bariatric Surgery in Children (BASIC trial, NCT01172899) [12]. In summary, inclusion criteria were adolescents with severe obesity (sex-and age-adjusted BMI ≥ 40 kg/m^2, or

≥ 35 kg/m^2 combined with the presence of obesity-associated comorbidity) between 14-16 years. Contraindications for surgery were severe cardiorespiratory impairment, syndromic disorders causing obesity, eating disorders, or unrealistic expectations of weight loss. Written informed consent was obtained from all participants and parents or guardians. The participants were randomly assigned to either the intervention group who received laparoscopic adjusted gastric banding (LAGB) and MLI, or the control group who received MLI. Baseline data about the prevalence and patient characteristics of OSA and one-years weight loss results in this study population have been published before [13,14]. The current study focuses on the effect of BS on OSA one-year after the intervention.

Measurements and follow up

Participants were medically examined at the clinical site and anthropometric measurements and blood tests were performed. OSA was assessed by polysomnography at baseline and 12 months. Video-assisted 12 channel polysomnography (PSG) (Brain RT, OSG, Rumst, Belgium) was performed at the pediatrics department of Maastricht University Medical Center. The sleep exam included measurement of AHI (apnea-hypopnea index) and ODI (oxygen desaturation index). OSA was defined as AHI ≥ 5.0 [15].

Outcome measurements

The primary goal of this study involved investigating the efficacy of bariatric surgery on the improvement of OSA one year after intervention, using the data from the BASIC trial. In addition, we assessed the influence of weight-independent factors, such as leptin and insulin resistance on OSA post-BS.

Statistical analysis

Numerical variables are presented as mean ± standard deviation (SD) and categorical ones as numbers and/or percentages. To evaluate the treatment effect, we performed a per protocol regression analysis with study arm as main independent variable and correction for baseline BMI-z score, and sex. Differences between study arms were presented as corrected mean difference (95% confidence interval). To evaluate the effect of different metabolic components on the change in OSA post-intervention; a post-hoc analysis was performed. Delta AHI was the dependent factor and multiple metabolic variables were analyzed one by one, while correcting for study arm and BMI-z score. Assumptions for linear regression analysis were checked using (partial) residual plots, histograms and qq-plots. Multicollinearity was also checked and was no issue as all variance inflation factors (VIF) were <5 (highest VIF 3.8). Additionally, all Cook's distances were close to 0 (greatest distance 0.4), indicating no influential outliers. To check for selection bias, the differences in baseline characteristics between individuals with complete and incomplete data were tested using independent-samples t-test. IBM SPSS Statistics for Windows (version 27.0; Armonk, NY, USA) was used for all statistical analyses. Two-sided p-values ≤ 0.05 were considered statistically significant.

Results

Participants and follow-up

The trial included 59 patients, with 53 of them undergoing PSG at baseline. Immediately after randomization six patients from the control group were lost to follow-up. Another ten patients did not receive a PSG at the 12-month assessment, due to reasons unrelated to the study. This resulted in 37 participants receiving PSG at the 12-month assessment, of whom 35 had complete PSG-data. The baseline characteristics of the total group (n=53) as well as the baseline characteristics of these 35 patients are presented in Table 7.1.

Table 7.1: *Baseline characteristics of the total study population and patients with pre-and post PSG.*

	Baseline characteristics			**Patients with pre-and-post intervention PSG**		
PSG-variables	**Total (n=53)**	**Intervention group (n=26)**	**Control group (n=27)**	**Total (n=35)**	**Intervention (n=19)**	**Control (n=16)**
Age - yr	15.7 ± 1.0	15.9 ± 1.0	15.6 ± 1.0	15.8 ±1.0	15.7±1.1	15.6±1.1
Female - n (%)	42 (79.2%)	22 (84.6%)	20 (74.1%)	28 (80.0%)	16 (84.2%)	12 (75.0%)
BMI - kg/m²	44.1± 5.2	44.1 ± 4.7	44.5 ± 5.7	44.4±5.6	43.7±5.0	45.2±6.3
BMI-z score	3.5 ± 0.3	3.5 ± 0.3	3.6 ± 0.3	3.5±0.3	3.5±0.3	3.6±0.3
AHI	5.77 ± 5.43	5.8 ± 5.3	5.7 ± 5.7	6.9±6.1	6.9±5.7	6.9±6.7
Average O2dip - %	3.0 ± 0.5	3.0 ± 0.4	3.0 ± 0.6	3.1±0.5	3.0±0.4	3.1±0.5
Maximum O2dip - %	6.4 ± 2.7	6.5 ± 2.6	6.2 ± 2.8	7.1±2.6	7.2±2.6	6.8±2.6
Lowest O2-sat. - %	89.4± 3.5	89.3 ± 3.8	89.5 ± 3.2	88.9±3.7	88.6±4.2	89.1±3.1
Wake O2-sat. - %	96.7 ± 0.8	96.6 ± 0.8	96.7±0.9	96.7±0.9	96.7±0.8	96.7±1.0
ODI>3% per h	6.5 ± 5.8	6.8 ± 6.1	6.1±5.6	7.8±6.5	8.2±6.6	7.3±6.6
HOMA-IR	5.6 (4.2-9.1)	5.7 (4.6-9.5)	5.6 (4.1-8.8)	6.02 (4.7-9.2)	5.8 (4.3-8.9)	5.8 (4.3-8.9)
Leptin - Ug/L	78.8 ±41.2	84.4 ±50.1	72.7±29.3	70.1±30.9	72.7 ±24.3	68.0 ±36.0

Data are presented as mean ±standard deviation. For non-normally distributed variables, data are presented as median (IQR)

Abbreviations: BMI=Body mass index, AHI=apnea-hypopnea index, O2 dip= oxygen dip, ODI= oxygen desaturation index, HOMA-IR=Homeostatic Model Assessment for Insulin Resistance

For the remaining 35 patients, the mean (±SD) age was 15.8 ± 1.0 and the majority was female (79%). The mean Body mass index (BMI) was 44.4 ± 5.6, BMI-z score was 3.5 ± 0.3, and mean AHI was 6.9 ± 6.1. At baseline 16/35 (45.7%) of the participants were diagnosed with OSA (AHI ≥ 5.0); seven patients from the control group and nine from the intervention group. Of these 16 participants, five (31.3%) had complete remission (AHI < 5) of OSA, all from the intervention group. Consequently, in 11 (68.8%) patients OSA continued (AHI ≥ 5.0) after one year. Sensitivity analyses showed significant differences between the group lost to follow-up and those who continued follow-up in AHI, O2 maximum, and ODI>3 per hour.

The intervention effect after 1-year

Linear regression analyses showed superior efficacy of BS with MLI in comparison to MLI for the improvement of the majority of the PSG variables after the first year. Table 7.2 presents the treatment effects (differences between the study groups), corrected for baseline BMI-z score and sex. PSG variables included AHI (mean difference -4.37, 95%CI -7.52 to -1.22), maximum O2 dip (mean difference -1.67, 95%CI -3.30 to -0.03), time O2 saturation under 90% (mean difference -0.67, 95%CI -1.23 to -0.12), and oxygen desaturation index (ODI>3%) (mean difference -5.18, 95%CI -8.67 to -1.68).

The effect of multiple metabolic variables on change in AHI

Post-hoc per protocol analyses were performed to evaluate the effect of different metabolic components on the change in OSA severity post-intervention (Table 7.3). There was no significant association between change in AHI and change in BMI-z score, corrected for sex and study arm. After adjustment for potential confounders (change in BMI-z score, study arm, and sex) there were no significant associations observed between change in AHI and change in HOMA-IR or change in leptin.

Table 7.2: *Per protocol regression analysis of PSG measurements pre-and post-intervention (n=35).*

Variable	Intervention Mean changes from baseline (95% CI)	Control Mean changes from baseline (95% CI)	Mean difference (95% CI) between study arms	P-value
BMI (Kg/m²)	-5.27 (-6.70, -3.84)	0.62 (-1.27,2.50)	-5.84 (-8.13, -3.55) **	**<0.001**
BMI-z score	-0.42 (-0.57, -0.28)	0.02 (-0.8,0.12)	-0.42 (-0.60, -0.25)**	**<0.001**
Leptin (Ug/L)	5.52 (-19.27,30.32)	-8.18 (-38.03,21.68)	22.11 (-13.35,57.57)*	0.211
HOMA-IR	-3.55 (-5.93, -1.17)	-0.76 (-2.47,0.96)	-1.91 (-3.41, -0.40)*	**0.02**
Polysomnographic variables				
AHI per h	-3.86 (-6.48, -1.25)	0.59 (-1.39,2.57)	-4.37 (-7.52, -1.22)*	**0.008**
Average O2dip (%)	-0.08 (-0.26,0.09)	0.13 (-0.10,0.35)	-0.19 (-0.44,0.06) *	0.13
Maximum O2dip (%)	-1.89 (-3.32, -0.47_	0.20 (-1.13,1.53)	-1.67 (-3.30, -0.03)*	**0.047**
Lowest O2-sat. (%)	1.37 (-0.52,3.26)	-0.80 (-2.39,0.79)	1.74 (-0.26,3.73)*	0.09
Wake O2-sat. (%)	0.09 (-0.18,0.36)	0.06 (-0.28,0.41)	-0.004 (-0.43,0.42)*	0.98
Time O2-Sat. under 90% (min.)	-0.40 (-1.00,0.20)	0.51 (-0.07,1.08)	-0.67 (-1.23, -0.12)*	**0.02**
ODI>3% per h	-4.70 (-7.83, -1.57)	0.91 (-1.27,3.08)	-5.18 (-8.67, -1.68)*	**0.005**

Data are presented as mean changes from baseline (95% CI) to one year and mean difference between the groups (intervention versus control). *Corrected for sex and baseline BMI-z score **corrected for sex

Table 7.3: *Post-hoc per protocol analyses to evaluate the effect of different metabolic components on the change in OSA (n=35). Dependent factor: change in AHI).*

Variables	Unstandardized B coefficient	95% CI	P-value
Δ BMI *	0.26	-0.26 to 0.78	0.32
Δ BMI-z score*	-0.60	-7.28 to 6.08	0.86
Δ waist circumference (cm)	0.07	-0.09 to 0.22	0.40
Δ abdominal circumference (cm)	0.17	-0.05 to 0.40	0.13
Δ neck circumference (cm)	0.19	-0.12 to 0.49	0.49
Δ HOMA-IR	-0.06	-0.53 to 0.41	0.79
Δ leptin (Ug/L)	0.02	-0.03 to 0.07	0.48

Data are corrected for study arm and weight loss (change in BMI-z score), * not corrected for weight loss (change in BMI-z score)

Additionally, we did not establish a relationship between waist, abdominal, and neck circumference and change in AHI.

DISCUSSION

This is the first RCT investigating the effect of BS on OSA in adolescents with objective measurement of OSA by means of polysomnography. BS with MLI demonstrated superiority over MLI alone after one year for the improvement of the majority of the PSG-specific variables, including the AHI. The study design (including the presence of a control group and randomization) decreases the chances of bias and minimizes confounding. This is especially relevant during the adolescent years, when numerous physiological changes take place, that may influence OSA.

At baseline, 16 (45.7%) out of the 35 participants who received a postoperative PSG were diagnosed with OSA (AHI>5). Five of these participants (31.3%) had remission of OSA one year after surgery and in 11(68.8%) patients OSA continued. The patients who had complete remission of OSA all underwent LAGB. The limited studies that investigated remission of OSA after BS in adolescents found remission rates of 66% and 59.2%, respectively [8,16]. A recent systematic review that analyzed remission of OSA in adults found a pooled effect of 65% remission post-BS, defined as no longer use of CPAP [6]. Notably, the use of this definition may have led to an overestimation of remission. Most of the studies included in this review used laparoscopic Roux and Y bypass (LRYGB) or sleeve gastrectomy (LSG) as bariatric intervention. Our lower remission rates could be explained by the surgical method that was used, namely purely restrictive surgery (LAGB). Currently, there is no literature available in adolescents but previous research in adults suggested that interventions primarily focused on malabsorption (LRYGB) tend to be more effective in resolving OSA compared to restrictive methods. An explanation for this difference may be linked to a greater decrease in inflammation and therefore higher remission rates after RYGB [17,18].

In line with previous retrospective and observational studies in adolescents, we found reduction in OSA severity after BS [8,9,11]. Although our data showed significant improvement in the AHI after surgery, the aforementioned studies found a greater decrease in AHI. This is likely attributed to the preclusion of correction for significant confounders in these studies, and varying surgical methods. Specifically, Kaar et al. reported a median decrease in AHI of -24.7 events per hour 10 months after LRYGB and Amin et al. observed a mean decrease in AHI of -9.1 events per hour 5 weeks after LSG or LRYGB. As mentioned previously, LRYGB and LSG tend to be more effective in decreasing OSA severity compared to LAGB.

In the current study the intervention group lost on average BMI-z score -0.42 (95%CI -0.57 to -0.28) compared to a small increase of 0.02 (95%CI -0.8 to 0.12) in the control group. However, when correction for weight loss (change in BMI-z score) was applied, OSA

improvement was still significantly greater in the intervention group. This emphasizes the multifactorial aspect of OSA, as it is not only the result of obesity but is independently associated with various components of the metabolic syndrome, for example leptin, insulin resistance, and inflammation [19-21].

Insulin resistance is a potential metabolic factor influencing OSA. Intermittent hypoxia induces a pro-inflammatory state, which is a crucial mechanism leading to insulin resistance and vice versa. Thus, insulin resistance is independent of obesity associated with OSA, with inflammation as the common factor [22,23]. Insulin resistance (HOMA-IR) improved significantly in the surgical group after one year, potentially leading to a positive effect on OSA. Supporting this notion is the significant decrease in AHI and ODI>3% postoperative, as these are clinical indicators for the severity of hypoxia.

Leptin is a hormone produced in white adipose tissue and functions as a long-term regulator of appetite and energy-homeostasis (amongst others) [24]. Hyperleptinemia is often found in obesity, due to leptin resistance. Paradoxically, it has been reported that leptin levels initially increase after BS, particularly in the early postoperative period. This temporary increase is thought to be related to the changes in weight and metabolism after surgery. However, one year after BS leptin usually decreases significantly [25,26]. In both obese and normal weight patients with OSA, leptin levels can be increased [27]. It is assumed that leptin has a protective role in OSA by promoting respiratory stimulation in the case of intermittent hypoxia caused by respiratory depression [28]. In our study we did not find a significant difference in leptin between the study groups after one year, while a difference was observed for AHI and BMI. Although not statistically significant, leptin levels trended towards an increase postoperatively. Perhaps this can be explained by the relatively limited weight loss that was achieved after one year and the small sample size, which could have led to a lack in statistical power.

The current study did not find significant associations between change in leptin and AHI, or change in HOMA-IR and AHI. This is likely attributed to the sample size of the study, as it was not powered to perform these analyses and we could not correct for all potential confounders. An alternative explanation may be that the variables analyzed do not affect change in AHI after BS. However, a more plausible theory is that all variables together lead to change in AHI. OSA remission is likely mediated through weight dependent and weight independent pathways, which makes it challenging to analyze all potential factors [29]. Nonetheless, weight loss in combination with its beneficial effect on insulin resistance and inflammation, likely results in OSA improvement after BS.

Strengths and Limitations

The main strengths of this study are the randomized study design and the objective measurement of OSA with PSG (gold standard). All PSGs were conducted 12 months after the start of the intervention, ensuring consistency in the follow-up period. Another unique feature is the measurement of adipokines and insulin resistance, which provided the opportunity to analyze their impact on OSA after BS. Limitations include a relatively small sample size and missing data at follow-up. Although the reasons for missing data indicated that these were unrelated to the study, there were significant differences in AHI, O2 maximum, and ODI>3 per hour between the group that was lost to follow-up and those who continued follow-up and were included in the per-protocol analysis.

Clinical implications

A case-control study evaluating the effects of OSA in children revealed concerning long-term health consequences, such as an increased risk of chronic diseases later in life and premature mortality [21]. The concerning long-term consequences of childhood OSA and the observation that younger age is associated with greater OSA remission following BS, supports the notion for early intervention in this group [8,30]. The current study found promising results for OSA improvement after BS. Our data validates early intervention in adolescents, especially when OSA is present. We emphasize the importance of postoperative assessment of OSA, as OSA continued in a substantial number of patients, who may need additional treatment

Conclusion

To conclude, this RCT confirmed the beneficial effect of BS on OSA severity in adolescents with severe obesity. We emphasize the multifactorial nature of OSA and highlight that the metabolic alterations following BS, together with anatomical changes resulting from weight loss, drive OSA improvement. Additional research is necessary to further elucidate and identify factors that contribute to remission and improvement of OSA postoperative in adolescents.

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SUMMARY AND DISCUSSION

SUMMARY

This thesis provides new insights for a better understanding of the difficulties that adolescents with severe obesity encounter regarding access to specialized care and weight loss surgery. Furthermore, it evaluates the physiological impact of severe obesity in adolescents, and the risks and challenges of (surgical) treatment in this specific age group.

The first part of this thesis focused on the healthcare landscape for adolescents with severe obesity. As with bariatric surgery in adults, the common opinion for bariatric surgery in adolescents has long been predominated by safety concerns, insufficient understanding of mechanisms and stigmatization.

Chapter 1 of this thesis revealed that Dutch general practitioners (GPs) only adhered to the national treatment guidelines for childhood obesity in 55.4% of the cases, and the vast majority of the GPs estimated that the available non-surgical treatment modalities are only sufficient in less than half of the patients. Although bariatric surgery was regarded as effective last-resort treatment, only 41.3% of the GPs would refer for surgery in case of therapy resistance to other treatment modalities. Main reasons for reluctance were uncertainty regarding complications in the long term and uncertainty regarding long-term efficacy. **Chapter 2** showed that the healthcare landscape for children and adolescents with severe obesity differs significantly per country. At the time of the survey amongst pediatric surgeons, bariatric surgery in children and/or adolescents was allowed in several countries, however only few countries had established clinical guidelines regarding bariatric surgery in youngsters. Most pediatric surgeons regarded bariatric surgery as a viable option for adolescents with severe obesity and advocated for collaboration with adult bariatric surgeons in the treatment of this population. In **chapter 3**, the study protocol of the BAriatric Surgery In Children trial (BASIC) trial was presented: a randomized controlled trial (RCT) comparing laparoscopic adjustable gastric banding (LAGB) as addition to multidisciplinary lifestyle interventions (MLI) with only MLI as treatment of adolescents with severe obesity and not responding to earlier MLI treatment. Main outcome parameters were total weight loss and change in body mass index (BMI); secondary outcomes were metabolic and endocrine changes, cardiovascular abnormalities, quality of sleep, non-alcoholic steatohepatitis and several others. The reversibility of the LAGB formed a strong argument to decide for gastric banding over other surgical procedures, since the long-term risks and complications of other surgical procedures in adolescents had not been examined.

After finishing the inclusion phase of the BASIC trial, a unique cohort had been formed consisting of adolescents aged 14-16 years who had been suffering from severe obesity

despite of various conservative treatment modalities (of which at least 12 months of MLI for each participant). The second part of this thesis showed the impact of severe obesity on specific health aspects in the total BASIC trial cohort at baseline.

Chapter 4 evaluated the presence of obstructive sleep apnea (OSA) in the BASIC trial cohort at baseline. Since (severe) obesity is a significant risk factor for developing OSA in adults, the main goal was to examine if OSA had already developed at such an early age. None of the analyzed participants had a prior diagnosis of OSA or had received treatment for it. 90% of the participants showed to have sleep-disordered breathing, 37.7% were classified as having moderate to severe OSA (defined as an apnea-hypopnea index (AHI) of 5 or more). The participants with moderate to severe OSA were slightly older than the non-OSA participants, had a higher weight (137.9 ± 23.7 vs. 123.5 ± 14.3 kg, p=0.008), and exhibited a higher BMI (46.9 ± 5.5 vs. 42.4 ± 4.3 kg/m^2, p=0.002) and BMI z-score (3.7 ± 0.3 vs. 3.4 ± 0.3, p=0.003). This suggests that every amount of weight loss can be beneficial, even though this cohort already finds itself at the extremes of the obesity spectrum. Significant differences in plasma triglyceride and insulin-like growth factor 1 (IGF-1) levels were also observed between participants with OSA and those without, and both BMI z-score and triglyceride levels were significantly associated with AHI.

Chapter 5 presented the prevalence and determinants of left ventricular geometrical changes in the BASIC trial cohort at baseline. Obesity is an independent risk factor for left ventricular hypertrophy (LVH), which is associated with a higher risk of cardiovascular morbidity and mortality in adults. LVH was found in 55.8% of the participants, predominantly in an eccentric form. Neither traditional anthropometric measures (including BMI) nor cardiovascular parameters (including blood pressure, lipid profile, etc.) correlated significantly with LVH, however multivariable linear regression analysis (correcting for BMI z-score, age and gender) showed that LVH was associated with a higher AHI (suggesting a pathophysiological relationship between nocturnal hypoxemia and LVH). Hypertrophy of the ventricular septum was associated with a higher AHI, insulin sensitivity and fasting insulin levels (after correction for BMI, age and gender). Early detection and treatment of these risk factors, particularly OSA, could improve cardiovascular outcomes.

The third part of this thesis focused on BASIC trial outcomes after one year of follow-up. **Chapter 6** showed the results of the RCT after one year of follow-up, focusing on safety of the procedure, weight loss and change in BMI, and several metabolic parameters. After one year, the participants who underwent surgery (as additional treatment to MLI) achieved a significant and clinically relevant weight reduction of 11.2% on average, contrasting with a 1.7% weight gain in the control group (only MLI treatment). Improvements were also noted in fasting insulin, insulin sensitivity and serum triglycerides levels in the surgery group. Complications of the surgical treatment were mild and all successfully treated. Although

the amount of weight loss might seem confined when compared to other studies, it must be taken into account that the BASIC trial was based on a stepped care approach in which comprehensive MLI had already been practiced over a year. This means that the observed health benefits could be assigned to the LAGB only and not (as in many other studies) to a combination of surgery and MLI. Despite concerns about bariatric surgery in adolescents, results suggest that it can be effective for those unresponsive to lifestyle changes.

In **chapter 7**, the changes in quality of sleep after one year of follow-up in the BASIC trial were evaluated. In comparison to the control group, a significant improvement in AHI was found in the surgery group, independently of BMI. The patients who had complete remission of OSA all underwent LAGB. There was no significant association between change in AHI and insulin sensitivity, or between change in AHI and leptin levels; although other studies have reported evidence for such associations, the sample size of the BASIC trial was assumed to be too small to correct for all potential confounders.

DISCUSSION

Already highly prevalent in adults worldwide, and increasingly in childhood, obesity is viewed as one of the most important and challenging public health problems of our time. In the life of the developing child, three periods may be important for the development of obesity: the perinatal period (0-1 years), the period of adiposity rebound (5-7 years), and puberty/adolescence (10-19 years) [1]. During puberty, rapid changes in body composition and physiology come after another while future (adult) behaviors such as dietary patterns and levels of physical activity are formed. This suggests that adolescence offers a unique window of opportunity to modify the prevalence of future obesity and its consequences.
Although prevention of future obesity is key, (severe) obesity can also present itself already before the stage of puberty. For adolescents already suffering from severe obesity, preventive measures are far too late and intensive treatment is necessary.
To this very day, bariatric surgery is not part of standardized care of severe obesity in children or adolescents in The Netherlands and only allowed in research settings. The rationale of the BASIC trial was based on several elements: the importance of the period of adolescence as a starting point for (a healthier) adult life, the need for more effective treatment modalities than MLI (as the core treatment strategy offered in childhood obesity), and the hypothesis that obesity-associated comorbidities might be more easily reversible when treated sooner. Because of the physiological changes throughout puberty in all adolescents regardless of weight, the BASIC trial was designed with a control group in order to correct for those influences as much as possible and distillate a pure intervention effect.

In the field of adult bariatric surgery, the laparoscopic sleeve gastrectomy (LSG) and the laparoscopic Roux-and-Y gastric bypass (LRYGB) are the most commonly used surgical procedures. Both procedures are based on restrictive and malabsorptive mechanisms and come with specific risks on complications. For example, nutritional disorders have been reported five times more often in patients who had LSG or LRYGB compared to non-operated individuals, despite routinely prescribed nutritional supplements in post-surgery follow-up [2]. Conditions such as anemia (due to iron or vitamin B12 deficiency) and decreased bone mineral density (calcium and vitamin D deficiencies) are commonly observed in long-term follow-up of LSG and LRYGB. One out of ten adults undergoing LSG develops a Barrett's esophagus, a premalignant condition of the distal esophagus due to gastro-esophageal reflux disease [3]. After LRYGB, the reported incidence of internal herniation (resulting in bowel obstruction) is at least 10%, and even more during pregnancy [4]. Because the lifetime risk on such complications after LSG and LRYGB only increases when bariatric surgery is forwarded to adolescence, the choice for a purely restrictive and reversible surgical procedure in the form of LAGB was made in designing the BASIC trial. The risk of a smaller amount of weight loss during the trial that accompanied the choice for a purely restrictive type of surgery was known and regarded as acceptable. Safety on both the short and long term were regarded as a main priority since efficacy on the long term was still being investigated in bariatric surgery in adolescents; the cure may never be worse than the disease.

The presented studies in part III of this thesis only report the short-term results of the BASIC trial. Obviously, the long-term efficacy and the long-term complication rate are still to be evaluated.

FUTURE PERSPECTIVES

The obesity pandemic in children and adolescents is a relatively recent problem when compared to other non-communicable diseases. Only just a few decades ago, the problem was still to be recognized and its impact had to gain attendance, after which treatments such as MLI had to be professionalized and incorporated in (inter)national treatment guidelines. More experimental treatments such as pharmaceuticals and surgery for obesity had to be approved for the adolescent population and have only become widely applied in the last decade. Long-term efficacy and severity of long-term side effects of these treatments have yet to be established.

For the BASIC trial, representing LAGB treatment in adolescents, various outcome parameters are yet to be analyzed to evaluate weight loss and obesity-associated comorbidities on the long term after LAGB treatment. During the recruitment and follow-

up phases of the BASIC trial, several other initiatives were established to study efficacy of various types of bariatric surgery; long-term results are still awaited in order to gain knowledge regarding serious adverse events such as malnutrition, Barrett's esophagus and bowel obstructions [5-7].

The scope of interest in future adolescent bariatric surgery research is much wider than only safety and efficacy of different surgical techniques. Other possible predictors of success of surgery, such as the influence of social support, mental health status and motivation and compliance are still to be explored more thoroughly within the adolescent population, in order to optimize patient selection [8]. Another field of interest is the evaluation of decisional capacity of adolescents; the younger a patient is, the more difficult it might be to assess accurate awareness of the benefits and risks of the offered treatment. Since most types of bariatric surgery lead to structural gastrointestinal changes, it is essential that the patient is mature enough to comprehend the effects of surgical procedures that are irreversible. Procedures such as LAGB might not be the technique of first choice in future surgical treatment of severe obesity in adolescents, but may become a 'bridge to definitive surgery' since decisional capacity also gets a chance to mature through those years.

Furthermore, a variety of innovative treatment modalities other than surgical techniques have been developed the past decades, including pharmacotherapy and minimally invasive endoscopic techniques. Pharmacological treatments, such as orlistat and newer agents like semaglutide (better known as Ozempic®), induce gastrointestinal changes such as malabsorption of dietary fats, slower gastric emptying and reduce appetite which can also aid in weight loss [9]. When administered as additional treatment to MLI in adolescents living with obesity, semaglutide has shown to result in a significant greater weight (and BMI) loss than placebo treatment [10]. However, adverse events (mostly gastrointestinal events) occur in roughly 10% of the patients treated with semaglutide, and long-term effects of these pharmaceuticals have yet to be investigated. Endoscopic techniques, such as intragastric balloon placement, offer a minimally invasive option that can promote weight loss through mechanisms of gastric volume reduction and altered satiety signaling. Safe and effective weight loss results have been reported in the short term, however long-term data is lacking [11, 12].

The overarching principle of obesity treatment algorithms are based on personalization of treatment, recognizing that obesity is a complex, multifactorial condition requiring tailored approaches for effective management. Obesity has genetic, physiologic, behavioral, socioeconomic and environmental contributors. Surgical and/or pharmaceutical treatment of severe obesity should therefore always be offered as addition to a comprehensive treatment plan including MLI at least. Future research exploring the

impact of social determinants of health on the development of early obesity is needed to enable a deeper understanding of the complexity of both obesity risk and treatment [13]. As the environment of children and adolescents has become increasingly obesogenic, both prevention and access to evidence-based treatment have become even more crucial and impose increased involvement of national health institutes and governments [14].

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APPENDICES

IMPACT PARAGRAPH

The alarming increase in adolescents living with severe obesity, combined with the relatively recent origin of this condition, advocate for extensive and thorough research regarding prevention, screening and treatment modalities. Although the worldwide knowledge on *adult* severe obesity has increased significantly during the past two decades, the general principles in treating severe obesity cannot merely be extrapolated to children and adolescents. Dogmas and guidelines in adult care need to be reexamined and tested in children and adolescents. This thesis explores both the healthcare landscape for adolescents living with severe obesity and the physiological impact of the condition. It also evaluates the safety and short-term effects of laparoscopic adjustable gastric banding (LAGB) as an addition to intensive lifestyle treatment, within the context of the BAriatric Surgery In Children (BASIC) trial.

AIM AND MAIN FINDINGS

The central goal of this research was to better understand the barriers adolescents face in accessing effective obesity care and to evaluate both the risks and benefits of surgical treatment in this age group.

The first part of the thesis revealed that adolescents with severe obesity often struggle to access specialized care. Many general practitioners are hesitant to refer these patients for bariatric surgery, mainly due to concerns about safety and long-term outcomes. Internationally, the availability and acceptance of surgery for this population vary widely, and clear clinical guidelines are still lacking in many countries.

The second part of the thesis demonstrated the profound health consequences of severe obesity in adolescence. Even before adulthood, many participants showed signs of obstructive sleep apnea and early heart changes, such as left ventricular hypertrophy; conditions that can increase long-term cardiovascular risk. These findings highlight the urgency of effective interventions.

The third part of the thesis reported the short-term outcomes of the BASIC trial. Adolescents who underwent LAGB in addition to multidisciplinary lifestyle treatment achieved meaningful weight loss and improvements in metabolic health, including better insulin sensitivity and lower triglyceride levels. Importantly, the surgery proved safe in the short term, with only mild and treatable complications. Quality of sleep also improved significantly in the surgery group, with some participants achieving complete remission of sleep apnea.

SCIENTIFIC AND SOCIETAL RELEVANCE

From a scientific perspective, this research contributes to the growing body of evidence on adolescent obesity and bariatric surgery. It provides new insights into the prevalence of obesity-related complications at a young age, emphasizing that the physiological consequences of severe obesity are not limited to adults. These findings support the notion that timely interventions may prevent the progression of life-threatening conditions.

The BASIC trial also offers valuable data on the safety and efficacy of a reversible surgical procedure in adolescents. This is particularly relevant in light of ongoing debates about the ethical and medical considerations of performing bariatric surgery in youth. The results can guide clinical decision-making, improve treatment guidelines, and serve as a foundation for future research on long-term outcomes, patient selection, and the role of social and psychological factors in treatment success.

By identifying barriers in the healthcare system and demonstrating that early intervention can yield significant health benefits, this thesis provides arguments for policy-makers and healthcare providers to improve access to evidence-based care. Although prevention of obesity is of great importance in order to turn the tide of the obesity-pandemic, the adolescents who are living with severe obesity already will not be helped with preventive measures. Addressing severe obesity in adolescence does not only impact individual health and quality of life but may also reduce future healthcare costs related to cardiovascular disease, diabetes, and other complications of untreated obesity.

TARGET AUDIENCE

The findings of this research are relevant to multiple groups:

1. **Healthcare professionals** such as pediatricians, general practitioners, dietitians, and bariatric surgeons, who play a key role in early recognition, referral, and treatment of adolescent obesity.
2. **Policy-makers and healthcare organizations**, who can use these insights to improve guidelines, streamline referral pathways, and support evidence-based interventions for young patients.
3. **Researchers** in the fields of pediatrics, endocrinology, cardiology, and public health, who can build on these findings to further explore long-term outcomes, optimal patient selection, and the psychosocial dimensions of obesity treatment.
4. **Patients and their families**, who gain a better understanding of the health risks associated with untreated obesity and the potential benefits and limitations of surgical interventions.

In conclusion, this thesis provides essential evidence that severe obesity in adolescence is not only a pressing health concern but also a treatable condition when approached with a structured, multidisciplinary strategy. By improving understanding, addressing healthcare gaps, and evaluating innovative treatments, this work contributes to both scientific progress and societal well-being. Its findings have the potential to inform policymakers, optimize clinical care, and ultimately improve the lives of young individuals living with obesity.

DUTCH SUMMARY

SAMENVATTING EN DISCUSSIE

SAMENVATTING

Dit proefschrift biedt nieuwe inzichten betreffende de hindernissen die adolescenten met ernstige obesitas (klasse III) ervaren op het gebied van toegang tot gespecialiseerde zorg en specifiek bariatrische chirurgie. Daarnaast evalueert dit proefschrift de fysiologische impact van ernstig obesitas op de gezondheid van adolescenten, evenals de risico's en uitdagingen van een chirurgische behandeling in deze specifieke leeftijdsgroep.

Het eerste deel van dit proefschrift richtte zich op het zorglandschap voor adolescenten met ernstige obesitas. Overeenkomstig met de situatie bij volwassenen, werd de heersende opvatting over bariatrische chirurgie bij adolescenten lange tijd gedomineerd door zorgen omtrent veiligheid, een ontoereikend begrip van de onderliggende ziektemechanismen en stigmatisering.

Hoofdstuk 1 van dit proefschrift toonde aan dat Nederlandse huisartsen (HA) zich slechts in 55,4% van de gevallen hielden aan de nationale behandelrichtlijnen voor obesitas bij kinderen, en dat de overgrote meerderheid van de HA inschatte dat de beschikbare niet-chirurgische behandelmodaliteiten slechts bij minder dan de helft van de patiënten toereikend zijn. Hoewel bariatrische chirurgie werd beschouwd als een effectieve 'last resort' behandeloptie, zou slechts 41,3% van de HA verwijzen voor chirurgie in geval van therapieresistentie binnen de andere beschikbare behandelmodaliteiten. De belangrijkste redenen voor terughoudendheid waren onzekerheid over complicaties op de lange termijn en onzekerheid over de effectiviteit op lange termijn. **Hoofdstuk 2** liet zien dat het zorglandschap voor kinderen en adolescenten met ernstige obesitas aanzienlijk verschilt per land. Ten tijde van de enquête onder kinderchirurgen was bariatrische chirurgie bij kinderen en/of adolescenten in meerdere landen toegestaan, maar slechts in enkele landen waren klinische richtlijnen voor bariatrische chirurgie bij jongeren vastgesteld. De meeste kinderchirurgen beschouwden bariatrische chirurgie als een geschikte behandeloptie voor adolescenten met ernstige obesitas en pleitten voor samenwerking met bariatrisch chirurgen bij de behandeling van deze populatie.

In **hoofdstuk 3** werd het studieprotocol van de BAriatric Surgery In Children (BASIC)-trial gepresenteerd: een gerandomiseerde gecontroleerde studie (RCT) waarin bariatrische chirurgie als toevoeging aan multidisciplinaire leefstijlinterventies (MLI) werd vergeleken met uitsluitend MLI als behandeling voor adolescenten met ernstige obesitas die niet reageerden op eerdere MLI-behandeling. Binnen deze studie werd gekozen voor de laparoscopisch geplaatste, verstelbare maagband (LAGB) als vorm van bariatrische chirurgie. De primaire uitkomstmaten waren totaal gewichtsverlies en verandering in body mass index (BMI); secundaire uitkomstmaten betroffen metabole en endocriene veranderingen, cardiovasculaire afwijkingen, slaapkwaliteit, niet-alcoholische

leververvetting en diverse andere parameters. De reversibiliteit van de LAGB vormde een belangrijk argument om te kiezen voor maagbanding boven andere chirurgische procedures, aangezien de lange-termijn risico's en complicaties van andere chirurgische ingrepen bij adolescenten nog niet waren onderzocht.

Na afronding van de inclusiefase van de BASIC-trial was een uniek cohort gevormd, bestaande uit adolescenten van 14–16 jaar die leden aan ernstige obesitas ondanks diverse conservatieve behandelmodaliteiten (waaronder ten minste 12 maanden MLI per deelnemer). Het tweede deel van dit proefschrift beschreef de impact van ernstige obesitas op specifieke gezondheidsaspecten in het totale BASIC-cohort bij aanvang van de studie.

Hoofdstuk 4 evalueerde de aanwezigheid van obstructief slaapapneu (OSA) in het BASIC-cohort bij aanvang. Aangezien (ernstige) obesitas een belangrijke risicofactor is voor het ontwikkelen van OSA bij volwassenen, was het primaire doel te onderzoeken of OSA zich reeds op deze jonge leeftijd had ontwikkeld. Geen van de geanalyseerde deelnemers had een voorafgaande diagnose van OSA of had hiervoor behandeling ontvangen. Negentig procent van de deelnemers vertoonde slaapgerelateerde ademhalingsstoornissen, en 37,7% werd geclassificeerd als hebbende matig tot ernstig OSA (gedefinieerd als een apnea-hypopnea-index (AHI) van ≥5). De deelnemers met matig tot ernstig OSA waren iets ouder dan de niet-OSA-deelnemers, hadden een hoger lichaamsgewicht (137,9 ± 23,7 vs. 123,5 ± 14,3 kg, p=0,008), en vertoonden een hogere BMI (46,9 ± 5,5 vs. 42,4 ± 4,3 kg/m^2, p=0,002) en BMI-z-score (3,7 ± 0,3 vs. 3,4 ± 0,3, p=0,003). Dit suggereert dat elke mate van gewichtsreductie klinisch relevant kan zijn, zelfs in een cohort dat zich reeds aan de extremen van het obesitas-spectrum bevindt. Daarnaast werden significante verschillen waargenomen in plasmaconcentraties van triglyceriden en insulin-like growth factor 1 (IGF-1) tussen deelnemers met en zonder OSA, en bleken zowel de BMI-z-score als de triglyceridenspiegels significant geassocieerd met de AHI.

Hoofdstuk 5 presenteerde de prevalentie en determinanten van geometrische veranderingen van het linker hartventrikel in het BASIC-cohort bij aanvang van de studie. Obesitas is een onafhankelijke risicofactor voor linkerventrikelhypertrofie (LVH), wat bij volwassenen geassocieerd is met een verhoogd risico op cardiovasculaire morbiditeit en mortaliteit. LVH werd vastgesteld bij 55,8% van de deelnemers, voornamelijk in een excentrische vorm. Noch traditionele antropometrische maten (inclusief BMI), noch cardiovasculaire parameters (waaronder bloeddruk en lipidenprofiel) correleerden significant met LVH. Multivariabele lineaire regressieanalyse (gecorrigeerd voor BMI-z-score, leeftijd en geslacht) toonde echter aan dat LVH geassocieerd was met een hogere AHI, hetgeen wijst op een mogelijke pathofysiologische relatie tussen nachtelijke hypoxemie en LVH. Hypertrofie van het ventriculaire septum was geassocieerd met een

hogere AHI, insulinegevoeligheid en nuchtere insulinespiegels (na correctie voor BMI, leeftijd en geslacht). Vroege detectie en behandeling van deze risicofactoren, in het bijzonder OSA, zouden cardiovasculaire uitkomsten kunnen verbeteren.

Het derde deel van dit proefschrift richtte zich op de uitkomsten van de BASIC-trial na één jaar follow-up. **Hoofdstuk 6** beschreef de resultaten van de gerandomiseerde gecontroleerde studie (RCT) na één jaar follow-up, met focus op de veiligheid van de procedure, gewichtsverlies en verandering in BMI, evenals diverse metabole parameters. Na één jaar bereikten de deelnemers die chirurgie ondergingen (als aanvullende behandeling op MLI) een significante en klinisch relevante gemiddelde gewichtsreductie van 11,2%, in tegenstelling tot een gewichtstoename van 1,7% in de controlegroep die werd behandeld met uitsluitend MLI. Tevens werden verbeteringen waargenomen in nuchtere insuline, insulinegevoeligheid en serumtriglyceriden in de chirurgiegroep. Complicaties van de chirurgische behandeling waren mild en konden allen succesvol worden behandeld. Hoewel de mate van gewichtsverlies relatief beperkt lijkt in vergelijking met andere studies, dient te worden benadrukt dat de BASIC-trial gebaseerd was op een 'stepped-care' benadering, waarbij reeds gedurende een jaar intensieve MLI was toegepast. Dit impliceert dat de waargenomen gezondheidswinst primair kan worden toegeschreven aan de LAGB en niet, zoals in veel andere studies, aan een combinatie van chirurgie en MLI. Ondanks bestaande zorgen omtrent bariatrische chirurgie bij adolescenten suggereren deze resultaten dat deze behandelvorm effectief kan zijn voor patiënten die niet reageren op leefstijlinterventies.

In **hoofdstuk 7** werden veranderingen in slaapkwaliteit na één jaar follow-up binnen de BASIC-trial geëvalueerd. In vergelijking met de controlegroep werd in de chirurgiegroep een significante verbetering van de AHI waargenomen, onafhankelijk van BMI. De patiënten bij wie volledige remissie van OSA optrad bleken allen te zijn behandeld middels chirurgie als aanvulling op MLI. Er werd geen significante associatie gevonden tussen verandering in AHI en insulinegevoeligheid, noch tussen verandering in AHI en leptinespiegels. Hoewel andere studies aanwijzingen geven voor dergelijke verbanden, werd aangenomen dat de steekproefgrootte van de BASIC-trial te klein was om voor alle potentiële confounders te corrigeren.

DISCUSSIE

Wereldwijd wordt obesitas beschouwd als een van de belangrijkste en meest uitdagende volksgezondheidsproblemen van deze tijd. In de ontwikkeling van een kind kunnen drie perioden van bijzonder belang zijn voor het ontstaan van obesitas: de perinatale periode (0–1 jaar), de periode van 'adiposity rebound' (5–7 jaar) en de puberteit/adolescentie (10–

19 jaar) [1]. Tijdens de puberteit volgen snelle veranderingen in lichaamssamenstelling en fysiologie elkaar in hoog tempo op, terwijl toekomstige (volwassen) gedragingen, zoals voedingspatronen en mate van lichamelijke activiteit, worden gevormd. Dit suggereert dat de adolescentie een uniek venster biedt om de prevalentie van toekomstige obesitas en de daarmee samenhangende gevolgen te beïnvloeden.

Hoewel preventie van toekomstige obesitas essentieel is, kan (ernstige) obesitas zich reeds vóór de puberteit manifesteren. Voor adolescenten die reeds lijden aan ernstige obesitas komen preventieve maatregelen te laat en is intensieve behandeling noodzakelijk. Tot op heden maakt bariatrische chirurgie geen deel uit van de gestandaardiseerde zorg voor ernstige obesitas bij kinderen of adolescenten in Nederland en is deze uitsluitend toegestaan binnen onderzoeks-omstandigheden. De rationale van de BASIC-trial was gebaseerd op meerdere elementen: het belang van de adolescentie als startpunt voor een (gezond) volwassen leven, de noodzaak voor effectievere behandelmodaliteiten dan MLI (als kernstrategie binnen de behandeling van obesitas bij kinderen), en de hypothese dat obesitas gerelateerde aandoeningen mogelijk beter reversibel zijn bij vroegtijdige behandeling. Vanwege de fysiologische veranderingen gedurende de puberteit bij alle adolescenten, ongeacht gewicht, werd de BASIC-trial opgezet met een controlegroep om deze invloeden zo goed mogelijk te corrigeren en een zuiver interventie-effect te kunnen isoleren.

Binnen de volwassen populatie behoren laparoscopische maagverkleining (laparoscopische sleeve gastrectomie (LSG)) en laparoscopische Roux-en-Y gastric bypass (LRYGB) tot de meest toegepaste chirurgische technieken. Beide procedures berusten op restrictieve en malabsorptieve mechanismen en gaan gepaard met specifieke complicatierisico's. Zo zijn voedingsdeficiënties tot vijfmaal vaker gerapporteerd bij patiënten die een LSG of LRYGB ondergingen in vergelijking met niet-geopereerde individuen, ondanks routinematig voorgeschreven suppletie in de postoperatieve follow-up [2]. Aandoeningen zoals anemie (ten gevolge van ijzer- of vitamine B12-deficiëntie) en een verminderde botmineraaldichtheid (door calcium- en vitamine D-deficiënties) worden frequent gezien op lange termijn na het ondergaan van ofwel LSG of LRYGB. Bij één op de tien volwassenen die een LSG ondergaan ontwikkelt zich een Barrett-slokdarm, een premaligne aandoening van het distale deel van de slokdarm als gevolg van gastro-oesofageale refluxziekte [3]. Na LRYGB wordt een incidentie van interne herniatie (leidend tot darmobstructie) van ten minste 10% gerapporteerd, en zelfs hoger tijdens zwangerschap [4]. Aangezien het levenslange risico op dergelijke complicaties na LSG en LRYGB toeneemt wanneer bariatrische chirurgie reeds in de adolescentie wordt toegepast, is bij het ontwerp van de BASIC-trial gekozen voor een puur restrictieve en reversibele chirurgische techniek in de vorm van LAGB. Het risico op een relatief beperkter gewichtsverlies, inherent aan deze keuze, was bekend en werd als acceptabel beschouwd.

Veiligheid op zowel korte als lange termijn werd als eerste prioriteit beschouwd, aangezien de effectiviteit op lange termijn van bariatrische chirurgie bij adolescenten nog onderwerp van onderzoek is; de behandeling mag nimmer schadelijker zijn dan de aandoening zelf.

De in deel III van dit proefschrift gepresenteerde studies rapporteren uitsluitend de korte-termijn resultaten van de BASIC-trial. De lange-termijneffectiviteit en het lange-termijncomplicatieprofiel dienen derhalve nog te worden geëvalueerd.

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Cesare Pavese, 1908-1950

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De allergrootste dank gaat natuurlijk uit naar 'mijn' mannen. Lieve *Tim*, natuurlijk wil ik je bedanken voor je betrokkenheid, je visie op het promotietraject en mijn carrière pad, en je bereidheid om alle teksten die ik je maar onder de neus schoof kritisch door te nemen en te verbeteren. Maar dat dekt maar een klein deel van alles wat je de afgelopen jaren voor me hebt betekend. Wat jou echt een bijzondere man en partner maakt, is dat je me de ruimte gunt om mijn ambities waar te maken, ondanks dat deze soms aardig wat consequenties hebben voor ons gezinsleven. Je tomeloze enthousiasme over mijn ervaringen binnen de officiersopleiding heeft veel voor me betekend. Helemaal terecht dat je tijdens die weken

ook even gebruik hebt gemaakt van de kans om ongezien je jeugddroom te realiseren door een Mercedes bij ons op de oprit te parkeren. Ik ben je enorm dankbaar voor de liefde die je me geeft en het vertrouwen dat je in ons hebt. Samen blijven we verder bouwen we aan onze droom, vanaf nu is het weer jouw beurt om wat steentjes te mogen metselen!

Lieve *James*, zonder het te weten leverde jij ook al je bijdrage aan dit proefschrift: tijdens het zwangerschapsverlof in afwachting op jouw komst werden de laatste teksten geschreven. En dat is maar goed ook, want inmiddels ben jij volop in ons leven aanwezig en genieten we met volle teugen. Ook jij beschikt over een grenzeloos enthousiasme en dat werkt aanstekelijk, thuiskomen is iedere dag weer bijzonder.

De herinneringen voor later maken we nu; laten we genieten!

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CURRICULUM VITAE



Yvonne Roebroek werd geboren op 8 oktober 1989 in Heerlen en groeide op in het naburige Schimmert. In 2007 slaagde ze aan het Stella Maris College te Meerssen voor het VWO. Aansluitend startte zij met de opleiding geneeskunde aan de Universiteit van Maastricht waar zij in 2013 haar artsdiploma in ontvangst mocht nemen. Nadien startte zij haar chirurgische carrière als arts-niet-in-opleiding-tot-specialist (ANIOS) bij de afdelingen chirurgie van het Laurentius Ziekenhuis te Roermond en het Maastricht UMC+.

In de periode september 2014 t/m mei 2018 verrichtte ze het wetenschappelijk onderzoek dat aan de basis ligt van dit proefschrift onder supervisie van prof. dr. L.W.E. van Heurn en prof. dr. N.D. Bouvy bij de vakgroep algemene heelkunde van het Maastricht UMC+. In juni 2018 vervolgde ze haar klinische carrière als ANIOS in het Máxima Medisch Centrum te Veldhoven. Sinds juli 2019 is ze in opleiding tot chirurg in het Máxima Medisch Centrum en het Maastricht UMC+, welke ze verwacht af te ronden in juli 2026.

Gedurende haar opleiding koos ze voor de differentiatie traumachirurgie en volgde zij de Elementaire Militaire Opleiding aan de Nederlandse Defensie Academie te Breda. In december 2022 werd zij bevorderd tot majoor bij de landmacht. Na afronding van haar opleiding tot chirurg zal ze worden bevorderd tot kolonel en haar chirurgische carrière voortzetten als militair chirurg in dienst van Defensie bij het Maastricht UMC+.

Sinds haar coschap chirurgie in 2010 is zij samen met Tim Boymans met wie zij in 2017 trouwde. In oktober 2024 werden zij de gelukkige ouders van James.

LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
ACE	angiotensin-converting enzyme
AHI	apnea-hypopnea index
ALT	alanine transaminase
ANIOS	arts niet in opleiding tot specialist
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
BASIC-trial	'bariatric surgery in children'-trial
BDI	Beck Depression Inventory
BIC	Bayesian Information Criterion
BMI	body mass index
BS	bariatric surgery
CBT	cognitive behavioural therapy
CDC	Centers for Disease Control and Prevention
Ce	centile equivalent
chEDE-Q	Eating Disorders Examination Questionnaire for Children
CLI	combined lifestyle interventions
cLVH	concentric left ventricular hypertrophy
cLVR	concentric left ventricular remodeling
CPAP	continuous positive airway pressure
CRP	c-reactive protein
DBP	diastolic blood pressure
DOHS	Dutch Obesity Healthcare Standard
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data Safety Monitoring Board
DXA	dual energy X-ray absorptiometry
eLVH	eccentric left ventricular hypertrophy
EUPSA	European Paediatric Surgeons' Association
FFA	free fatty acids
GP	general practitioner
HA	huisarts
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HDL-c	high-density lipoprotein cholesterole
HOMA-IR	Homeostatic model assessment of insulin resistance
HRQOL	health related quality of life
IGF	insulin like growth factor
IGT	Iowa Gambling Task
IOTF	International Obesity Task Force
IVST	interventricular septal thickness

LAGB	laparoscopic adjustable gastric band
LDL-c	low-density lipoprotein cholesterole
LMS	lambda-mu-sigma
LRYGB	laparoscopic Roux-and-Y gastric bypass
LSG	laparoscopic sleeve gastrectomy
LVEDD	left ventricular end-diastolic dimension
LVESD	left ventricular end-systolic dimension
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
LVPWT	left ventricular end-diastolic posterior wall thickness
MAR	missing at random
MLI	multidisciplinary lifestyle interventions
NAFLD	nonalcoholic fatty liver disease
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PedsQL	Pediatric Quality of Life Inventory
PFS	Power of Food Scale
PS	Paediatric surgeon
PSG	polysomnography
RCT	randomized controlled trial
RWT	relative wall thickness
SBP	systolic blood pressure
SDS	standard deviation
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SPSS	Statistical Package for Social Sciences
sqrt	square-root
SST	Stop Signal Test
T2DM	type 2 diabetes mellitus
TBW	total body water
TC	total cholesterole
TFEQ	Three Factor Eating Questionnaire
TG	triglycerides
TWL	total weight loss
USA	United States of America
WHO	World Health Organization
WLT	Wanting and Liking Test
WOF	World Obesity Federation

