Novel insights in the clinical evaluation and management of childhood obesity

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Novel insights in the clinical evaluation and management of childhood obesity

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Abbreviations

4-C model	4-compartment model
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BCM	Body Composition Monitor
BMI	Body mass index
BIS	Bioimpedance spectroscopy
BRIEF	Behavior Rating Inventory of Executive Functioning
CI	Confidence Interval
DEBQ	Dutch Eating Behavior Questionnaire
DEXA	Dual Energy X-ray Absorptiometry
DP	Dot Probe task
ECS	Effortful Control Scale
ECW	Extracellular water
ELISA	Enzyme-Linked Immuno Sorbent Assay
FU	Follow-up
GLP-1	Glucagon-like peptide 1
GNG	Go/no-go task
HDL	High Density Lipoprotein
HOMA-IR	Homeostasis model assessment for insulin resistance
Hs-CRP	High-sensitive C-reactive protein
ICW	Intracellular water
IL	Interleukin
ISRCTN	International standard randomized controlled trial number
JPG	Jan Palfijn Hospital Gent
kDa	KiloDalton
LDL	Low Density Lipoprotein

MOT	Multidisciplinary obesity treatment
oAHI	Obstructive apnea-hypopnea index
OH	Overhydration
OSA	Obstructive sleep apnea
RCT	Randomized controlled trial
SC	Self-control
SD	Standard deviation
SDS	Standard deviation score
SPSS	Statistical Package for Social Sciences
T	Time-point
TBW	Total body water
TNF-α	Tumor necrosis factor alpha
UZA	Universitair Ziekenhuis Antwerpen/ Antwerp University Hospital
WHO	World Health Organization
ZPM	Zeepreventorium

Chapter 1: General introduction

Worldwide, the number of individuals affected by obesity is alarmingly high, with an obesity rate that has nearly tripled since 1975. In 2016, according to the World Health Organization (WHO) 1.9 billion adults were estimated to have excess body weight and 650 million of them obesity. Additionally, an increasing prevalence is registered within the pediatric age range. The percentage of children suffering from excess body weight quadrupled from 4% in 1975 to 18% in 2016. This corresponds to 340 million children suffering from excess body weight of which 124 million are diagnosed with obesity (1).

As obesity at any age is complicated by many comorbidities, the obesity pandemic forms a threat to public health from a medical, psychosocial and economic perspective (2). In the USA, the annual outpatient costs of childhood obesity are estimated to be more than 14 billion dollars (3). In Belgium excess body weight (across all ages) is estimated to account for 6-8% of the total health expenditure based on the numbers of the Organization of Economic Co-operation and Development (OECD) (2), which corresponds to an estimated annual expenditure of 3 billion euros (2).

Therefore, prevention at population level and an early treatment of affected individuals before complications arise are crucial steps needed to tackle the growing obesity burden.

Children with overweight have twice the risk of becoming adults with overweight. These odds are even higher for children with obesity and increase with age. This results in up to 90% of adolescents with obesity becoming adults with obesity (4). Therefore, treatment of obesity during childhood is of primordial importance to control the obesity pandemic and its consequences (5).

This chapter will serve as an introduction to childhood obesity as a medical condition, e.g. its diagnosis, prevalence, etiology and related comorbidities. Secondly, we will outline the current treatment recommendations and their long-term outcome, while indicating current knowledge gaps. Throughout this thesis, we acknowledge that obesity is a disease that can be diagnosed and aim to avoid any stigmatization of the affected individuals.

1.1 Childhood obesity

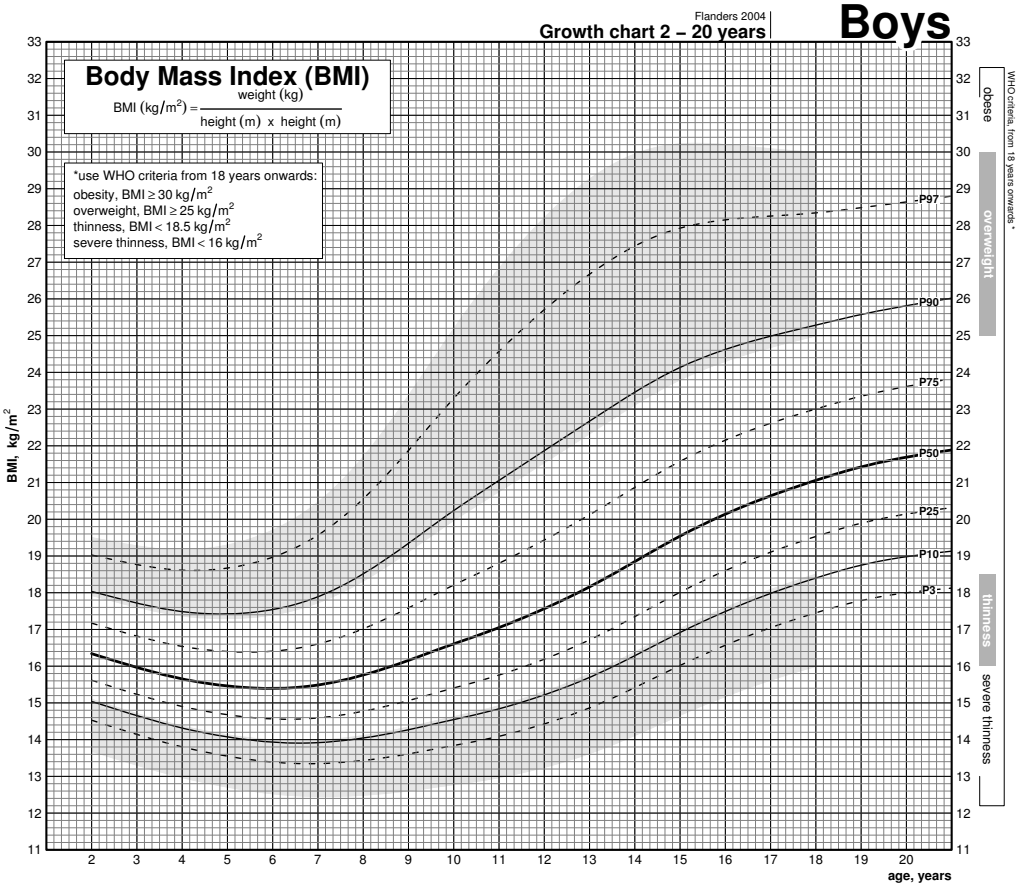
1.1.1 Definition

The definition of obesity in adults and children is based on the body mass index (BMI), which is calculated by dividing body weight expressed in kg by its squared height in meters (1).

In adults, overweight and obesity can be defined by means of a fixed cut-off: a BMI above 25.0 kg/m^2 is classified as overweight and a BMI above 30.0 kg/m^2 as obesity (6). These cut-offs have been linked to an increased risk in weight-related morbidity and all-cause mortality (7,8).

In children the cut-off for a normal BMI is highly dependent on age and gender, therefore the International Obesity Task Force (IOTF) proposed separate guidelines for the pediatric population. These are based on the centiles for age- and gender-specific BMI growth charts corresponding to the adult cut-off points of 25 and 30 kg/m^2(9).

The Flemish growth charts for boys and girls aged 2-20 years are depicted in **Figure 1.1** (10).


Flanders 2004
Growth chart 2 – 20 years
Boys
Body Mass Index (BMI)
BMI (kg/m²) = weight (kg) / height (m) x height (m)
*use WHO criteria from 18 years onwards:
obesity, BMI ≥ 30 kg/m²
overweight, BMI ≥ 25 kg/m²
thinness, BMI < 18.5 kg/m²
severe thinness, BMI < 16 kg/m²
BMI, kg/m²
age, years
P97
P90
P75
P50
P25
P10
P3
obese
overweight
thinness
severe thinness
WHO criteria, from 18 years onwards *

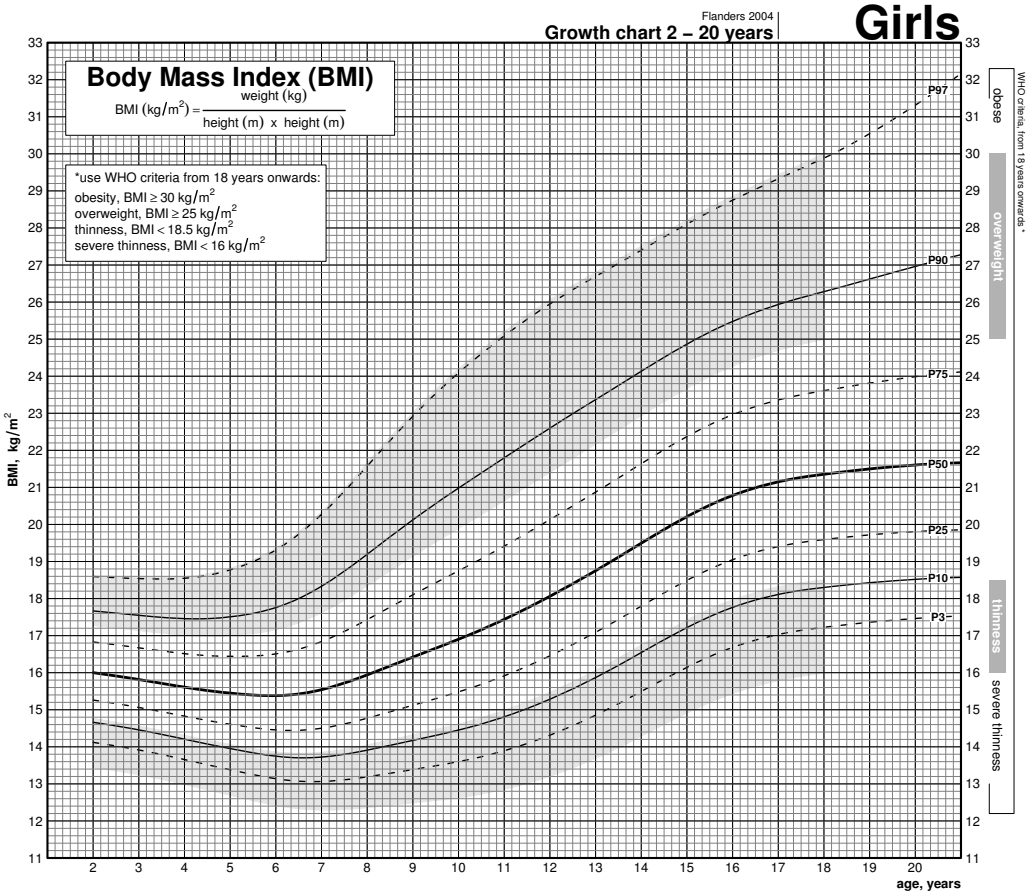


Figure 1.1: Flemish growth charts for BMI in boys (upper) and girls (lower). Adapted from http://www.vub.ac.be/groeicurven.

1.1.2 Prevalence

Worldwide, 124 million children and adolescents were affected by obesity and another 216 million by overweight in 2016. This is more than a 10-fold increase over the past 40 years (11).

In Belgium, 19% of the children aged 2-17 years were found overweight, of which 5.8% were diagnosed with obesity in 2018 (12). This percentage is not significantly different compared with a previous report, published in 2013 and confirms the international finding that the mean BMI in children and adolescents is stabilizing in developed Northwestern countries (11). Currently, the largest rise is seen in low- and middle income countries, especially in the urban regions (1). Although previously the prevalence of overweight and obesity in children in Belgium was increasing with age, a 2018 public health project indicated that the highest prevalence of overweight and obesity in Belgium is now found in children aged 2 to 4 years old (12).

1.1.3 Etiology

The rapid worldwide increase in obesity rates can be explained by a combination of excessive caloric intake combined with decreased caloric expenditure. Although heritable factors might explain 30-50% of the variation in adiposity (13), the intake of 'energy-dense' foods (e.g. sugar-sweetened beverages, fast-food and food with a high level of carbohydrates) combined with large portion sizes contributes to a rapid increase in the consumed calories resulting in an increased risk of obesity (14,15). Furthermore, children spend more time sitting in front of a screen (e.g. television, computer, mobile phone). This again increases the risk for developing obesity (16) due to a decrease in physical activity and its related energy-expenditure. Other factors contributing to the development of obesity include: perinatal factors (e.g. maternal weight status/weight gain and gestational diabetes, breastfeeding) (17), socioeconomic status (18), parent or family-related factors (e.g. uninvolved, indulgent or highly protective parenting styles (19), perceived stress (20), parents with psychological problems (21)) and sleep-related factors (22).

A secondary origin for obesity can be found in less than 1% of the cases (23). **Table 1.1** provides a short list of the possible secondary causes of pediatric obesity based on a 2017 review (24).

Table 1.1: Overview of secondary etiologies of obesity, including some examples for each etiologic category.

Endocrine pathology	Hypothyroidism, Cushing syndrome, growth hormone deficiency, pseudohypoparathyroidism…
Genetic syndromes	Prader-Willi, Bardet-Biedl, Beckwith-Wiedemann…
Drug-induced	Glucocorticoids, antipsychotics, tricyclic antidepressants…
Monogenic disorders	Leptin (receptor) deficiency, melanocortin 4 receptor mutation, proopiomelanocortin (POMC) deficiency…
Neurologic pathology	Brain tumor (and surgery- or radiation-related consequences), brain injury…

Content of table based on a review of Kumar *et al.* (24)

A thorough history and a physical examination is required to identify secondary origins of obesity, e.g. drug-related, endocrine diseases, psychological problems, and possible obesity-related complications (25). This can be further extended with laboratory screening tests or other investigations, e.g. polysomnography for detecting obstructive sleep apnea, if indicated. Identification of secondary causes is important as some of these causes require (urgent) treatment.

1.1.3.1 *Early adiposity rebound (EAR)*

In the normal growth of a child, a rapid BMI increase is observed from birth to one year, whereafter a downward evolution is reported until the age of 6 years, as seen on the growth charts in **Fig 1.1**. Thereafter, a second increase from the BMI low point is found, the adiposity rebound (26). An early adiposity rebound (EAR) refers to a premature increase in BMI occurring before 5.5 years (26). An EAR predicts future obesity (27) and is associated with cardiometabolic risk factors in adolescence, such as insulin resistance, HDL-cholesterol and systolic blood pressure (28). The prevalence of EAR in children varies largely between studies ranging from 27 up to 58% (29,30) and is fortunately much higher than the current prevalence of overweight and obesity, indicating that not every child with an EAR becomes overweight. So, a heterogeneity in this group of EAR children exists.

To better predict which children are at risk of developing obesity, recently the type A-EAR and type B-EAR were defined (31).Type A was defined as a pre-adiposity rebound BMI SDS ≥ 0 combined with an increase ≥ 0.5 BMI SDS on the last measurement or an initial BMI SDS < 0 combined with an increase ≥ 1.0 BMI SDS on the last visit. Type B was defined as an initial BMI SDS < 0 combined with an increase of 0.5-1.0 BMI SDS on the last collected data. Of the children in type A-EAR, 2/3 had excess body weight by age 6-8 years compared to only one in ten children in the type B-EAR group, confirming the importance of subdividing the EAR group and the importance of BMI trajectories already early in life.

1.2 Physical and psychological impact of childhood obesity

Obesity is a multisystem-disease, affecting almost every organ in the human body (24). Children with obesity are likely to become adults with obesity, and multiple origins of adult debilitating diseases can be found in childhood (32). For example, endothelial dysfunction is a precedent of adult cardiovascular morbidity and mortality. Besides the physical impact, the psychological consequences already influence the quality of life from childhood on (33).

Although obesity reflects a state of excess adipose tissue, the distribution can vary greatly between individuals and has an important contribution to a person's risk for developing obesity-related (medical) comorbidities. More specifically, abdominal obesity resulting from an increased amount of visceral adipose tissue poses the highest risk for adverse health consequences (34).

The medical adverse health consequences resulting from obesity can be divided in cardiovascular, metabolic and mechanical complications (35), as depicted in **Figure 1.2** and described in the next paragraphs.

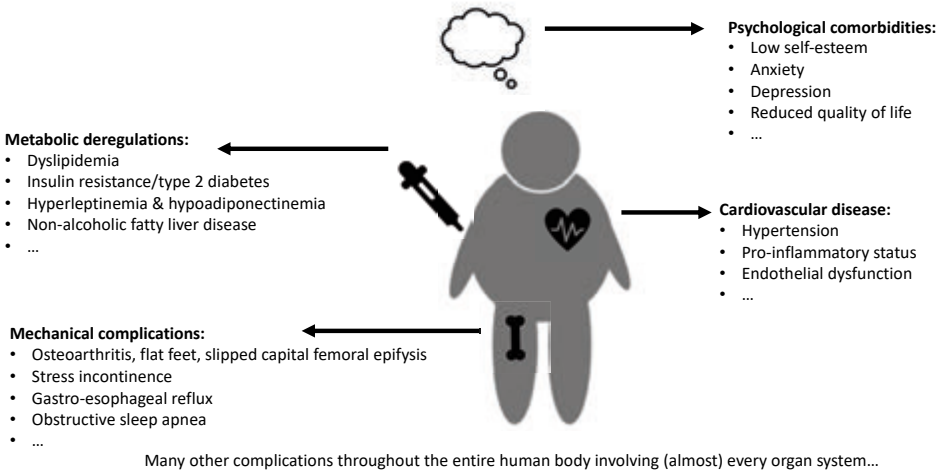


Figure 1.2: Visual overview of some common complications in children with obesity. The content in this figure is adapted from Daniel and co-workers (35). The visual presentation was created by the author of this thesis.

1.2.1 Metabolic deregulations

1.2.1.1 *The metabolic syndrome*

The metabolic derangements in obesity represent a commonly observed clustering of multiple cardiovascular risk factors sharing a common pathophysiologic origin in the insulin resistant state associated with obesity and have therefore previously been referred to as the metabolic syndrome (36). The following factors are included in the metabolic syndrome:

- central obesity (defined by the waist circumference)
- triglyceride elevations
- a lowered HDL-cholesterol
- arterial hypertension
- a disturbed glucose tolerance

Pathophysiology

Central obesity and the accompanying inflammation contribute to insulin resistance (37). When the storage capacity in the subcutaneous adipose tissue is exceeded (38), other ectopic storage sites will be used such as the visceral adipose tissue and insulin-responsive tissues such as the liver and the muscle, where peripheral insulin resistance is induced (39).

At the visceral adipose tissue, obesity leads to adipocyte hypertrophy and the release of more pro-inflammatory cytokines, leading to more insulin resistance locally and in other peripheral tissues (40). As insulin normally acts to suppress lipolysis by inhibiting hormone sensitive lipase, this results in breakdown of triglycerides to glycerol and free fatty acids. These free fatty acids are released in the circulation, resulting in different metabolic derangements (41) and further promoting insulin resistance, hereby creating a vicious cycle.

At the muscle, the increased free fatty acids impairs the insulin-mediated uptake of glucose, which can result in *hyperglycemia* (42). Furthermore, carbohydrates will be used for lipogenesis (rather than storing them for muscle glycogen). This leads to *hypertriglyceridemia* and *lowered HDL-cholesterol*, as well as more triglyceride synthesis at the liver (43).

At the liver, insulin limits hepatic glucose output by suppressing gluconeogenesis. As a consequence, resistance to these actions results in impaired glucose homeostasis and *hyperglycemia* (44). Secondly, insulin resistance and more free fatty acids lead to more hepatic de novo lipogenesis of triglycerides, which results in *hypertriglyceridemia*. Part of these newly produced triglycerides will be stored in the liver contributing to the development of non-alcoholic fatty liver disease which reinforces the hepatic insulin resistance, again a vicious cycle (45). The other part of newly formed triglycerides will be stored in very low density lipoprotein (VLDL) particles.

As insulin normally inhibits the secretion of VLDL in the circulation, the reduced activity leads to more triglyceride-rich VLDL in the circulation (45). Here, VLDL is modified to intermediate density lipoprotein (IDL) and subsequently to small dense atherogenic triglyceride-rich low density lipoprotein (LDL) particles (45). By the cholesterol esther transfer protein, the cholesterol from the circulating HDL particles is exchanged for the triglycerides of the VLDL and LDL particles, resulting in triglyceride-rich HDL particles. The triglyceride-enriched HDL particles are broken down by the hepatic lipase, resulting in the *lowered HDL* found in insulin resistant individuals (45).

Insulin also exerts actions on the intestine, so insulin resistance contributes to postprandial dyslipidemia, but little is known on these effects, so therefore this is not further discussed in this thesis (37).

Lastly, only the pathophysiology of *arterial hypertension* remains to be discussed. A recent study indicated that it is mainly the insulin resistance at the level of the adipose tissue that is responsible for hypertension, although the exact mechanisms are not yet clear (46). However, it is known that increased insulin can induce sympathetic nervous system activation leading to vasoconstriction and subsequent hypertension (47). Nevertheless, alterations in adipokines such as increased leptin (discussed below) can similarly induced sympathetic nervous system overactivation (48). Furthermore, hyperinsulinism can stimulate the kidney for increased sodium reabsorption (49). Obesity-related complications could also have a causal role. For example, obstructive sleep apnea (OSA) could also induce sympathetic activation and contribute to hypertension (50). Additionally, insulin normally promotes vasodilatation, but endothelial dysfunction might lead to an impair this aimed vasodilatation (51). These two comorbidities will be further discussed below in their respective sections. Many other explanations can link hypertension to obesity, but discussing all of these would go beyond the scope of this section (47).

Challenges in the definition

The last few decades multiple attempts to define the metabolic syndrome in pediatrics have been made (52–54).

Logically, one cannot simply apply the adult criteria on children, as blood pressure for example is influenced by age, gender and height (55). Furthermore, alterations in body size occur with growing and ageing. Therefore, features require age (and gender) corrected normative values. Additionally, during puberty all children develop a temporarily insulin resistant state (56) and insulin resistance is the main driver of the metabolic syndrome features indicating the complexity of the metabolic syndrome in children. The complexity of the pediatric metabolic syndrome is again illustrated by previous research reporting a large within-person variability of fulfilling the metabolic syndrome diagnosis on short- and long-term follow-up visits (57–59).

Although alterations throughout growth occur, many definitions of the metabolic syndrome were created (60). These definitions all rely on the same above-named key features, however the cut-offs of normality might vary strongly. As a person's ethnicity or racial background determines the vulnerability to develop certain cardiometabolic diseases (61), the developed definitions became population-specific with different threshold values being used for different ethnic groups. For example, the International Diabetes Federation (IDF) definition is applicable to European children older than 10 years (52), whereas the IDEFICS focused on European children 2-11 years old (62).

Current approach

Whereas the prevalence differs based on the definition used, over 90% of the children with obesity have at least one cardiovascular risk factor of which high triglycerides and low HDL-cholesterol are the most prevalent (53). Although the presence of the metabolic syndrome is unstable, the cardiometabolic comorbidities generally tend to cluster.

Therefore, it is currently advised to focus more on recognizing the clustering of risk factors, rather than determining the presence of the metabolic syndrome (63). Furthermore, the metabolic syndrome does not include every comorbidity that can result from insulin resistance. For example, non-alcoholic fatty liver disease and polycystic ovary syndrome are not mentioned. Therefore, a clinicians' evaluation should go beyond solely determining the presence of the metabolic syndrome in a child with obesity-related insulin resistance.

Treatment

Treatment options for the metabolic syndrome components are similar to those for childhood obesity in general, e.g. losing weight/lowering the fat percentage by increasing physical activity, decreasing caloric intake, which might be added by the use of medications targeted at specific comorbidities, for example anti-hypertensive drugs (64).

1.2.1.2 *Changes in adipocyte hormone production*

Where the adipose tissue was previously assumed to be just a storage site consisting of adipocytes and connective tissue, it is now considered an important production site of hormones. These hormones, named adipokines, are involved in many physiological processes throughout the human body, such as energy homeostasis and the immune system (65). By now, hundreds of protein hormones secreted by the adipose tissue have been identified of which Lehr and colleagues have provided an extensive list in the supplements of their review (66). Of all the adipokines, leptin and adiponectin have been studied the most. In the context of obesity, increased serum levels of leptin and reduced levels of adiponectin have been described (67). These 2 important adipokines are described in more detail underneath.

1.2.1.2.1 Hyperleptinemia

Leptin is a 16 kDa hormone primarily involved in regulating appetite and satiety and subsequently food intake, energy homeostasis and body fat regulation due to its central-acting properties on the hypothalamus (68). People with obesity are known to have higher circulating leptin levels (67,69). Although this might seem counterintuitive, these patients are hypothesized to be leptin resistant, resembling the more widely known concept of insulin resistance in individuals with obesity. Nevertheless the exact underlying mechanism responsible for this leptin resistance is not completely understood yet (70). Additionally, leptin possesses pro-inflammatory capacities and therefore might contribute to the low-grade inflammation present in subjects with obesity and subsequently contribute to the increased risk for adverse cardiometabolic health consequences associated with obesity (71).

1.2.1.2.2 Hypoadiponectinemia

Adiponectin generally exerts health-protective effects as it has antidiabetic, anti-inflammatory, anti-atherogenic, insulin-sensitizing and cardioprotective properties (72). Some evidence also indicates a role in regulating energy homeostasis, with adiponectin exerting both peripheral and central effects that increase energy consumption and counteract obesity development (72–74). Its levels are mostly reduced in individuals with obesity (75,76), thus also contributing to the pro-inflammatory state described below.

1.2.2 Cardiovascular disorders

Ischemic heart disease and strokes remain the two most prevalent causes of death worldwide (77). The precursors of advanced atherosclerosis can already appear in the first decade of life with the presence of fatty streaks (78). In short, these fatty streaks develop to become fibrous plaques. When these plaques become unstable and subsequently rupture, this might cause thrombosis of the involved vessel and clinically evident cardiovascular disease, for example acute myocardial infarction (79). The speed by which these lesions progress is subject to individual variability and depends on the amount of cardiovascular risk factors present (80).

1.2.2.1 *Pro-inflammatory status*

Besides the classic cardiovascular risk factors described in the metabolic syndrome above, the importance of non-classical risk factors such as low-grade inflammation is increasingly being recognized. One manifestation of this low-grade inflammation is an increase in high-sensitivity CRP (hs-CRP). Hs-CRP is produced by the liver under stimulation of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α. Hs-CRP has been found to be an individual predictor of cardiovascular morbidity and mortality (81). An elevation of hs-CRP has been described in both adults (82) and children (83,84) with obesity. Fortunately, the general treatment for children with obesity, namely making lifestyle changes aimed at losing weight, can significantly reduce these increased hs-CRP levels (85).

1.2.2.2 *Endothelial dysfunction*

A first step in the atherosclerotic process is called 'endothelial dysfunction'. These functional changes in the endothelium occur long before structural changes can be visualized. The primary function of endothelium is the regulation of the blood vessel diameter by controlling the vascular smooth muscle cells. Therefore the initial definition of endothelial dysfunction was an impaired vasodilatory response to specific stimuli. Later on, this definition was broadened to include the pro-inflammatory and prothrombotic status (86), as the healthy endothelium counteracts platelet aggregation, leukocyte infiltration and smooth muscle proliferation. Since the endothelium is the inner cell layer lining the blood vessel, it is in direct contact with the blood and directly exposed to multiple harmful cardiovascular risk factors (87). As a result, it integrates the influence of all these damaging and protective factors present in the circulating blood (88). Clinically, endothelial function can be assessed non-invasively by flow-mediated dilatation (FMD), which measures macrovascular endothelial function, and peripheral arterial tonometry (PAT) (89), which evaluates microvascular endothelial function. Since the first manifestations of endothelial function starts to develop in the first decade of life (90) with microvascular endothelial dysfunction preceding macrovascular dysfunction, PAT was chosen as a tool for the evaluation of endothelial function in this thesis.

Previous studies found that the micro- and macrovascular endothelial function in children with obesity was worse compared with children with a normal body weight (91–93). Additionally, different cardiovascular risk factors have already been proven to negatively affect endothelial function. Beyond the 'classic' risk factors (e.g. blood pressure, dyslipidemia, hyperglycemia), the pro-inflammatory cytokines, adipokines, sleep apnea, psychological distress… have been described to influence the endothelium (94,95).

Fortunately, literature proofs that the endothelial function in children with obesity can be improved by diet and exercise (96–98), pharmacological interventions (e.g. GLP-1 agonists and metformin) (99,100) and possibly by dietary supplementation with omega-3 fatty acids and vitamin C (101,102), but more research is needed to allow a definite conclusion.

1.2.3 Mechanical complications

Mechanical comorbidities arise due to the physical pressure of the excess adipose tissue on the body and the most prevalent mechanical complications include gastro-esophageal reflux, osteoarthritis, stress incontinence and obstructive sleep apnea (35).

1.2.3.1 *Obstructive sleep apnea (OSA)*

OSA results from repeated collapse of the upper airway during a patients' sleep, leading to intermittent hypoxia, arousals and sleep fragmentation. Clinically, patients can present with a wide spectrum of complaints such as excessive daytime sleepiness, snoring, morning headache, nocturia and neurocognitive complaints (103). The golden standard to diagnose OSA is an in-hospital polysomnography, but home-sleep devices are increasingly employed with a reported sensitivity of 80% to diagnose OSA in adults (104).

OSA in children can be diagnosed based on the obstructive apnea-hypopnea index (oAHI). An apnea is defined as the interruption of airflow during at least two respiratory cycles. An apnea is classified as obstructive when a respiratory effort is present without the respiratory airflow. A hypopnea is defined as a 30% decrease in the airflow during at least two respiratory cycles accompanied by a 3% decrease in saturation and/or an arousal.

The oAHI is then calculated as the average obstructive apneas and hypopneas per hour of sleep. In children, an oAHI between 2 and 5 is considered as mild OSA and a oAHI above 5 as moderate-to-severe OSA (105). OSA is present in up to 60% of the children with obesity (106). Previous research of our own group indicated that OSA is an independent risk factor for metabolic deregulations, such as endothelial dysfunction, in children with obesity (107).

The primary treatment for mild OSA in children with obesity is weight loss, because this is more effective than adenotonsillectomy in this population (108) with a treatment success rate of 71%, as documented by our research group (109). For more severe OSA in these children, besides weight loss, a multidisciplinary evaluation and additional therapies, such as continuous positive airway pressure (CPAP), might be required.

1.2.4 Psychological comorbidities

The motivations of youngsters with obesity to seek treatment are often related to psychological comorbidities. Frequently mentioned motivations to lose weight are an improvement of self-esteem and an avoidance of bullying, accompanied by the desire for peer acceptance (110). The impact of the psychological comorbidities related to obesity should not be underestimated. One study even reported that the quality of life of a child with obesity is comparable to that of a child with cancer (111). This might be due to obesity itself as well as to the obesity-associated comorbidities. Other frequently reported but often underestimated psychological problems are depression and anxiety (112,113). As these psychological difficulties are related to the severity of obesity and might complicate treatment results, these problems - when detected - need to be addressed in the management of a child with obesity (114).

1.3 Treatment of childhood obesity

1.3.1 Current treatment recommendations for obesity in children

The cornerstone of treating a child with obesity remains weight loss by a lifestyle intervention aimed at increasing physical activity and decreasing caloric intake (115).

Multiple effective in- and outpatient pediatric obesity treatment programs are available, but clear indications on which patient to refer to which treatment setting are missing. Outpatient treatment can achieve a modest, but significant weight reduction of 1-3 kg/m^2 (24). Inpatient obesity treatment programs have reported higher success rates, with an average BMI decrease of 4.5 kg/m^2 (range -1.4 to -11.8 kg/m^2). Nevertheless drop-out and weight regain are commonly faced challenges in both treatment settings (116,117).

Additional pharmacologic treatment is not routinely recommended. Only in addition to a lifestyle intervention if treatment is unsuccessful or with worsening of comorbidities, this option can be considered (115). In Belgium, metformin and orlistat are available, but off-label. Recently, several glucagon like peptide-1 (GLP-1) receptor agonists were approved by the European Medicines Agency for use in adolescents with obesity.

The biguanide metformin is used for lowering blood glucose level in patients with diabetes mellitus type 2 by increasing insulin sensitivity and decreasing endogenous glucose production by the liver. It is used in children with obesity and insulin resistance, where it has been shown to reduce BMI significantly by on average 1.1 kg/m^2 (95% CI 0.7 – 1.4 kg/m^2) (118). Orlistat, a gastro-intestinal lipase inhibitor, was previously found to reduce BMI by 0.5 kg/m^2 in adolescents with obesity, however the common gastro-intestinal side effects in up to 50% of the users results in high discontinuation rates (119).

Last years, the GLP-1 analogues (e.g. liraglutide, semaglutide…) are studied in pediatric cohorts (120–122). These drugs were formerly used for treating diabetes mellitus type 2 as they lower the blood glucose level by regulating glucagon and insulin secretion.

GLP-1 analogues mainly act on the body weight by promoting satiety which leads to a reduced energy intake and facilitates weight loss (120). The first studies are promising regarding safety, tolerability and BMI reduction (e.g. an average BMI SDS change of -0.22 SDS after 52 weeks liraglutide and -1.1 SDS after 68 weeks semaglutide), although data on long-term effectiveness after treatment discontinuation are still missing (121,122). These findings unfortunately also point to at least a partial regain of lost body weight after treatment cessation.

If all other options fail, bariatric surgery remains as the last treatment option. Only post-pubertal (Tanner stage 4 or 5) adolescents, with a BMI $\geq$ 40 kg/m^2 or $\geq$ 35 kg/m^2 with minimal two comorbidities in the absence of underlying psychological comorbidities and with adherence to a healthy diet and sufficient activity are eligible (115). Although recent evidence indicates bariatric surgery is promising (123,124), in many European centers it does not belong to the standard of care for adolescents with obesity due to the lack of reimbursement and doubts concerning safety and long-term efficacy (125).

1.3.2 Long-term outcome of current treatment

Generally, 80% of children with obesity will eventually have obesity in adult life (126). One part of this issue is that parents often incorrectly recognize the weight status of their child (127). Although nowadays in certain countries, doctors that regularly visit schools help in screening children for the development of excess body weight and create awareness for the weight problem among their parents. Secondly, the long-term outcome of the currently available treatment programs is modest. A first contributor to these suboptimal long-term results are the high drop-out rates ranging from 27 up to 73% in previous research (128,129), indicating current treatment is unfeasible for many children with obesity. This is problematic as discontinuing a weight loss program is negatively affects the body weight (116). For those who complete an in- or outpatient weight loss program, long-term outcomes are highly variable, but weight regain is often the reality (130–135). In literature, these repeated episodes of weight loss followed by weight regain are referred to as ‘weight cycling’ or ‘yoyo-dieting’ (136).

1.3.3 Self-control as a potential treatment target in children with obesity

One contributor to the rather modest long-term outcomes of the currently available treatment programs is the previous documented lower self-control in children with obesity, leading to decreased behavioral control (137,138). As stated in the Dual Pathway model and depicted in **Figure 1.3**, self-control is considered the results of bottom-up reactivity being regulated by top-down executive functioning (139). Bottom-up reactivity comprises the automatic, habit-driven responses towards stimuli in the direct environment (140). One such bottom-up process is attention, and "attention bias" refers to how salient stimuli with a high motivational or affective value quickly grasp attention (141). Top-down executive functions are neuropsychological control processes involved in initiating goal-directed behavior and overcoming the automatic reaction to external environmental stimuli (142,143). Executive functioning encompasses different cognitive control tasks, such as inhibition, cognitive flexibility and working memory (144), which are all involved in successful self-control (142,145).

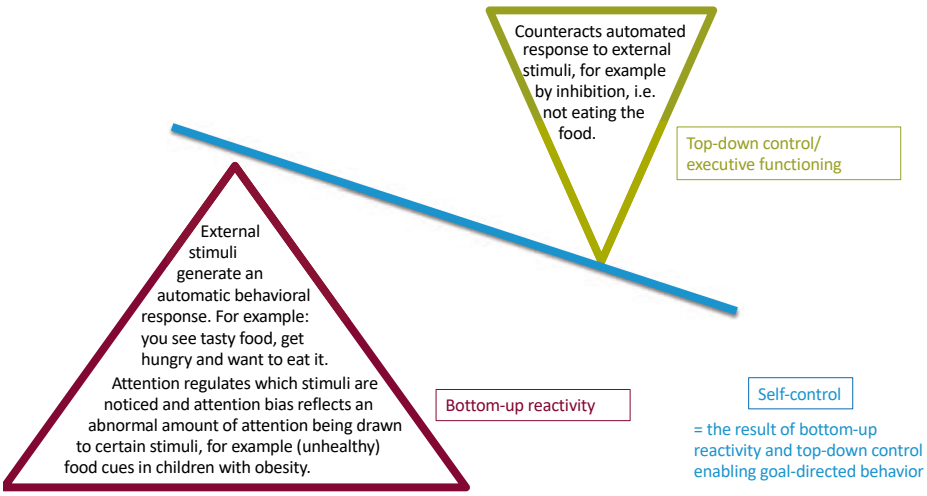


Figure 1.3: Visual overview of the main principles in the Dual Pathway model, including an example.

In subjects with excess body weight, a general imbalance exists between an observed increased bottom-up reactivity, which is reflected in an attentional bias towards (unhealthy) foods (146,147), and a lowered top-down inhibitory control to counteract the automatic reaction on environmental stimuli, which is reflected in being unable to resist palatable food even in the absence of hunger (148,149). Previous research in children and adolescents with obesity has found an association between lower self-control and less weight loss during treatment (77,150–154). Poor self-control also results in more difficulties in maintaining weight loss after treatment cessation (155). Therefore, enhancing the self-control in children with obesity seems highly indicated.

Fortunately, experimental lab studies show the potential of self-control training by tempering attention bias (141) or increasing inhibition (156) in adults with obesity. Some studies also show the potential of self-control training in children (157–159). Therefore, strengthening the self-control of children engaging in weight loss interventions might improve the outcome during treatment and promote long term weight maintenance.

1.3.4 BMI fluctuations and cardiometabolic health

As illustrated in **section 1.1.3.1**, BMI trajectories might be of equal or even more importance in affecting later cardiometabolic health(30). Previous research in adults linked weight fluctuations to an increased risk for cardiovascular morbidity and mortality. In the Framingham population, an association was found between the variation of body weight around the mean and cardiovascular morbidity and mortality (160). Another study reported similar results in middle-aged men: the group reporting that large weight gains and large weight losses had a doubled relative risk of coronary heart disease related death compared with a weight stable group (161).

To explain these increases in cardiovascular risk, the repeated overshoot theory was developed, stating that at the moment of weight regain multiple cardiovascular risk factors (temporarily) transcend their baseline values and hereby negatively affect cardiovascular health (162).

A second plausible hypothesis for this increased cardiovascular risk has been found in the repartitioning of the fat- and lean mass after weight regain (163), favoring the development of (abdominal) obesity (164).

However, subjects with obesity seem to be less vulnerable to the detrimental effects of weight cycling compared to subjects without excess body weight (164,165). Rzehak *et al.* reported an association between all-cause mortality and weight fluctuations in 55-74 year old men, which was not present for weight-stable patients with or without obesity (166).

Recent publications show that yo-yo dieting increasingly occurs within the pediatric age range (165). In children however, only very limited research has been performed on weight regain after weight loss and the concurrent alterations in their cardiometabolic risk. Until now, only one recent study addressed this question in a cohort consisting of 1718 children that were prospectively followed up for 20 years (167). Du *et al.* reported an increased risk for the development of type 2 diabetes related to BMI and cardiovascular risk factor variability (167). Interestingly, adult studies have taught us that obesity can influence the association between weight cycling and cardiometabolic risk.

Therefore, the previous results from children without obesity cannot be simply transferred to a cohort of children with obesity. Therefore, we think that it is of major importance to study the children with obesity as a separate group. As obesity in children is continuously increasing and the current treatment has only limited long-term results, the question of how the BMI trajectory, and more specifically the BMI variability, can influence the cardiometabolic health of these children should urgently be answered.

Chapter 2: Objectives and outline of the thesis

Obesity has become one of the most prevalent chronic diseases in childhood. Currently, treatment consists of reducing weight by adapting caloric intake and energy expenditure. However, the question 'How should the treatment effect be evaluated?' is unanswered because BMI SDS suffers limitations, but a reliable and feasible device to measure body composition is yet to be found. As simple as treating pediatric obesity sounds, it is still difficult to obtain firm long-term results. Despite children frequently re-increase in BMI, little is known on how this impacts a child's health. Further knowledge on this could help us answer the question 'Should we change our point of view on a patient's BMI trajectory?'. Lastly, self-control predicts treatment outcome, so training self-control could improve treatment outcome. In addition, digital innovations are increasingly being employed in medicine, so it is pivotal to answer the question: 'Is there a role for e-health (interventions) in pediatric obesity treatment?'.

As the number of children with obesity is ever-increasing, the challenges faced with the current evaluation and treatment need to be addressed and new innovations with potential to improve clinical evaluation and long-term outcome evaluated. Therefore, the current thesis has prospectively followed a large cohort of Belgian children with obesity participating in pre-existing treatment programs. We aim to answer these pending questions related to the clinical evaluation, management and treatment outcome of these children with obesity.

In **chapter 1** a general introduction on childhood obesity was provided including the currently unanswered questions. In this **chapter 2**, we have listed the research questions and outline of this thesis, followed by **chapter 3** that describes the methodology.

Currently, reliable and clinical feasible techniques allowing a rapid bedside evaluation of body composition are needed. Bioimpedance devices are promising as they are inexpensive and portable devices with a short measurement time of only a few seconds. Unfortunately, previous research indicated clinical relevant biases in their body composition measurements compared with conventional methods. These biases increased in line with the amount of excess body weight. Interestingly, the Body Composition Monitor (BCM®, Fresenius Medical Care, St. Wendel, Germany) is based on bioimpedance spectroscopy integrating a volume with a body composition model and it has been proven valid over a wide range of body compositions. Hypothesizing the BCM might be a reliable tool to measure body composition in children with obesity, we have evaluated the comparability of its measurements with the measurements of a Dual Energy X-ray Absorptiometry (DEXA) scan in **chapter 4**. The research question was: "Are the body composition measurements of a DEXA scan and the BCM comparable in children with obesity?" Both methods were compared in children before and after inpatient obesity treatment and for determining longitudinal changes.

As mentioned above self-control as a treatment target for obesity could have potential. Therefore, the WELCOME trial was developed, which stands for 'Improving **WE**ight contro**L** and **CO**-**M**orbidities in children with obesity via **E**xecutive function training', FWO-TBM project number 150179**. Chapter 5** presents the results of this randomized controlled trial where we hypothesized that a group provided with an online self-control training (compared to an online sham training) added to their pediatric obesity treatment would have superior results regarding BMI loss and maintenance. The research question was: "Can an online self-control training added to the existing obesity treatment programs improve treatment outcome in children with obesity?" This study aimed to translate the current in-lab evidence to clinical application in a large cohort of treatment-seeking children with obesity from in- and outpatient care.

As already known, the treatment response in children with obesity is highly heterogenic, even within the same treatment program. Psychosocial factors are known contributors to these observed differences and we hypothesized that pretreatment metabolic comorbidities and adipokines have a role in predicting treatment outcome. Therefore, in **chapter 6,** the research question was: "Can pretreatment patient characteristics, metabolic comorbidities and adipokines predict treatment drop-out and response in children with obesity?". This question was studied for children treated in in- and outpatient care.

Lastly, we focused on the association of weight regain or weight fluctuations and the cardiometabolic risk factors in this population consisting of children with excess body weight. To start, we have reviewed the current knowledge on weight regain after weight loss in children with obesity in **chapter 7.** We hypothesized that certain benefits persist for an amount of time despite weight regain. Subsequently, following the same hypothesis, the question on how the BMI trajectory alters the cardiometabolic risk factors was assessed in our own cohort. These results are reported in **chapter 8**. The research question was: "Do BMI fluctuations have detrimental consequences on the cardiometabolic health in children with obesity?"

The results of this thesis are further discussed in **chapter 9** and the summaries in English and Dutch are provided in **chapter 10 and 11** respectively.

Chapter 3: Methodology

This chapter provides a general overview of the methods used in this dissertation. However, depending on the study there might be differences in the length of follow-up, the outcome measures or added interventions. Study-specific deviations to the general protocol will therefore be discussed separately in the corresponding chapters.

3.1 Study design

A prospective study was set up, including a cohort of children with obesity participating in an inpatient pediatric obesity treatment program and a cohort participating in an outpatient pediatric obesity treatment program. The content of the treatment programs is described below in more detail (**see 3.3**). **Figure 3.1** visually represents the study protocol.

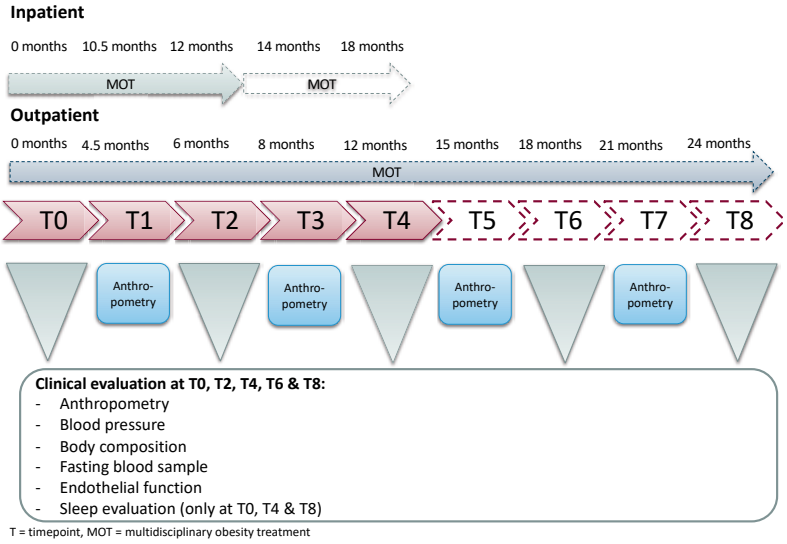


Figure 3.1: Visual representation of the study protocol. Visits T0 to T4 were part of the WELCOME trial (FWO-TBM project n° 150179) and visits T5-T8 were added afterwards solely for the study participants in the Antwerp University Hospital. The MOT (= multidisciplinary obesity treatment) bar after inpatient treatment is not colored since patients are referred to outpatient care, but compliance with outpatient visits was not determined in our study.

A thorough clinical evaluation, including measurements of body composition, determinations of the metabolic profile in the blood and endothelial function was conducted every 6 months in the outpatient cohort over a period of 12 months and later extended to 24 months (if a new informed consent was signed). For the inpatient cohort, this evaluation occurred at the start and at the end of inpatient treatment and 6 months after discharge over a period of 18 months. In the visits between those moments, solely anthropometric data (height, weight and BMI) were collected.

The first part of the study was 'the WELCOME trial', an FWO-TBM project (number 150179) to study the effect of an online self-control training added to previously existing pediatric obesity treatment programs (T0 – T4) (168). The content of the self-control training and how it is implemented is described in more detail in **chapter 5**. Afterwards, the follow-up of the cohort treated in the Antwerp University Hospital was extended to two years upon signing a new informed consent (T4 – T8).

The study was approved by the Ethics Committees of the University Hospital of Antwerp and Ghent (EC n°B670201731779) and was performed according to the principles of the declaration of Helsinki (169).

3.2 Participants

Children aged 8 – 18 years old with obesity were recruited between July 2017 and January 2020 upon admission to an in- or outpatient multidisciplinary obesity treatment (MOT). The presence of obesity was defined by the criteria of the International Obesity Task Force based on the Flemish growth charts (9,10). Patients were not eligible for inclusion in case of a genetic or endogenous origin of their obesity, the intake of weight-loss antagonizing medications, the presence of a mental or physical condition complicating optimal treatment participation (mental retardation, cardiac disease, active malignant hematological disease…) or simultaneous participation in another interventional trial.

Written informed assent/consent was obtained from the patient and their caregiver before the start of the study. For the participants treated in the Antwerp University Hospital, a second informed consent was signed after 12 months to participate in the extension study.

3.3 Multidisciplinary obesity treatment (MOT)

All participants engaged in a standard MOT aimed at reducing BMI by altering dietary patterns and increasing physical activity. This was combined with (cognitive) behavioral change techniques and parents were always involved.

3.3.1 Inpatient treatment

In the inpatient setting, participants with severe obesity and comorbidities entered a 12-month MOT at a pediatric rehabilitation center 'Het Zeepreventorium' (ZPM) (De Haan, Belgium). This program has been elaborately discussed previously (170). Briefly summarized, the multidisciplinary program is targeted at reducing BMI by increasing physical activity up to a minimum 10 hours a week and decreasing caloric intake by implementing a healthy diet according to caloric needs based on sex and age in a highly structured environment. Additionally, psychological and contextual support is offered individually and in groups. The caregivers are invited for sessions where parenting styles are discussed and education on a healthy lifestyle is offered simultaneously. After treatment, follow-up sessions are offered as well and are provided up to a maximum of 3 years after discharge. If the need for referral to outpatient treatment is detected during the aftercare sessions, this outpatient follow-up was planned.

3.3.2 Outpatient treatment

Two outpatient programs were included: one at Antwerp University Hospital (UZA) and one at Jan Palfijn Hospital (JPG) in Gent. Participants were included upon the start of the MOT, where (similar to inpatient treatment) a dietician and pediatrician (and if required a psychologist) are involved in the guidance. The dietician works on a step-by-step approach to establish a sustainable healthy lifestyle, whereas the pediatrician monitors the evolution of the obesity severity and its related comorbidities if present. Psychological support can be provided on a patients' or physicians' request. Throughout the sessions, physical activity with a minimum of one hour a day is highly encouraged. Patients are followed clinically as long as required based on their BMI and obesity-related comorbidities.

3.4 Clinical evaluation

3.4.1 Anthropometry

At every time point, patients' height and weight were measured up to the nearest 0.1 cm and 0.05 kg. The BMI was calculated as weight (in kg) over squared height (m^2) and further analyzed as the corresponding SDS, adjusted for age and gender based on previously published Flemish growth curves (10). Additionally, waist circumference was measured with a non-retractable tape at the midpoint between the lowest rib and the iliac crest and hip circumference was measured at the maximal circumference around the buttocks and the corresponding waist-to-hip ratio was calculated.

3.4.2 Blood pressure

Blood pressure was measured three times by an automated oscillometric device with the patient in supine position. The average for the systolic and diastolic blood pressure was determined and further analyzed as the corresponding percentile adjusted for age, sex and height (171).

3.4.3 Body composition

Body composition was evaluated by the Body Composition Monitor® (BCM) (Fresenius Medical Care, St. Wendel, Germany), a device based on the principles of bioimpedance spectroscopy. The patient was measured the morning after an overnight fast lying in supine position with arms and legs spread. Electrodes were attached following the wrist-ankle approach in a tetrapolar arrangement with two electrodes placed on the hands and two on the feet (172), as seen in **Figure 3.2.** Age, sex, height, weight and blood pressure were registered by the device before starting the measurement. The measurement quality calculated by the BCM was above 80% for all measurements. Data on fat mass, fat percentage, fat-free mass and fat-free percentage were collected.

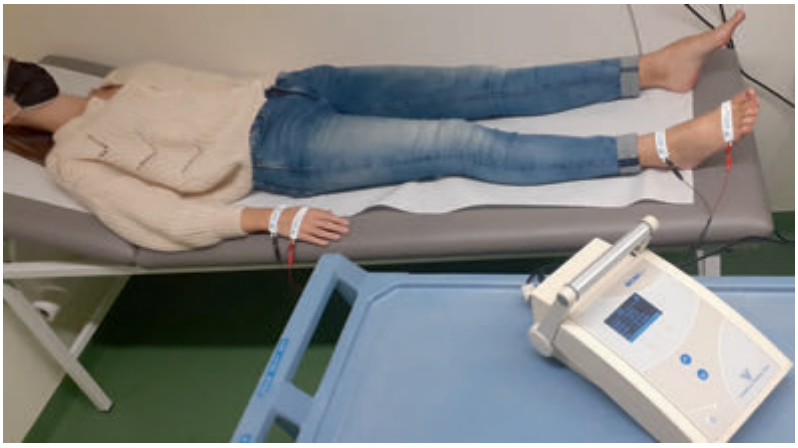


Figure 3.2: Set-up of a measurement with the Body Composition Monitor® on a volunteer.

Reference values for children and adolescents aged 3 – 18.5 years based on age and gender have recently been published (173), however this device was not yet validated for the use in children and adolescents with obesity. Therefore, we compared the BCM to the dual-energy X-ray absorptiometry (DEXA) scan in **chapter 4**.

3.4.4 Fasting blood sample

3.4.4.1 Metabolic profile

A fasting venous blood sample was drawn to determine:

- the lipid profile: triglycerides, HDL, non-HDL and total cholesterol and the LDL-cholesterol calculated by Friedewalds' formula (e.g. total cholesterol – HDL-cholesterol – (triglycerides/5)) (174)
- the pro-inflammatory status: hs-CRP, leukocytes
- the glucose metabolism: fasting glucose, fasting insulin, HOMA-IR (calculated as glucose (in mg/dl) x insulin (in µU/mL) / 405)(175)
- the liver transaminases: AST, ALT, AST/ALT ratio

All analyses were performed in the central laboratory of each participating center utilizing standardized techniques.

3.4.5 Endothelial function

Endothelial function was assessed at the microvascular level by the Endo-PAT 2000®(Endo-PAT, Itamar Medical, Caesarea, Israel). Measurements were performed after an overnight fast and in a temperature controlled room (21-24°C) following recommendations in children as described by Bruyndonckx *et al.* (176). The set-up is depicted in **Figure 3.3**. The patients were placed in supine position with pneumatic finger probes at both index fingers measuring the pulsatile pressure changes in the small arteries. A blood pressure cuff was placed at the non-dominant arm of the patient with the other arm serving as control. After a 5-minute baseline assessment, an occlusion period followed where the blood pressure cuff was inflated to 60 mm Hg suprasystolic pressure for 5 minutes. Afterwards, the cuff was deflated and a period of reactive hyperemia occurred which was recorded for another 5 minutes. The output of an EndoPAT measurement is shown in **Figure 3.4**.

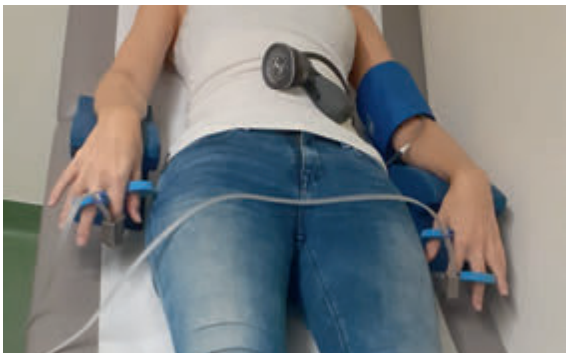


Figure 3.3: Set-up of an EndoPAT measurement on a volunteer.

Parameters of interest were:

- the maximal dilatation during the period of reactive hyperemia

- the time to maximal dilatation

- the reactive hyperemia index (RHI), of which the calculation is depicted in **Figure 3.4**.

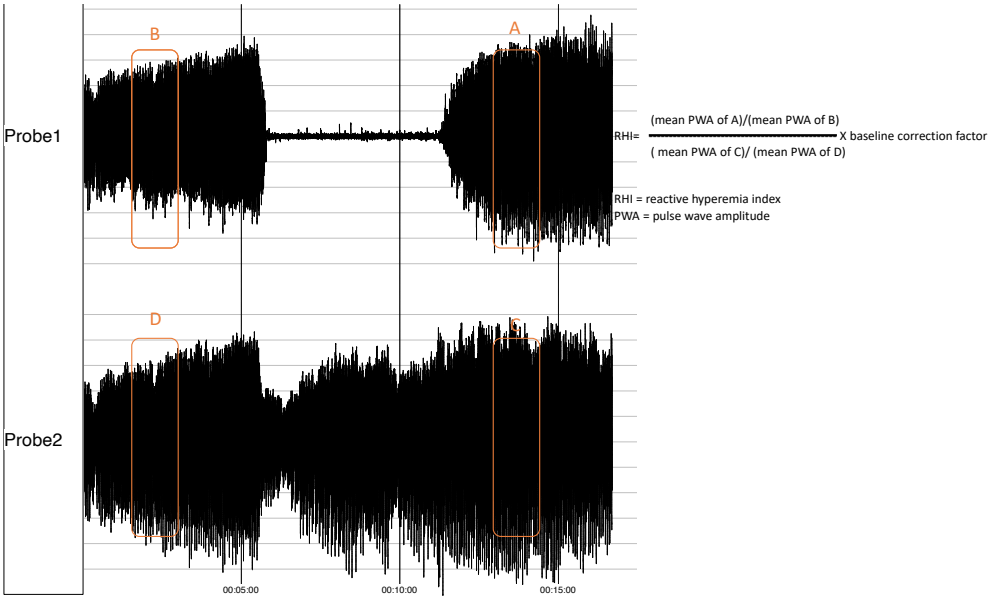


Figure 3.4: Output of an EndoPAT® measurement.

3.4.6 Sleep evaluation

Patients underwent a sleep polygraphy by a portable screening device, the Apnealink Air® (Apnealink, Resmed, Basel, Switzerland) to screen for the presence of sleep apnea (177). The respiratory airflow is measured by a nasal pressure cannula (detecting -10 hPa to +10hPa), the saturation is measured by a pulse oximeter and the respiratory effort by a pressure sensor attached around the thorax (sampling rate of 10 Hz, detecting -6 hPa to +6 hPa). A minimum of 4 hours of good quality signal was required.

The recordings were manually scored for the presence of:

- Apneas: an interruption of airflow during at least two respiratory cycles. These were scored as obstructive when respiratory effort was present without airflow. An example of an obstructive apnea is shown in **Figure 3.5A**.
- Desaturations: a stepwise decrease in the oxygen saturation $\geq$ 3%. An example of a desaturation is shown in Figure **3.5B** (dark blue color).
- Hypopneas: a 30% decrease in respiratory airflow during at least two respiratory cycles accompanied by a 3% decrease in saturation, as shown in **Figure 3.5B**.

The parameters of interest were:

- The obstructive apnea-hypopnea index (oAHI) = the average an average obstructive apneas and hypopneas per hour of sleep.
- The oxygen desaturation index (ODI) = the average number of desaturations per hour of sleep.

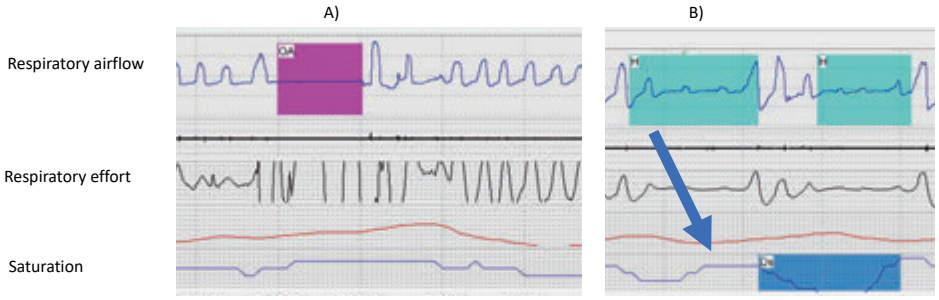


Figure 3.5: Overview of respiratory events measured by the ApneaLink device. Panel A presents an obstructive apnea. Panel B presents a hypopnea.

In the outpatient cohort of the Antwerp University Hospital, at baseline additionally a one-night in-hospital sleep polysomnography was performed. During one night a patient is continuously monitored by a computerized polysomnography (Brain RT; OSG, Rumst Belgium) for a minimal period of 6 hours, including evaluation by an electroencephalography, electrooculography, electromyography of the anterior tibialis and chin muscles and electrocardiography. The breathing movements, reflecting the respiratory effort, are measured by a respiratory inductance plethysmography. The patients' saturation is registered by a pulse oximeter placed on the patients' fingertip and respiratory flow is detected through a nasal pressure cannula and thermistor. These measurements are supplemented by audio (for snoring detection) and visual monitoring by a microphone at the suprasternal notch and an infrared camera. The parameters of interest were the same as for the ApneaLink® registration.

3.5 Statistical analysis

Most statistical analyses were performed with Statistical Package for Social Sciences version 26, 27 and 28 (SPSS, NY, USA).

Normality was assessed by a Kolmogorov-Smirnov test combined with the visual representation in a histogram and based on the sample size. Normally distributed data were presented by the mean $\pm$ standard deviation and skewed data as median (minimum – maximum).

Independent groups were compared using an independent-samples t-test (2 groups, normal distribution, equal variance), an ANOVA (2 or more groups, normal distribution, equal variances), a Welch's t-test (2 or more groups, normal distribution, no assumption on variance), Mann-Whitney U test (2 groups, skewed data) or Kruskal-Wallis test (2 or more groups, skewed data), as appropriate. For categorical data, a chi-square test was used.

Pairwise comparisons were performed by a paired samples t-test, a repeated measures ANOVA or a linear mixed model, depending on the number of visits and the amount of missing data.

Pearson or Spearman correlations were used to analyze associations between two continuous variables, as appropriate based on the distribution of the data. The association between multiple independent variables and one dependent variable was assessed by fitting a linear or logistic regression model based on the dependent variable being continuous or categorical. For every regression, the partial correlation coefficients (r), significance of each parameter and the adjusted R square (in case of linear regression) or Nagelkerke R square (in case of a logistic regression) were reported.

For all analyses, statistical significance was set at $p<0.05$. More specific statistical approaches will be described in each chapter separately.

Chapter 4: Comparing bioimpedance spectroscopy with dual energy X-ray absorptiometry

This chapter is adapted from:

Comparison of bioimpedance spectroscopy and dual energy X-ray absorptiometry for assessing body composition changes in obese children during weight loss.

Vermeiren E, Ysebaert M, Van Hoorenbeeck K, Bruyndonckx L, Van Dessel K, Van Helvoirt M, De Guchtenaere A, De Winter B, Verhulst S, Van Eyck A.

Eur J Clin Nutr. 2021 Jan;75(1):73-84.

4.1 Abstract

Background: Obesity and age influence the reliability of dual energy X-ray absorptiometry scanning (DEXA) and bioimpedance spectroscopy (BIS). Both are used in clinical settings, but have not been compared for measurements in children with obesity. We compared DEXA and BIS for evaluating body composition and inherent changes in children with obesity before and after a 10-month weight loss program.

Methods: DEXA and BIS were used to evaluate 130 patients at baseline and 75 at follow-up. We tested agreement between the two techniques using Bland-Altman plots and proportional bias using Passing-Bablok regressions.

Results: The Bland-Altman plots showed wide agreement limits before and after weight loss when monitoring longitudinal changes. At baseline, the Passing-Bablok regressions revealed a proportional bias for all body compartments. After significant weight loss no proportional bias was found for fat mass and percentage, although BIS systematically underestimated fat mass by 2.9 kg. Longitudinally, no proportional bias was found in the measured changes of absolute fat, fat-free mass and fat-free percentage between both methods, although BIS systematically underestimated fat and fat-free mass by 2.6 kg and 0.7 kg, respectively.

Conclusion: While BIS and DEXA are not interchangeable at baseline, the agreement between the two improved after significant weight loss. Proportional changes in fat mass, fat-free mass and fat-free percentage were similar for both techniques. BIS is a viable alternative to DEXA for future pediatric obesity studies measuring treatment effect at group levels, but is not superior to DEXA and cannot be used for monitoring individual changes due to wide limits of agreement.

4.2 Introduction

The obesity pandemic is growing and has become a serious public health challenge (178). Body Mass Index (BMI), although widely used, misses the obesity diagnosis in 25% of children. Therefore, the interest in body composition is increasing (179,180).

The dual energy X-ray absorptiometry (DEXA) scan is a regularly used method to assess body composition (179), but it is expensive, requires the patient to lie still for 20 min, is not portable and exposes the patient to a low dose of radiation. In patients with obesity, the body surface of the patient can exceed the scanning area (181,182). DEXA is known to overestimate adiposity in children with obesity as compared to a 4-compartment model (183). The 4-C model is considered the gold standard, but is expensive, time-consuming and therefore unfeasible in clinical practice (184). This establishes a need for accurate and reliable techniques to measure body composition that are inexpensive and suitable for bedside evaluation. The Body Composition Monitor® (BCM, Fresenius Medical Care, Germany) that uses bioimpedance spectroscopy (BIS), might meet these needs. It is a safe, easy to use, inexpensive and portable device. Comparison studies of BIS and DEXA in adults with obesity suggest that high body fat decreases the comparability between both methods (185). The BCM measurements are valid over a wide range of body compositions (186). BCM integrates a volume model with a body composition model and has been validated against DEXA for the measurement of fat and fat-free mass in healthy adults and adults with underlying conditions (187). In children, Dasgupta *et al.* have validated the volume model for determination of fluid overload and normally hydrated weight (188). However, studies comparing the BIS-derived body composition model with DEXA in a pediatric population with obesity, including a longitudinal follow-up, have not been conducted. Given the prediction by Matthie *et al*. regarding BIS becoming the standard for determining fat% and fat-free mass of subjects with obesity, the validity of BIS needs to be examined in a pediatric population with obesity (189). Our objective is to compare DEXA and BIS in children with obesity aged 8-18 years before and after weight loss and to evaluate whether BIS can accurately track longitudinal changes in body composition.

4.3 Materials and methods

4.3.1 Study population and design

For this study, only the data of the inpatient cohort have been used and evaluations were planned before and after inpatient treatment. Inclusion and exclusion criteria are described in **chapter 3.2** and information on the treatment program in **chapter 3.3**.

4.3.2 Anthropometry and bioimpedance spectroscopy

These measurements have been described previously in **chapters 3.4.1** and **3.4.3.**

4.3.3 Dual Energy X-Ray Absorptiometry

A DEXA scan (Lunar Prodigy Advance, utilizing a narrow-angle fan beam technology, encore pediatric software: version ENC V13.6, GE Healthcare, Madison, WI, USA) was performed by a trained technician. As previously shown, this device has high reproducibility (190,191). Patients were scanned lying supine and wearing only their underwear. Patients were non-fasting. Data on fat mass, fat percentage, fat-free mass and fat-free percentage were obtained. Fat-free mass was defined as lean tissue mass plus the bone mineral content.

The scanned images were scored based on quality of the study and more specifically, whether the scanned image covered the complete body surface. A scan was considered incomplete when parts of the upper arm fell out of the image, even though these missing values were extrapolated from measurements performed on the other side (192). Complete scans were scored as zero and incomplete scans as one.

4.3.4 Statistical analysis

An overview of the general statistical approach has been reported in **chapter 3.5**.

The agreement between the BCM and DEXA was evaluated using Bland-Altman plots (193). Passing-Bablok regressions were used to investigate proportional bias between both techniques (194). Statistical analysis was performed using XLSTAT (195).

The between-method difference (Δ) for each compartment at baseline was calculated and the absolute value of this difference was taken to identify predictors of non-agreement between both methods using linear regression models.

4.4 Results

4.4.1 Baseline assessment

One hundred and thirty patients with a mean BMI SDS of 2.7 (range 1.6 - 3.7) were included in the study. The mean age was 14.4 $\pm$ 2.2 years, and 40% of patients were male. Patient characteristics at baseline and follow-up are shown in **Table 4.1**.

Table 4.1: Patient characteristics before and after weight loss treatment

	Baseline	After inpatient treatment	p-value
N	130	75	
Gender (♂/♀)	52/78	25/50	0.3[1]
Age (y)	**14.4 ± 2.2**	**15.3 ± 2.3**	**<0.001[2]**
BMI SDS (SDS)	**2.7 (1.6 – 3.7)**	**1.8 (0.5 – 2.7)**	**<0.001[3]**
DEXA fat mass (kg)	**46.3 (22.3 - 88.1) [b]**	**27.2 (8.9 – 49.3) [a]**	**<0.001[3]**
DEXA fat percentage (%)	**48.9 ± 4.6 [a]**	**35.8 ± 8.7 [a]**	**<0.001[2]**
DEXA fat-free mass (kg)	51.9 ± 12.0 [b]	49.2 ± 10.9 [a]	0.3[2]
DEXA fat-free percentage (%)	**51.6 ± 4.6 [a]**	**64.2 ± 8.7 [a]**	**<0.001[2]**
BIS fat mass (kg)	**43.1 (14.4 – 93.8)**	**24.5 (8.1 – 53.8)**	**<0.001[3]**
BIS fat percentage (%)	**43.9 ± 5.8**	**32.7 ± 8.2**	**<0.001[2]**
BIS fat-free mass (kg)	**41.8 (24.9 – 67.9)**	**41.5 (27.4 – 71.4)**	**0.019[3]**
BIS fat-free percentage (%)	**42.4 ± 7.5**	**56.1 ± 10.8**	**<0.001[2]**

Results are presented as mean ± standard deviation or median (minimum - maximum)

[1]Chi-square test, [2]paired t-test, [3]Wilcoxon sign rank test

[a] p<0.05 compared with the BCM measurement at the same time point, paired t-test

[b] p<0.05 compared to the BCM measurement at the same time point, Wilcoxon sign rank test

Bland-Altman plots showed wide limits of agreement for all four parameters of body composition when comparing DEXA with BIS, with a high average bias of 2.584 (95% confidence interval [CI] 1.822–3.346) for fat mass, 4.566 (95% CI 3.810–5.322) for fat percentage, 8.967 (95% CI 7.590–10.344) for fat-free mass, and 9.156 (95% CI 8.173–10.139) for fat-free percentage **(Figure 4.1)**.

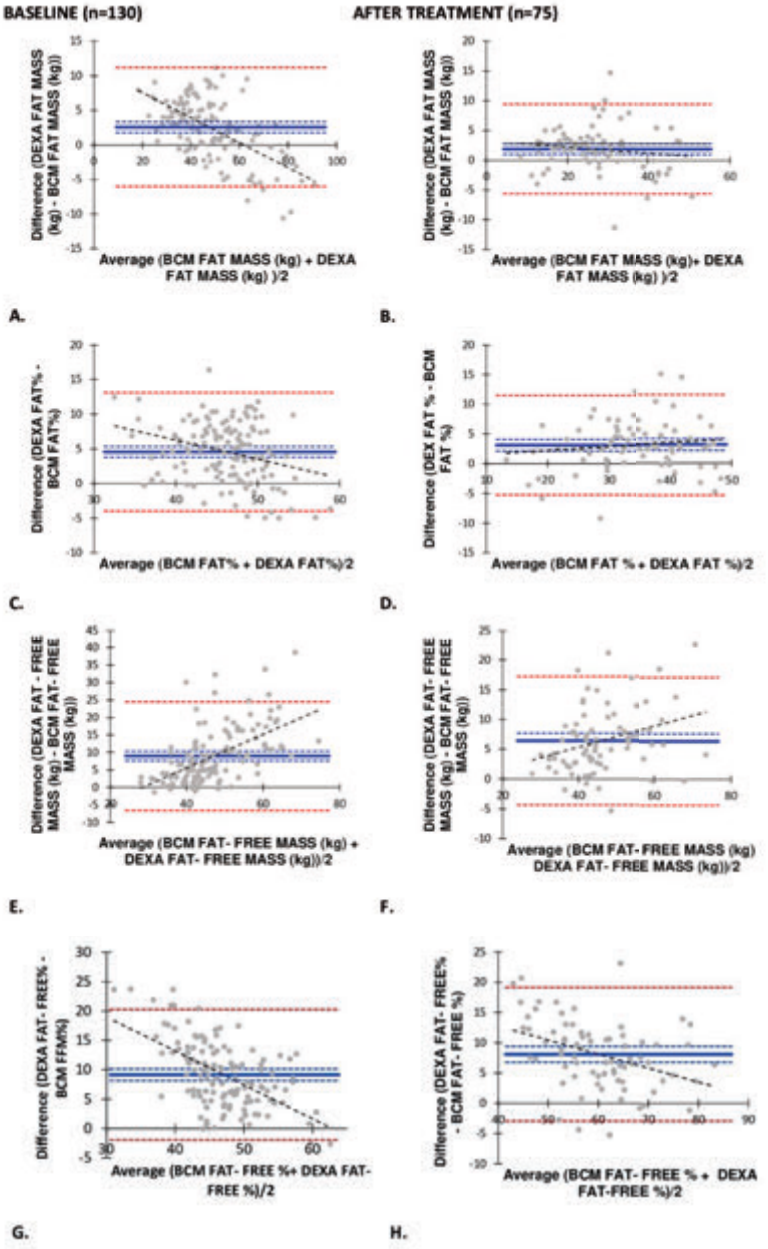


Figure 4.1: Bland-Altman plots before and after treatment comparing fat mass **(A,B)**, fat percentage **(C,D)**, fat-free mass **(E, F)**, and fat-free percentage **(G, H)** measured by BCM and DEXA. The blue solid line indicates the mean difference and the blue dashed lines the 95% confidence interval (CI) around the mean. The red dashed lines indicate the mean $\pm$ 1.96 SD. The black dashed line represents the linear regression line of difference.

Passing - Bablok regressions found a proportional and systematic bias between both methods for all four parameters of body composition **(Figure 4.2, Table 4.2)**.

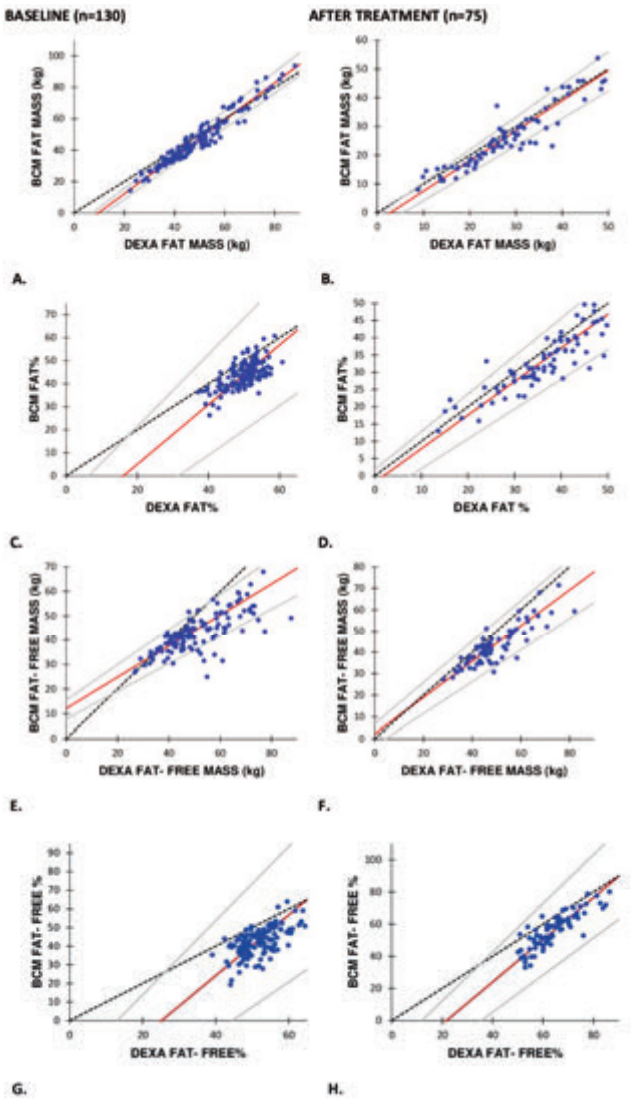


Figure 4.2: Passing - Bablok regressions before and after treatment comparing fat mass **(A,B)**, fat percentage **(C, D)**, fat-free mass **(E, F)**, and fat-free percentage **(G, H)** measured by BCM and DEXA. The black dashed line indicates the regression in case of perfect agreement. The red solid line represents the actual regression obtained by the comparison of DEXA with BIS. The grey solid lines represent the 95% CI around the obtained regression.

Table 4.2: Passing - Bablok regressions comparing body composition measured by bioimpedance spectroscopy (BIS) and dual energy x-ray absorptiometry (DEXA).

Moment	Parameter		Value	Lower bound 95% CI	Upper bound 95% CI
Baseline	Fat mass (kg)	Intercept	-11.431	-13.967	-9.143
		Slope	1.180	1.129	1.236
	Fat mass % (%)	Intercept	-20.128	-32.075	-9.051
		Slope	1.317	1.092	1.567
	Fat-free mass (kg)	Intercept	10.061	6.648	13.929
		Slope	0.649	0.569	0.724
	Fat-free % (%)	Intercept	-51.751	-70.787	-37.153
		Slope	1.828	1.540	2.198
After treatment	Fat mass (kg)	Intercept	-2.946	-5.147	-0.977
		Slope	**1.049**	0.957	1.137
	Fat % (%)	Intercept	**-1.870**	-6.542	1.825
		Slope	**0.973**	0.863	1.096
	Fat-free mass (kg)	Intercept	**2.251**	-3.299	6.793
		Slope	0.837	0.740	0.958
	Fat-free % (%)	Intercept	-28.579	-40.913	-17.989
		Slope	1.314	1.153	1.514
Change Over Time	Fat mass (kg)	Intercept	-2.603	-5.211	-0.722
		Slope	**1.079**	0.930	1.222
	Fat % (%)	Intercept	**0.129**	-1.611	1.628
		Slope	0.833	0.710	0.991
	Fat-free mass (kg)	Intercept	-0.691	-0.927	-0.455
		Slope	**1.113**	0.769	1.565
	Fat-free % (%)	Intercept	**0.114**	2.422	-1.563
		Slope	**1.045**	0.902	1.244

Results in bold indicate that the slope or intercept is similar to the line of identity (e.g. slope equals 1; intercept equals 0).

Age and BMI SDS were associated with the change in fat percentage (Δfat%), change in fat-free mass (Δfat-free mass), and change in fat-free percentage (Δfat-free%) (all $p<0.05$). Age also correlated with the change in fat mass (Δfat mass), while BMI SDS did not ($p=0.9$). Female patients had a greater difference in fat and fat percentage between DEXA and BIS as compared to male patients (4.86 ± 2.82 kg and 6.11 ± 3.58% in females as compared to 3.49 ± 2.31 kg and 4 ± 2.89% in males, both $p<0.01$). Δfat-free mass and Δfat-free% did not differ between genders ($p=0.2$).

A final linear regression model for the between-method difference (delta (Δ) values) of all parameters is shown in **Table 4.3**. The combination of gender, age, BMI SDS and completeness of the scanned image results in an explained proportion of the variance of 14.6% for fat mass, 40.5% for fat percentage, 62.2% for fat-free mass and 61.0% for fat-free percentage. The interaction between gender and BMI SDS was a significant contributor to the model of Δfat-free mass. Therefore, the linear regression model for the between-method difference in fat-free mass has also been made separately for boys and girls, accounting for the proportion of the variance of 72.9 % in boys and 57.9% in girls **(Table 4.4)**.

Table 4.3: Linear regression models identifying determinants of the between-method difference at baseline.

Outcome		r	p-value	Adjusted R^2
Δ fat mass (kg)				0.146
	Age	**-0.214**	**0.016**	
	Gender	**0.182**	**0.041**	
	BMI SDS	**0.203**	**0.022**	
	Complete	**-0.223**	**0.012**	
Δ fat % (%)				0.405
	Age	**-0.375**	**<0.01**	
	Gender	**0.318**	**<0.01**	
	BMI SDS	-0.058	0.5	
	Complete	**-0.261**	**<0.01**	
Δ fat-free mass (kg)				0.622
	Age	**0.549**	**<0.01**	
	Gender	**-0.251**	**<0.01**	
	BMI SDS	**0.458**	**<0.01**	
	Complete	0.102	0.3	
Δ fat-free % (%)				0.610
	Age	**0.601**	**<0.01**	
	Gender	**-0.203**	**0.022**	
	BMI SDS	**0.278**	**<0.01**	
	Complete	**0.210**	**0.018**	

Table 4.4: Linear regression model identifying determinants of the between-method difference in fat-free mass at baseline for boys and girls separately.

Outcome		r	p-value	Adjusted R^2
Δ fat-free mass (kg)				
Boys				0.729
	Age	0.432	<0.01	
	BMI SDS	0.680	<0.01	
	Complete	-0.204	0.2	
Girls				0.579
	Age	0.575	<0.01	
	BMI SDS	0.334	<0.01	
	Complete	0.237	0.04	

4.4.2 Follow-up Assessment

Seventy-five patients participated in the follow-up visit, implying a drop-out rate of 42%. This was attributable to premature finishing of the program by 54 participants and insufficient cooperation during the BIS measurement by one participant. At the time of the follow-up, 12 patients had reached a normal weight, 36 remained overweight, and 27 were still classified as obese. On average, the BMI of patients had significantly reduced by 1.0 $\pm$ 0.4 SDS. **Table 4.1** shows the evolution of the parameters measured by BIS and DEXA.

Baseline characteristics of age (p=0.5), gender (p=0.07), or BMI SDS (p=0.5) of those who came for the follow-up did not differ. However, patients who dropped out had a higher weight as compared to those who did not (mean 108.57 $\pm$ 25.86 kg and 99.39 $\pm$ 22.95 kg, respectively; p=0.04). Those who dropped out also had a higher DEXA-measured fat-free mass than those who did not (mean 51.17 $\pm$ 12.31 kg and 46.78 $\pm$ 10.90 kg, respectively; p=0.04).

The fat mass, fat percentage, fat-free mass and fat-free percentage measured by BIS correlated strongly and significantly with the corresponding DEXA scan measurements (r = 0.926, SE 0.043, r = 0.849, SE 0.057, r = 0.805 SE 0.059, r = 0.830 SE 0.061, all p<0.01).

The Bland-Altman plots found wide limits of agreement, although the average bias diminished when compared with the baseline for fat mass (1.908; 95% CI 1.024 - 2.792), fat percentage (3.11; 95% CI 2.130 - 4.091), fat-free mass (6.436; 95% CI 5.169 - 7.703), and fat-free percentage (8.103; 95% CI 6.806 - 9.399) **(Figure 4.1)**. No proportional differences were found by the Passing - Bablok regression analysis for fat mass and fat percentage, although BIS underestimated the fat mass by 2.9 kg on average as compared to DEXA **(Figure 4.2, Table 4.2).**

Female patients had a higher between-method difference for fat percentage compared to male patients (4.18 $\pm$ 4.09% and 0.98 $\pm$ 3.85, respectively, p<0.01). No gender differences

were found for the between-method differences in fat mass (p = 0.052), fat-free mass (p=0.3) and fat-free percentage (p=0.5).

The differences between BCM and DEXA for measurement of fat-free mass and fat-free percentage were lower in participants with a normal weight and overweight when compared with patients with obesity (p<0.01), with an average bias of 3.7 ± 3.3 kg (5.7 ± 5.2%) in patients with a normal weight and 4.5 ± 3.5 kg (6.5 ± 4.6%) in patients with overweight as compared to 10.4 ± 6.5 kg (11.4 ± 5.9%) in patients with obesity.

4.4.3 Longitudinal changes in body composition

To assess whether both methods equivalently report longitudinal changes in body composition, the differences between baseline and follow-up were calculated for each parameter. Subsequently, the differences detected in each compartment were compared between both methods.

As observed earlier, highly significant correlations were obtained for each body compartment measured by both BIS and DEXA (all p<0.01). Strong correlations were found between fat mass (r = 0.875, SE 0.055), fat percentage (r = 0.782, SE 0.073), and fat-free percentage (r = 0.788, SE 0.086). A weak to moderate correlation was found for fat-free mass (r = 0.439, SE 0.107) as measured by DEXA and BIS.

The Bland-Altman plots found wide limits of agreement for the changes in fat mass, fat percentage, fat-free mass, and fat-free percentage. No systematic bias was found in the measurement of fat-free percentage, with an average bias of 0.607 (95% CI 0.383 - 1.597). A positive bias was found for fat mass (1.112; 95% CI 0.197 - 2.028), fat percentage (1.886; 95% CI 0.955 - 2.818) and fat-free mass (1.693; 95%CI 0.651 - 2.736). Passing - Bablok regressions analysis showed no proportional bias for fat mass, fat-free mass, and fat-free percentage, although BIS underestimated fat mass and fat-free mass **(Figure 4.3, Table 4.2)**. No gender differences were found in the longitudinal changes measured between both methods.

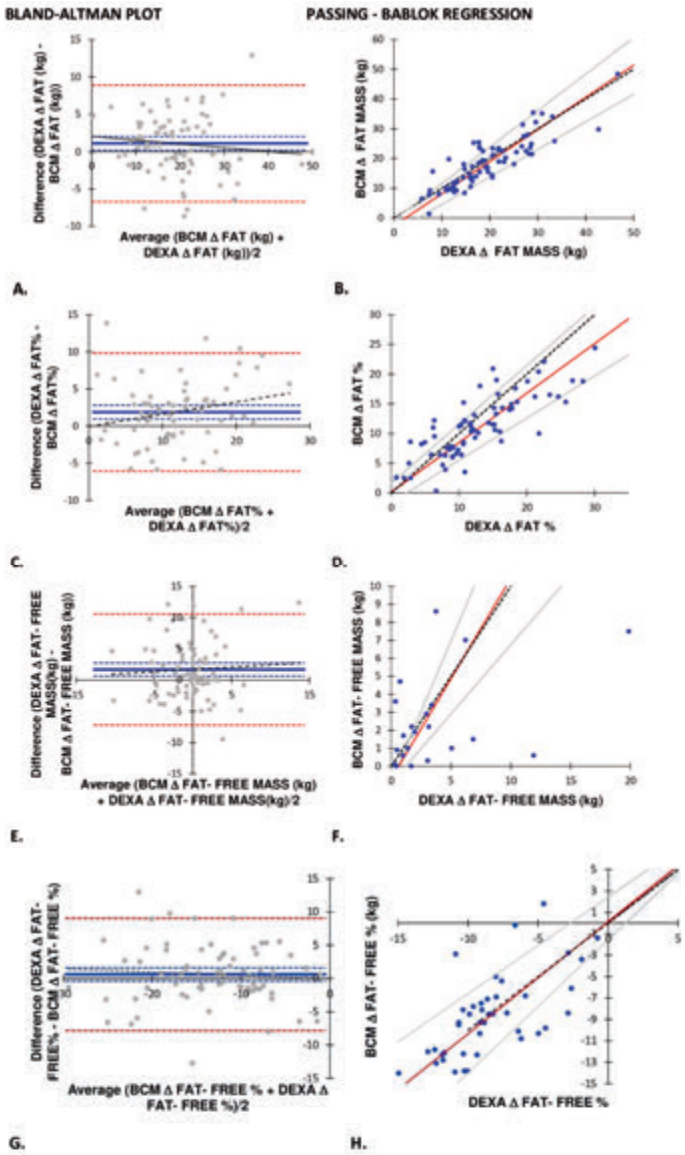


Figure 4.3: Bland-Altman plots and Passing - Bablok regressions comparing the longitudinal changes in fat mass **(A,B)**, fat percentage **(C,D)**, fat-free mass **(E, F)**, and fat-free percentage **(G, H)**. In the Bland-Altman plot, the blue solid line indicates the mean difference and the blue dashed lines the 95% CI around the mean. The red dashed lines indicate the mean $\pm$ 1.96 SD. In the Passing - Bablok regression, the black dashed line indicates the regression in case of perfect agreement. The red solid line represents the actual regression obtained by the comparison of DEXA with BIS. The grey solid lines represent the 95% CI around the obtained regression. The black dashed line represents the linear regression line of difference.

4.5 Discussion

Our findings suggest that DEXA and BIS are not interchangeable methods of measuring body composition in a pediatric population with obesity. After an inpatient weight loss program, all participants had reduced BMI SDS, but most were still overweight. The agreement between body composition measurements improved at follow-up, but the overall results showed an underestimation of fat mass and an overestimation of fat-free mass by BIS as compared to DEXA.

The results of our baseline and follow-up comparisons are in agreement with a previous study concluding that BIS (Xitron Hydra 4000B) underestimates fat mass in children with overweight as compared to DEXA (Lunar-DPX-L) (196). Similar results were found in adults with obesity when comparing BIS (Xitron Hydra 4200 and Impedimed SFB7) to Prodigy DEXA (197–199). With respect to fat-free mass, the results in literature are more ambiguous. Ellegard *et al*. found no significant differences between fat-free postpartum mass measurements from women with obesity using BIS (Xitron Hydra 4200) and Prodigy DEXA, although there were wide limits of agreement at the individual level (197). Whereas in men with overweight or obesity, BIS (Impedimed SFB7) overestimated fat-free mass when compared with Prodigy DEXA (198).

Previous studies comparing BCM with Prodigy DEXA have been conducted in adults and revealed similar between-method differences for fat mass and fat percentage, as seen in our study at the follow-up assessment. They reported an average underestimation of fat mass determined by BIS, ranging from 0.5 - 3.1 kg, compared to DEXA in healthy adults and adults with liver, renal or oncological diseases (187,200–203), and an underestimation of fat percentage by 1.78% (202). Females showed a larger difference in fat percentage estimates than males, which was consistent with our findings (202). The mean BMI in these studies ranged from 25.4 - 28.0 kg/m^2 which is similar to the BMI of our population at follow-up.

Our bias in fat-free mass was much larger than those reported in two studies on dialysis patients, but these studies calculated fat-free mass differently (201,203). At follow-up, the bias in fat-free mass and fat-free percentage was significantly lower in normal and overweight patients compared to patients with obesity. Therefore, BMI seems to be an important confounder. Indeed, the influence of BMI on the agreement between DEXA and BIS has previously been reported in other studies (196,202,204,205).

In children with a normal weight, the overestimation of fat percentage by Hologic QDR-2000W DEXA compared to the 4-C model varies from 1.13 - 3.9% (206,207). In children with overweight and obesity, the average overestimation of fat percentage measured by a Prodigy DEXA scan, as compared to a 4-C model, was 1.9% (95% limits of agreement 2.1 - 5.9) (208). Our values indicating an underestimation of fat percentage by BIS compared to DEXA are within the range that DEXA overestimates the fat percentage compared with the 4-C model (even in normal weight children), implying that the difference found at follow-up might be due to an error of DEXA rather than BIS.

Multiple explanations can be found for the lack of agreement at baseline. First, most subjects had an anteroposterior thickness of > 20 cm, which amplifies the error in measuring fat and fat-free mass by DEXA due to beam hardening (182,209,210). Second, most individuals had a body surface exceeding the scanning area at baseline. Although the values for missing body parts are estimated by the scanner software based on the fully scanned parts, the reliability of the initial measurements might be low. After weight loss, most of the scanned images covered the entire body surface, which might partly explain the better agreement seen in this case. In contrast with other studies (182), we have incorporated completeness of the scan as a predictor of the between-method differences at baseline. This was found to be significant for estimating the difference in fat mass, fat- and fat-free percentage in both genders and fat-free mass in girls between BIS and DEXA.

Third, DEXA and BIS assume a fixed hydration of soft tissues (211,212). The hydration keeps declining from 4 years of age until 20 years of age and increases in parallel with increases in adiposity (213,214). Moreover, alterations in extracellular water content only result in small effects on the DEXA-derived fat mass (215). BCM is corrected for BMI, but uses adult hydration references. The use of the adult references might also influence the comparability between both methods, although obesity seems to be the largest contributor to the lack of agreement, as can be inferred by the improved agreement after weight loss and smaller bias in fat-free mass in the normal weight group.

It has to be kept in mind that BCM was originally developed to assess the hydration status (216), although recently, it is increasingly being used for nutritional assessment as well (217). Using BIS, the measured resistance has been implemented in volume and body composition models. The volume model uses programmed software and the mixture theory with anthropometric measurements and certain assumptions to estimate total body water (TBW), intracellular (ICW), and extracellular water (ECW). Lean tissue, adipose tissue and overhydration (OH) are then calculated based on the determined ECW and TBW (186). We have used fat- and fat-free mass instead, because the adipose tissue mass as reported by BCM also contains adipose water (201). Individuals with excess adipose tissue have a higher extracellular water content (218) and alterations in body water can influence the DEXA-derived estimates of fat-free mass (219). This could enhance the bias between both methods if the extra body water had been assigned to the fat mass by the BCM.

We did not find any proportional biases between BIS and DEXA for the longitudinal changes in fat-free percentage, fat and fat-free mass induced by weight loss. Studies in bariatric surgery patients found that the degree of fat loss was associated with an overestimation of loss of TBW by BIS (Xitron Hydra 4200), caused by rapid and acute fluid shifts elicited by the severe weight loss (220).

Thomson *et al.* investigated women with overweight and obesity before and after a 10-week weight loss intervention and reported a good agreement between BIS (Impedimed SFB7) and Lunar Prodigy DEXA in assessing changes in body composition and found no significant differences in the fat percentage, fat and fat-free mass measured (221). This suggests that BIS might be more accurate in interventions with a slower weight loss. In our study, patients were measured after 10 months of weight loss resulting in an average BMI SDS decrease of 1.16 $\pm$ 0.33 SDS. Previous studies in the same center report a mean decrease of BMI SDS ranging from 0.76 - 0.86 SDS after 5 months (98,222). This suggests that the highest weight loss takes place in the first few months and that there is still some weight loss at a slower rate during the second part. Following the assumption of Thomson and colleagues (48), BIS can be used for assessing body composition longitudinally in these interventions where the weight loss occurs more slowly as opposed to rapid surgically-induced weight loss.

A few limitations of our study need to be considered. First, we had a drop-out rate of 42% at the follow-up assessment, which is in line with previous data (223). Since the population lost to follow-up only differed significantly in weight and DEXA-measured fat-free mass, we believe that the remaining follow-up population represented a considerable proportion of the initially included population. A bias between both methods at baseline was also observed only when the group that finished the program was analyzed. Secondly, as per protocol we performed only one BCM measurement, and a second one only in cases where the quality was < 75%. A previous study performed in 20 healthy children using BCM reported high intra- and interrater intraclass correlation coefficients for fat mass and fat-free mass, suggesting limited variability between multiple measurements and technicians (224). High *in vivo* reproducibility was also found in a study of Wabel and colleagues (225). Third, BCM relies on adult reference values, which is a limitation when using this equipment in children. If age-specific adipose tissue hydration parameters were introduced, it could extend the applicability to children for determination of excess fluid (216).

Our goal was to evaluate body composition measurements based on ECW and TBW, not OH. Using adult references can induce errors in body composition results since the ECW/ICW ratio might differ in children (213). Since both measurements were only 10 months apart, we expected a very limited age-related change in hydration status between both assessments, resulting in a similar error in the determination of body composition at both timepoints. Calculating the changes in body composition might overcome this limitation. Apart from age, our follow-up population is very similar to the one used to initially create the model concerning fat percentage, fat-free mass, and BMI (216). The similarity makes this an interesting pediatric population in which to assess the validity of BCM. Fourth, devices and software versions might differ in their body composition estimates. We therefore referred mostly to studies using the same devices for DEXA and BIS measurements, although we used a pediatric DEXA software unlike in adult studies. Besides the technological differences between BIS and DEXA, the software used to analyze the tissue attenuation might be an additional confounder in the agreement between DEXA and BIS. Finally, since there was high individual variability, as shown by the wide limits of agreement on the Bland-Altman plots, these data should not be used for interpretation on an individual level. Nevertheless, when considering the longitudinal results on a group level in a pediatric population with obesity, BIS might be an interesting technique to use, although both BIS and DEXA have their limitations.

Since there are very limited studies on the usability of BIS to track changes in body composition, these results will need to be confirmed by larger studies. Furthermore, the comparison of BIS with the real gold standard, the 4-C model, in a pediatric population with obesity would allow for a more definite conclusion. However, this is difficult to achieve in routine clinical practice due to the need for specialized equipment, time and trained technicians to perform these investigations.

The results of this study offer a first step towards implementing BCM in the clinical pediatric obesity research field. This would be of great value since BIS is an inexpensive and simple technique.

4.6 Conclusion

The agreement between DEXA and BIS improved after weight loss in children with obesity. However, a trend of underestimation of fat mass and overestimation of fat-free mass by BIS was observed. Both methods report the proportional changes in body composition during weight loss treatment in a similar manner for fat-free percentage and fat- and fat-free mass, although the latter two are systematically underestimated by BIS. These findings suggest that BIS might be an interesting, but not superior, alternative to DEXA for future research on pediatric obesity in which changes in body composition are measured at a group level. However, these results should not be used for monitoring individual changes.

Chapter 5: The 'WELCOME' trial

This chapter is adapted from

Improving treatment outcome in children with obesity by an online self-control training: a randomized controlled trial

Vermeiren E, Naets T, Van Eyck A, Vervoort L, Ysebaert M, Baeck N, De Guchtenaere A, Van Helvoirt M , Tanghe A, Bruyndonckx L, De Winter B, Verhulst S, Van Hoorenbeeck K, Braet C.

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5.1 Abstract

Background: Currently available treatment programs for children with obesity only have modest long-term results, which is (at least partially) due to the poorer self-control observed within this population. The present trial aimed to determine whether an online self-control training, training inhibition and redirecting attentional bias, can improve the short- and long-term treatment outcome of (in- or outpatient) pediatric obesity treatment programs.

Methods: In this double-blind multi-center randomized controlled trial, participants aged 8-18 years with obesity were allocated in a 1:1 ratio to receive an online self-control or sham training added to their in- or outpatient multidisciplinary obesity treatment program. The primary endpoint was BMI SDS. Data were analyzed by linear mixed models and the main interactions of interest were randomization by time and randomization by number of sessions, as the latter was cumulatively expressed and therefore represents the effect of increasing dose over time.

Results: 144 inpatient (mean age 14.3 $\pm$ 2.2 years, BMI 2.7 $\pm$ 0.4 SDS, 42% male) and 115 outpatient children (mean age 11.9 $\pm$ 2.1 years, BMI 2.4 $\pm$ 0.4 SDS, 45% male) were included. Children's BMI lowered significantly during treatment in both the in- and outpatient treatment centers, $p<0.001$. In a mixed model with BMI as dependent variable, randomization by time was non-significant, but the number of self-control trainings (randomization*number of sessions) interacted significantly with setting and with age ($p=0.002$ and $p=0.047$), indicating a potential effect in younger inpatient residents. Indeed, a subgroup analysis on 22 inpatient children of 8-12 years found a benefit of the number of self-control trainings on BMI ($p=0.026$).

Conclusion: The present trial found no benefit of the self-control training in the entire study population, however a subgroup of young, inpatient participants potentially benefited.

5.2 Introduction

As already described in **chapter 1.3.2**, the current long-term outcomes of the childhood obesity treatment programs could be improved (130,131). Interestingly, current evidence reports an important association between self-control and weight evolution during and after treatment (77,155). This self-control, resulting from the balance between bottom-up reactivity and top-down executive functioning, is often reduced in children with obesity (149,226) and might therefore be an interesting potential treatment target in children with obesity to improve the outcomes of current treatment programs, as highlighted in **chapter 1.3.3**. Preceding 'in-lab' studies have already provided some scientific evidence for the trainability of these different neuropsychological processes (141,156–159), however the translation and validation of these 'in-lab' findings to real-world clinical application has not yet been made.

This rationale led to the development of the 'WELCOME' trial, which stands for 'improving WEight controL and CO-Morbidities in children with obesity via Executive function training'. The present trial explored the effect of a self-control versus a sham training added to a multidisciplinary obesity treatment (MOT) program. This is the first randomized controlled trial assessing the 'real-world' effectivity (as opposed to the 'in-lab evaluation') of a combined self-control training (training both inhibition and attention) across different treatment settings (e.g. in- and outpatient) in a large sample of treatment-seeking children with obesity distributed over a broad age range (8-18 years). Furthermore, the present trial evaluated both short- and long-term BMI outcome and self-control.

We hypothesized that

1) the group with the self-control training would have a better BMI outcome compared to the group with the sham training. Here, effects of interest are:
   - the interaction of randomization (self-control vs sham training) *by* time
   - the interaction of randomization (self-control vs sham training) *by* number of sessions, as the latter incorporates the impact of the dose-response relation over time as 'number of sessions' is cumulatively expressed.

The decision to incorporate the number of sessions was based on a recent meta-analysis indicating that the number of sessions modulated the training effect (227). Furthermore, age, gender and treatment setting could likely influence the training effects and are therefore incorporated and controlled for in the analyses.

2) The training, when effective on BMI reduction, would result in training-related improvements in self-control. We specifically look at training-related improvements in self-control, as MOT itself improves behavior control (138).

5.3 Methodology

5.3.1 Study design and participants

A double-blind multi-centered randomized controlled trial (RCT) was conducted to objectify the added value of a bottom-up and top-down self-control training on top of the currently existing MOTs. Randomization was performed by an online program (QMinim (228)). Patients were randomized by a 1:1 allocation rate based on pretreatment age, sex and BMI SDS to receive either the self-control or the sham training. The training was added after the second study visit (T1) as depicted in **Figure 5.1.**

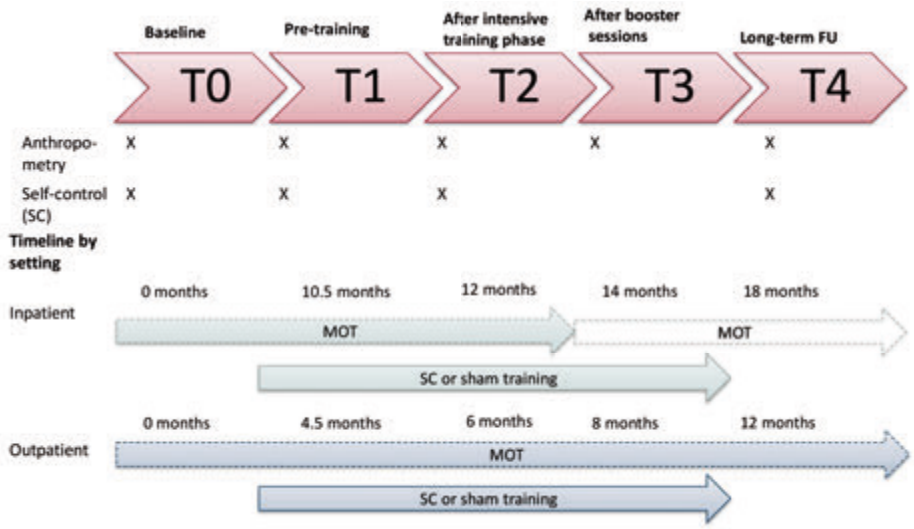


Figure 5.1: Visual representation of the study design by setting. T=timepoint, MOT = multidisciplinary obesity treatment, FU=follow-up, SC = self-control.

The trial was registered at the ISRCTN register (n°ISRCTN14722584).

The participant in- and exclusion criteria are reported in **chapter 3.2** and the content of the multidisciplinary treatment programs in **chapter 3.3**.

5.3.2 Self-control training

The self-control training consisted of a computer training containing a bottom-up attention training and a top-down inhibition training, an example of both is depicted in **Figure 5.2**.

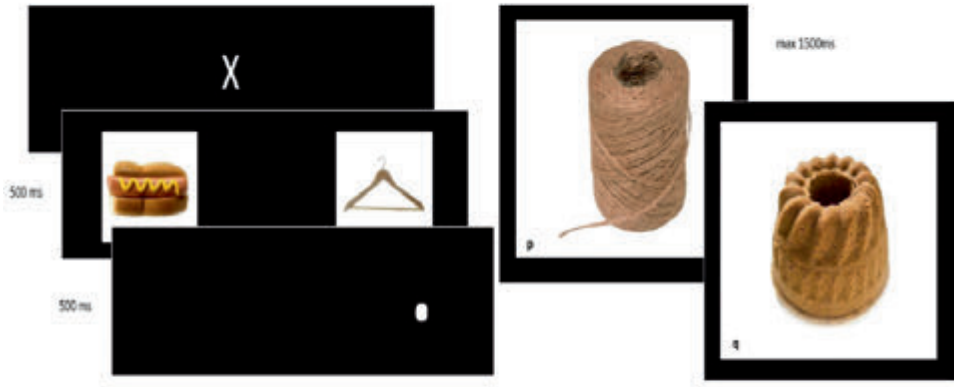


Figure 5.2: the left picture is an example of the dot-probe task, used for bottom-up attentional bias and the right picture of a go and no-go trial in the go/no-go task used to train top-down inhibitory control.

For the attention training, the Dot Probe task was used (229). First, a white cross was shown. Subsequently, two stimuli (food or neutral objects) were shown and followed by the appearance of a white dot at the location of the stimulus when these pictures were removed. Patients were asked to locate the dot and press 'e' or 'i', when the white dot was presented on the left ('e') or right ('i') side of the screen. In congruent trials, the dot was located at the same side of the salient (food) stimulus. In incongruent trials, the dot was located at the opposite side (at the location of the neutral stimulus). In the self-control training, 90% were incongruent trials where the dot appeared at the opposite side of the food stimulus, aiming to reduce this selective attentional bias by presenting the dot on the opposite side of the screen as where the 'attention drawing' cue is presented (229). This ratio was 50/50 in the sham training.

The inhibition training relied on a Go/No-Go (GNG) task (230), where a picture of a neutral or unhealthy food stimulus was accompanied by a "go" or "no-go" cue (in this case a letter, p or q). Rapid responses were evoked in "go trials", in which patients needed to respond by pressing the spacebar as fast as possible when the "go"-stimulus was presented. In "no-go trials", patients were required not to react. In the experimental training, 90% of the "no-go" trials were accompanied by a picture of unhealthy food, aiming to restrain impulsive responses towards unhealthy food stimuli (230). In the sham training, only 50% of the no-go trials were accompanied by an unhealthy food picture (and 50% with a neutral stimulus).

The online self-control training was provided in two phases: the intensive training phase and the booster phase (see **Figure 5.1**). The intensive phase was introduced after T1. Here, patients were required to complete 12 sessions, two sessions a week for six weeks until T2. After T2, booster sessions were started at a frequency of one session a week for eight weeks, till T3. Every training session had a duration of 30 minutes. In a final follow-up (T4) weight and length were collected.

The training software was developed by ImplicitMeasures.com (Ghent, Belgium).

5.3.3 Outcome measures

5.3.3.1 Anthropometry

The primary endpoint was BMI SDS. To rule out a possible underestimation of changes in BMI with BMI SDS in children with severe obesity (231), we have repeated the main analysis with BMI expressed as a percentage of the 95th percentile as recommended by Freedman *et al* (232,233). The collection of the anthropometric data is documented in **chapter 3.4.1.**

5.3.3.2 ***Self-control assessments***

Secondary, training-related improvements in self-control were studied.

1) *Bottom-up reactivity: DEBQ: the Dutch Eating Behavior Questionnaire* (234). The DEBQ is a self-report questionnaire that explores bottom-up reactivity in three different maladaptive eating styles within subjects, i.e. emotional eating, external eating and restraint eating (234). In this study, the focus will be on emotional eating and external eating (eating in reaction to external stimuli). A higher score indicates more maladaptive eating.

2) *Top-down: ECS: Effortful Control Scale* (235). The ECS is a self-report questionnaire that measures top-down self-control. A total effortful control score, as well as two subscale scores can be calculated: "lack of impulsivity" (reflecting general inhibition capacities) and "persistence" (reflecting low distractibility). Only these two subdomains will be further analyzed. A higher score indicates more problems with self-control.

3) *BRIEF: Behavior Rating Inventory of Executive Functioning (BRIEF*) (236), completed by the parents. The BRIEF is developed for assessment of top-down executive functioning as a self-report (for children older than 11), parent or teacher report. It contains a total score as well as 8 subscale scores: inhibition, shifting, emotional control, initiation, working memory, planning/organizing, organizing of materials and monitoring. The first three subscales form the "behavior regulation" index and the last five subscales the "metacognition" index. In this study, only the total score, the inhibition subscale and the behavior regulation factor are used. A higher score indicates more difficulties with executive functioning.

5.3.4 Statistical analysis

Based on a power calculation suggesting an effect size of f=0.10, a total number of 180 patients randomized 1:1 was required to detect a significant effect on BMI with a power of 0.80. A drop-out of 10% was expected, hereby needing 200 participants for inclusion. Due to a higher-than-expected drop-out, 59 additional participants were included (44 inpatient, 15 outpatient).

To detect changes in the outcome variables, i.e. BMI and different domains of self-control, a simple linear mixed model with only time and a random intercept was created. If a significant change over time of the outcome was found, further in-depth analysis was carried out using a second linear mixed model including a random intercept per subject with randomization (self-control or sham), gender, setting (in- or outpatient) and time (T0,T1,T2,T4) as fixed factors and age at baseline and number of sessions (ranging from 1 to 20) as fixed covariates, including all their possible interactions.

The number of sessions was cumulatively expressed and therefore increases over time. Therefore, besides the interaction randomization *by* time, the interaction randomization *by* number of sessions is of particular interest as this incorporates the impact of the increasing number of sessions on the experimental or control group over time (dose-response relation).

Timepoint T3 was excluded from this analysis, as only 20 inpatient participants attended this visit. Patients were excluded from the mixed model analysis if they never completed a single session as otherwise an effect of randomization condition would be assigned although they were never exposed to the self-control or sham training.

5.4 Results

5.4.1 Descriptive statistics

In total, 259 patients were included of which 144 participated in the inpatient and 115 in the outpatient program. The participants from inpatient care were older, had a higher BMI SDS and higher %BMI of the 95th percentile, had a higher score on baseline emotional eating and were more impulsive compared to the patients in the outpatient care, all p<0.001. Both groups were comparable for gender and other self-control-related characteristics (see **Table 5.1A**). There were no differences in baseline age, gender, BMI metrics or self-control between the group with the self-control training and the group with the sham training (see **Table 5.1B**).

Table 5.1: Baseline characteristics of patients in an inpatient setting and patients in an outpatient setting (A), of patients in the sham and patients in the self-control training group (B).

Table 1 A)	Inpatient (n=144)	Outpatient (n=115)	p-value
Age (years)	**14.3 ± 2.2**	**11.9 ± 2.1**	**<0.001**
♀/♂	84/60	63/52	0.7
BMI SDS	**2.7 ± 0.4**	**2.4 ± 0.4**	**<0.001**
%BMI p95	**140.3 ± 21.0**	**128.4 ± 16.3**	**<0.001**
ECS: lack of impulsivity	**34.0 ± 8.0**	**38.1 ± 6.7**	**<0.001**
ECS: persistence	41.5 ± 8.4	43.5 ± 8.4	0.1
BRIEF: total score	118.9 ± 27.0	117.1 ± 28.5	0.7
BRIEF: inhibition	14.5 ± 4.2	13.7 ± 4.4	0.2
BRIEF behavior regulation factor	42.7 ± 11.0	41.6 ± 11.4	0.5
DEBQ: external eating	30.9 ± 8.7	28.8 ± 6.2	0.054
DEBQ: emotional eating	**33.0 ± 14.0**	**24.7 ± 11.2**	**<0.001**

Table 1B)	Self-control training (n=90)	Sham training (n=86)	
Age (years)	13.2 ± 2.6	13.0 ± 2.5	0.7
♀/♂	53/33	53/37	0.8
BMI SDS	2.5 ± 0.4	2.5 ± 0.4	0.6
%BMI p95	132.5 ± 16.9	132.0 ± 18.7	0.8
ECS: lack of impulsivity	36.1 ± 6.7	36.0 ± 8.0	0.9
ECS: persistence	43.4 ± 8.4	40.9 ± 8.0	0.1
BRIEF: total score	116.6 ± 28.0	118.6 ± 26.7	0.7
BRIEF: inhibition	13.6 ± 4.1	14.2 ± 4.0	0.4
BRIEF: behavior regulation factor	41.2 ± 11.4	42.2 ± 10.5	0.7
DEBQ: external eating	30.4 ± 8.3	30.0 ± 7.5	0.7
DEBQ: emotional eating	28.3 ± 12.4	32.3 ± 14.4	0.1

ECS = effortful control scale, BRIEF = Behavior Rating Inventory of Executive Functioning, DEBQ=Dutch Eating Behavior Questionnaire

5.4.2 Participant flow

The participant flow throughout the study is depicted in **Figure 5.3**.

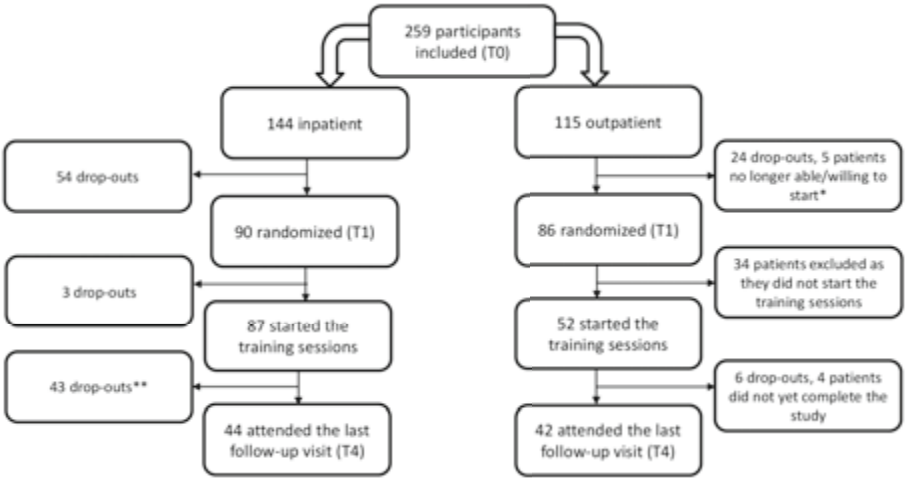


Figure 5.3: Flowchart of the evolution of the study participants by setting. * 3 participants were admitted to a psychiatric hospital during treatment and 2 no longer wished to start the training. ** all data of patients that dropped out prematurely or have not yet completed the last visit were included in the analysis until the last documented visit.

Inpatient, the highest drop-out was situated before the training started, during the first part of the inpatient treatment program (T0-T1) where 37.5 % (54 out of 144 participants) dropped out. The patients that left the inpatient treatment prematurely did not differ in baseline characteristics regarding age (p=0.3), gender (p=0.3), BMI SDS (p=0.1) or self-control ($p \geq 0.1$) from those that completed the entire program, except for absolute BMI (38.3 $\pm$ 35.6 kg/m^2 in patients dropping out compared to 35.6 $\pm$ 5.6 kg/m^2 in patients completing the program, p=0.005) and BMI% relative to the p95 (146.3 $\pm$ 24.0% compared to 136.4 $\pm$ 17.8%; p=0.009). Drop-out at follow-up (T4) resulted in a group of 44 participants that was younger and had a lower obesity severity than those lost to follow-up, witnessed by a mean age of 13.5 $\pm$ 2.3 compared to 14.7 $\pm$ 2.0 years (p=0.003), and a mean baseline BMI of 37.6 $\pm$ 6.4 kg/m^2 vs 34.6 $\pm$ 5.3 kg/m^2 (p=0.003), a mean BMI% of the p95 of 142.8 $\pm$ 22.2% vs 134.9 $\pm$ 17.1% (p=0.02) and a mean BMI SDS of 2.6 $\pm$ 0.4 compared to 2.8 $\pm$ 0.4 (p=0.02). There was no difference in terms of gender and self-control between the 44 participants that completed the entire study compared with those that dropped out prematurely, except for a higher lack of impulsivity score of 32.8 $\pm$ 8.2 in the patients that dropped out compared to 36.3 $\pm$ 7.0 in the patients that completed the study; p=0.014.

Outpatient, the largest drop-out (39.5%) was found between T1 and T2 at the start of the training sessions, as only 52 out of 86 participants (60.5%) started the training sessions. There was no difference in age (p=0.3), BMI metrics (p>0.4), gender (p=0.8) and self-control (p>0.1) or initial BMI reduction (p=0.6) between the participants that started the training sessions and those that did not, except for more emotional eating in those starting the training compared to those who never trained (27.8 $\pm$ 12.7 compared to 22.1 $\pm$ 9.0; p=0.042). Of these 52 patients, 42 completed the entire study. These 42 patients were comparable in pretreatment age (p=0.3), BMI metrics ($p \geq 0.8$), gender (p=0.95) and any domain of self-control (p>0.1) to those that did not start the training or dropped-out before finishing the study.

There was no difference in drop-out between the group with the self-control training and the sham group (p=0.3). Participant flow by randomization condition is shown in **Figure 5.4**.

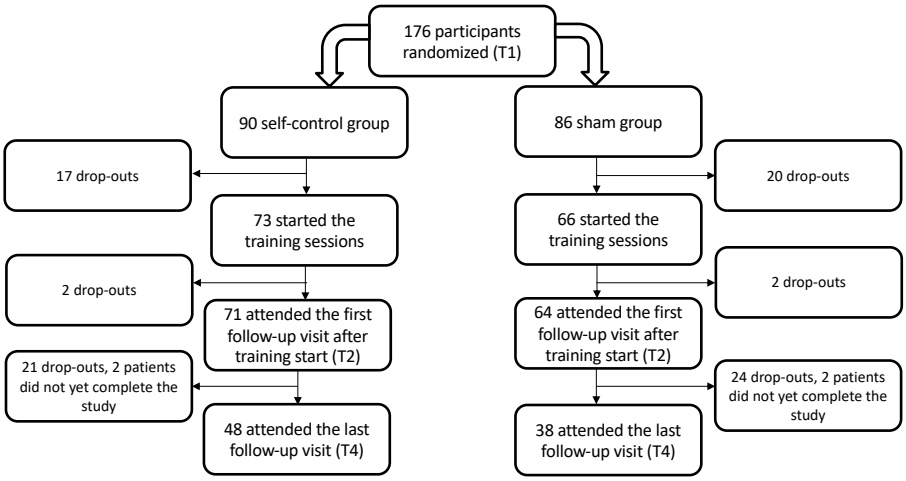


Figure 5.4: Flowchart of the study participants by allocated treatment group

In the self-control group, the 48 patients attending the last study visit were comparable to the 42 not attending in obesity severity ($p \geq 0.6$), male-to-female ratio (p=0.3), distribution across treatment settings (p=0.8) and any self-control measures ($p \geq 0.2$), except age as those not attending were significantly older with a mean age of 13.7 ± 2.6 years compared to 12.7 ± 2.4 years compared to those attending the last study visit, p=0.047. In the sham group, the 38 patients completing the entire study did not differ in age (p=0.1), obesity severity (p>0.1), gender (p=0.5), distribution across treatment settings (p=0.8) or any self-control measures ($p \geq 0.2$) from the 46 patients not attending the last study visit.

5.4.3 Training adherence

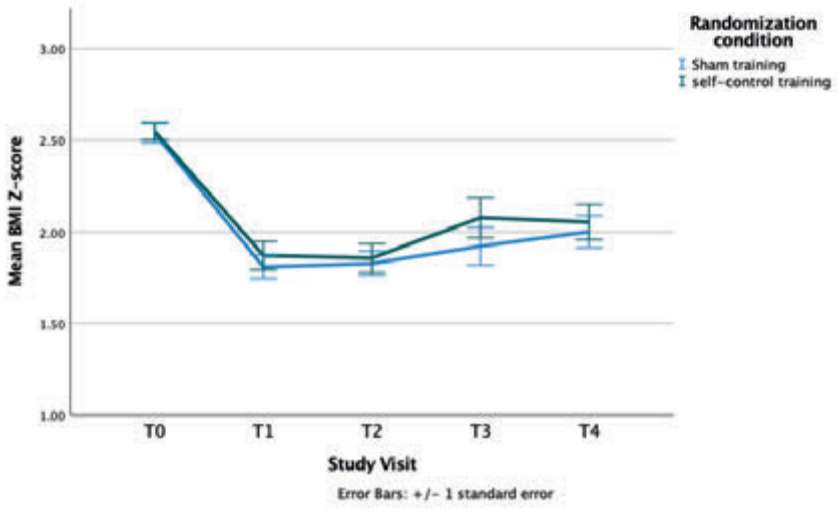
In the inpatient center, 97% of patients started with the intensive phase training sessions. After returning home from inpatient treatment, only 19% continued with the boosters. In the outpatient setting, 60% started the intensive phase training sessions, and solely 28% started the booster sessions.

Patients completed on average 7 $\pm$ 4 sessions, and there was no difference in number of executed sessions between both settings (7 $\pm$ 3 sessions inpatient compared to 8 $\pm$ 5 sessions outpatient; p=0.4), nor between both randomization conditions (p=0.1) or based on gender (p=0.9). However, an inverse correlation was found between age and number of sessions (r=-0.282, p<0.01). No significant associations were found between any of the self-control variables (measured by the DEBQ, ECS or BRIEF) and the number of sessions performed (all p>0.2).

5.4.4 Training effect on BMI reduction

In both settings, the participants' BMI decreased significantly throughout treatment as tested with a simple linear mixed model including time only, p<0.001 (**s**ee **Figure 5.5A**), but no significant differences in BMI could be demonstrated between the sham and self-control condition at any time point (see **Figure 5.5B**).

Panel A



Panel B

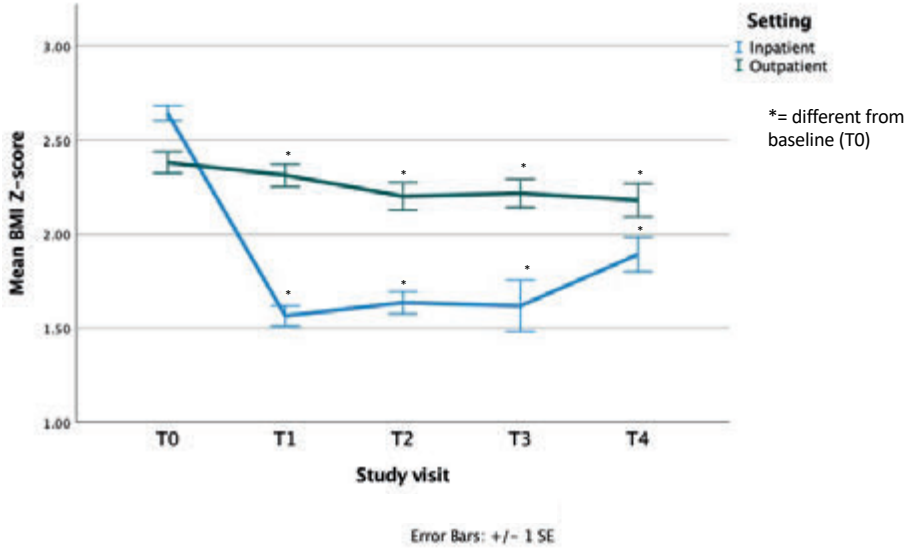


Figure 5.5 shows the BMI trajectory of the participants by setting (inpatient and outpatient - panel A) and by randomization condition (panel B). In panel A, the BMI decreases significantly over time in both settings, as shown by a simple linear mixed model with a time variable and a random intercept. Panel B depicts a similar decrease in BMI between the group treated with the sham training versus those treated with the self-control (SC) training when solely looking at the randomization condition. At none of the study visits, a statistically significant difference between the sham vs self-control group was found, tested with an independent sample's t-test and mixed model.

Next, we ran a mixed model analysis on the 139 participants that completed at least one session. The two main interactions of interest were not significant: randomization *by* time ($p>0.3$) or randomization *by* number of sessions ($p=0.1$), which was confirmed by analyzing the data as percentage relative to the 95^{th} percentile with $p>0.2$ for randomization *by* time and $p=0.8$ for randomization *by* number of sessions.

After removal of non-significant terms, a final model was obtained (see **Table 5.2A**) containing two significant three-way interactions: randomization *by* number of sessions *by* setting ($p=0.002$) favoring residential treatment and randomization *by* number of sessions *by* age ($p=0.047$) favoring younger age, hereby suggesting an effect in a subgroup.

Table 5.2 A) Linear mixed model to predict the evolution of BMI SDS over time on the entire population by setting, gender, randomization, time, age and number of sessions (n=139).

Parameter	Estimate	Standard error	p-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	2.77	0.68	<0.001	1.44	4.11
Setting	-1.03	0.83	0.2	-2.66	0.60
Gender	**-1.69**	**0.74**	**0.024**	**-3.15**	**-0.23**
Randomization	-0.12	0.42	0.8	-0.95	0.71
T0	0	0			
T1	**-0.10**	**0.039**	**0.011**	**-0.18**	**-0.02**
T2	**-0.18**	**0.048**	**<0.001**	**-0.28**	**-0.09**
T4	**-0.19**	**0.061**	**0.002**	**-0.31**	**-0.07**
Age	-0.036	0.060	0.5	-0.15	0.08
Number of sessions	-0.023	0.019	0.2	-0.06	0.01
Setting * gender	**2.00**	**0.98**	**0.044**	**0.06**	**3.94**
Setting * randomization	-0.06	0.18	0.7	-0.42	0.29
Setting * T0	**0**				
Setting * T1	**-0.98**	**0.05**	**<0.001**	**-1.08**	**-0.88**
Setting * T2	**-0.68**	**0.08**	**<0.001**	**-0.84**	**-0.52**
Setting * T4	**-0.30**	**0.09**	**0.002**	**-0.48**	**-0.11**
Setting * age	0.097	0.07	0.2	-0.04	0.23
Setting * number of sessions	-0.01	0.01	0.3	-0.03	0.01
Randomization * age	0.01	0.03	0.8	-0.06	0.08
Randomization * number of sessions	-0.04	0.03	0.2	-0.09	0.01
Gender * age	**0.15**	**0.06**	**0.025**	**0.02**	**0.27**
Age * number of sessions	0.0014	0.002	0.4	-0.002	0.005
Setting * gender * age	**-0.16**	**0.08**	**0.046**	**-0.31**	**-0.003**
Setting * randomization * number of sessions	**-0.03**	**0.01**	**0.002**	**-0.05**	**-0.012**
Age * randomization * number of sessions	**0.005**	**0.002**	**0.047**	**0.00006**	**0.01**

Parameters indicated in bold are significant. For factors, one category was used as the reference category and has coefficient 0, whereas the other category has a coefficient, that does not equal 0. This is illustrated in the table by the factor time, where T0 is used as a reference and has coefficient 0, whereas the other timepoints T1-T4 have a coefficient that describes the difference from T0. The documented coefficients in this table apply to the inpatient participants for setting (as compared to the outpatient participants that have coefficient 0), the girls for gender (compared to boys), the group provided with a self-control training for randomization (compared to the sham group). Number of sessions applies to all sessions performed, both the real self-control trainings, as the trainings offered to the control group.

An exploratory subgroup analysis indeed confirmed more BMI SDS reduction in 8- to 12-year-old inpatient-treated children in the self-control group compared to the sham group when considering the dose-response relation, as demonstrated by a significant interaction between randomization and number of sessions (p=0.027, see **Table 5.2B** and **Figure 5.6**).

Table 5.2 B) Subgroup analysis in 8- to 12-year-old children in residential care (n=22). Linear mixed model to predict the evolution of BMI SDS over time by randomization condition and number of training sessions.

Parameter	Estimate	Standard error	P-value	Lower bound 95% CI	Upper bound 95% CI
Intercept	**2.41**	**0.13**	**<0.001**	**2.14**	**2.68**
T0	0	0			
T1	**-0.97**	**0.072**	**<0.001**	**-1.13**	**-0.83**
T2	-0.35	0.37	0.3	-1.088	0.38
T4	-0.0015	0.40	0.997	-0.81	0.80
Randomization	-0.046	0.18	0.8	-0.41	0.32
Number of sessions	-0.070	0.045	0.1	-0.16	0.019
Randomization* number of sessions	**-0.030**	**0.013**	**0.027**	**-0.056**	**-0.0035**

Parameters indicated in bold are significant. For factors, one category was used as the reference category and has coefficient 0, whereas the other category has a coefficient, that does not equal 0. This is illustrated in the table by the factor time, where T0 is used as a reference and has coefficient 0, whereas the other timepoints T1-T4 have a coefficient that describes the difference from T0. The documented coefficient in this table for randomization applies to the group provided with a self-control training for randomization (compared to the sham group). Number of sessions applies to all sessions performed, both the real self-control trainings, as the trainings offered to the control group.

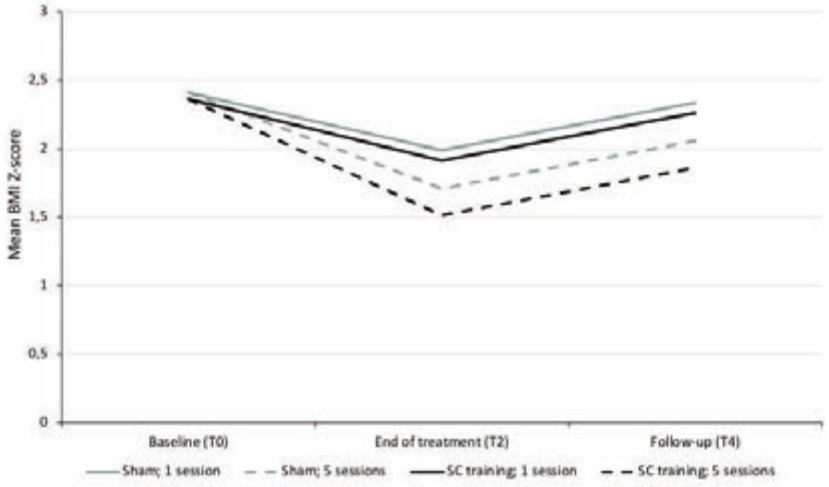


Figure 5.6: visual representation of the predicted evolution of BMI SDS in a subgroup of children aged 8-12 years old treated in residential care. This graph is based on the model in Table 2B, showing the most preferable BMI SDS evolution in those receiving the most sessions of the self-control training witnessed by the significant interaction of randomization by number of sessions (p=0.027).

When repeating the analyses with the BMI percentage relative to the 95th centile, again a positive effect of the number of self-control trainings (interaction randomization*number of sessions) was found, although this effect was (borderline) non-significant (p=0.08, see **Table 5.2C**).

Table 5.2 C) Subgroup analysis in 8- to 12-year-old children in residential care (n=22). Linear mixed model to predict the evolution of BMI percentage of the 95th centile over time by randomization condition and number of training sessions.

Parameter	Estimate	Standard error	P-value	Lower bound 95% CI	Upper bound 95% CI
Intercept	127.55	3.35	<0.001	120.26	134.84
T0	0	0			
T1	-29.64	1.92	<0.001	-33.47	-25.81
T2	-19.21	9.82	0.055	-38.85	0.43
T4	-11.30	10.73	0.3	-32.76	10.16
Randomization	-2.54	4.84	0.6	-12.54	7.47
Number of sessions	-1.22	1.19	0.3	-3.60	1.16
Randomization* number of sessions	-0.62	0.35	0.08	-1.32	0.08

Parameters indicated in bold are significant. For factors, one category was used as the reference category and has coefficient 0, whereas the other category has a coefficient, that does not equal 0. This is illustrated in the table by the factor time, where T0 is used as a reference and has coefficient 0 and the other timepoints T1-T4 have a coefficient that describes the difference from T0. The documented coefficient in this table for randomization applies to the group provided with a self-control training for randomization (compared to the sham group). Number of sessions applies to all sessions performed, both the real self-control trainings, as the trainings offered to the control group.

5.4.5 Training effect on self-control

To confirm the effect of the training in the younger aged residential participants, we assessed the effectivity of the training and its dose-response effect on self-control in this group. A simple mixed model found no changes in self-control over time, except for persistence and external eating behavior (**Table 5.3**).

Table 5.3: Evolution of self-control during treatment in the young inpatient participants as tested by a linear mixed model (n=22).

	T0	T2	T4	p-value T0 vs T2	p-value T0 vs T4
ECS: lack of impulsivity	36.1 ± 7.6	38.7 ± 6.9	36.2 ± 6.5	0.1	0.6
ECS: persistence	**38.7 ± 7.8**	**44.1 ± 6.8**	**42.3 ± 5.5**	**<0.001**	**0.002**
BRIEF: total score	125 (72-175)	106 (72-152)	116 (94-130)	0.068	0.1
BRIEF: inhibition	13 (10-27)	11 (10-22)	14 (10-17)	0.2	0.3
BRIEF: behavior regulation	38 (28-68)	35 (28-66)	37 (28-52)	0.3	0.4
DEBQ: external eating	**32.8 ± 10.1**	**23.6 ± 5.7**	**24.8 ± 7.2**	**0.001**	**0.001**
DEBQ: emotional eating	23.6 (13-65)	25.5 (13 – 63)	28.0 (13-50)	0.074	0.061

ECS = effortful control scale, BRIEF = Behavior Rating Inventory of Executive Functioning, DEBQ=Dutch Eating Behavior Questionnaire

Subsequently, in depth analysis in more complex models was performed for these two outcome variables.

Persistence: The first mixed model with persistence as outcome variable and randomization, gender and time as factors and number of sessions as covariate found no significant effect of randomization *by* time ($p>0.1$ at every timepoint) or randomization *by* number of sessions ($p=0.1$) on the evolution in persistence over time. After removal of the non-significant terms, only the effect of time was withheld, $p<0.01$, as depicted in **Table 5.4A.**

Table 5.4 A) Subgroup analysis in 8- to 12-year-old children in residential care (n=22). Final linear mixed model to predict the evolution of persistence (measured by ECS) over time.

Parameter	Estimate	Standard error	P-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	38.6	1.5	<0.001	35.5	41.6
T0	0				
T1	5.8	1.5	<0.001	2.9	8.7
T2	5.3	1.4	0.001	2.4	8.2
T4	5.4	1.6	0.001	2.3	8.5

ECS = effortful control scale. Variables that were non-significant were excluded from the final model.

External eating: Secondly, a complex mixed model was fitted incorporating the effects of randomization, gender, time and number of sessions. No significant effect of randomization *by* number of sessions or randomization *by* time was found (p=0.8 and p≥0.4 at any study visit), so these were removed from the model. A final model for the evolution in external eating is depicted in **Table 5.4B** identifying only gender and time as significant contributors of the evolution of external eating with p-values of 0.028 and <0.01.

Table 5.4 B) Subgroup analysis in 8- to 12-year-old children in residential care (n=22). Final linear mixed model to predict the evolution of external eating (measured by DEBQ) over time.

Parameter	Estimate	Standard error	P-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	28.6	2.5	<0.001	23.5	33.7
T0	0				
T1	-7.5	2.4	0.003	-12.4	-2.6
T2	-7.9	2.2	0.001	-12.3	-3.5
T4	-8.0	2.3	0.001	-12.7	-3.3
Gender	6.2	2.6	0.028	0.7	11.7

DEBQ = Dutch Eating Behavior Questionnaire. Randomization and number of sessions were excluded from the model as these were non-significant. The coefficient reported by gender indicates the difference in external eating behavior for girls compared to boys. Variables that were non-significant were excluded from the final model.

5.5 Discussion

This is the first multicenter RCT to evaluate the effect of a self-control training on BMI reduction as adjunct to available obesity treatment programs in a large pediatric population across different treatment settings.

In general, the training did not improve BMI outcome in the entire population, unlike previous research conducted by Verbeken *et al.* reporting better BMI maintenance in the self-control group compared to the control group (237). This previous study used a gamified self-control training, where most participants reported trying to score well on the tasks. In our study, a non-gamified training resulted in major challenges motivating our patients to complete the training sessions, with >25% of the children reporting the training was too demanding (238). As individual engagement is known to impact the efficacy, this might have contributed to the absence of a general effect (239). Another difference is the training tasks: Verbeken *et al.* used an inhibition and working memory task, whereas we combined an inhibition with an attention task. Possibly, the effect detected previously was explained by the working memory training rather than the inhibition training, as lately the longevity of training effects of the go-no-go task has been debated (240). Similarly, for the attention task, one adult study reports the one week maintenance of the training effect, but evidence on long-term maintenance and that this significantly alters real-life food intake/weight control behaviors could not (yet) be provided (141,146).

Secondly, an interaction of the 'received' dose of the self-control training (randomization *by* number of sessions) with the setting (favoring the inpatient center) was found. The supervision by the staff on the execution of the trainings might have contributed to the effect found only in residential care, as this guaranteed a restriction of environmental distraction and might have motivated to perform the trainings well. In the outpatient setting, caregivers were asked to supervise the training and ensure a quiet environment, however we could not objectify the compliance to these recommendations.

Thirdly, an interaction of the training effect was found with age in favor of the younger aged participants. As younger age was associated with more completed sessions, one could hypothesize that a minimum number of well-executed self-control trainings would be required before an effect can be found. At this moment, the minimal number of sessions necessary to detect an effect is yet unknown and requires further research. A second viable explanation is that the onset of puberty plays a role, as this is accompanied by an oversensitive activation of the reactive brain system, as well as a slower activation of the regulative brain system when confronted with emotional stimuli. This results in a more intense and fluctuating negative affect, which impedes overcoming impulsive behavior (241–243). Therefore, the training might have been more effective in the younger aged group, as these were not (yet) in full puberty.

When looking at training adherence, we notice a high drop-out when patients are asked to train at home. Although our outpatient participation is generally better than in previous e-health studies in this population (244,245), this remains a major challenge for successful implementation. Preceding adult studies report better participation (156,246,247), which can be explained by the offering of external rewards (247) and the patient selection (self-presenting participants specifically for the training vs children seeking general weight management treatment) (246,247). Therefore, the present study reflects more truthfully the expected participation when embedding this intervention in clinical pediatric obesity treatment programs and this real-world implementation constitutes an important strength as opposed to the preceding research evaluating almost exclusively the 'in-lab effectiveness' of these interventions in 'specifically for the training selected' individuals.

Lastly, in the 8- to 12-year-old inpatient participants (where a potential effect of the training on BMI was detected), no effect of the training on self-control was objectified by the questionnaires. A recent review on the mechanisms trained during GNG tasks describes that this task probably solely trains top-down inhibitory control at the very beginning of the training. Thereafter, the effect probably results from an affective devaluation of the no-go cues or possibly from an automatic inhibitory reaction towards these cues (248). As in our study, the questionnaires were filled in after multiple sessions, this might have limited the possibility to detect this improved inhibition. Additionally, questionnaires always carry the risk of recall bias and socially desirable answers (249). Therefore, some choose evaluations filled in by clinicians (250).

Strengths of our study include the multicenter design including a large number of participants distributed across a wide age range, the short- and long-term follow-up data, the evaluation of the training in existing clinical treatment settings and the analyses performed on both BMI SDS and BMI% relative to the p95. Nevertheless, certain limitations should be mentioned.

First, there was a considerable drop-out in both settings leading to a lower than expected number of participants available for randomization and training. To overcome this limitation, an additional 59 patients (15 outpatient, 44 inpatient) were included and a linear mixed model was used for the analysis, as these models are robust against missing data. Coinciding, a low adherence was observed. To address this limitation, we performed the mixed model analysis only on the group completing at least one session, as otherwise an effect of randomization condition was assigned to a participant who never experienced an effect of their randomization status. Additionally, the number of sessions completed was incorporated as a covariate in our statistical model to explore the dose-response relation. As previous research already demonstrated beneficial effects on self-reported weight after only 4 online training sessions in adults with obesity (156), the adjustment for the number of sessions should be considered a strength of our study.

Lastly, the presented food cues during the training were not personalized. However, the effect of the GNG training has been found to augment when the presented unhealthy cue was personalized towards the patients' food preferences (251). For the attention training, personalization is already employed in treating anxiety disorders (252) and with conflicting results in social drinkers (253,254). In obesity research, no evidence is available on whether this enhances the treatment effect, however in the study of Lawrence reporting a positive effect of an inhibition training on self-reported weight specifically selected individuals consuming the no-go snacks.

Looking at the future, researchers are encouraged to first define the optimal training form hereby answering which (combination of) self-control training tasks should be used, which frequency and duration of trainings is preferred and which motivational features are required to make the training attractive and motivating for children, for example by gamification (255), personalizing the presented food cues (251) or adjusting the reward systems to age and gender-related interests (240). Furthermore, although bad adherence results are reported across studies, little research has been devoted to identifying the best implementation strategy for online interventions within this population. As in the present trial setting was identified as a moderator of the training effect, which is probably due to the presence of external control, the role of external supervision on e-health interventions deserves to be further explored. A possible alternative would be to offer the training live by a psychologist as currently tested in adults with obesity (256). Lastly, the availability on smartphones could improve a participants' flexibility on when and how to train (156). However, the impact of these devices on adherence, potency and efficacy remains to be studied as well (156,246).

5.6 Conclusion

The benefit of embedding a computerized self-control training could not be objectified in our overall cohort, but a subgroup of younger children in residential care has potentially benefited regarding BMI reduction when considering the dose-response relation. However, as this finding only applied to a small subgroup, it should first be confirmed in future research. Finally, in future online trainings (and e-health interventions in general), we recommend to first identify suitable implementation strategies ensuring optimal participation, strategies for motivation and accessibility.

Chapter 6: Predicting treatment outcome in pediatric obesity

Parts of this chapter are adapted from:

The predictive value of adipokines and metabolic risk factors for drop-out and treatment outcome in children with obesity treated in a pediatric rehabilitation center.

Vermeiren E, Van Eyck A, Van De Maele K, Ysebaert M, Makhout S, De Guchtenaere A, Van Helvoirt M, Tanghe A, Naets T, Vervoort L, Braet C, Bruyndonckx L, De Winter B, Verhulst S, Van Hoorenbeeck K

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6.1 Abstract

Background: In- and outpatient pediatric obesity treatments have been proven effective in reducing BMI, although drop-outs and BMI regain threaten long-term results hereby impacting cost-effectiveness. Preliminary data indicate that leptin, adiponectin and cardiometabolic comorbidities might predict treatment outcome. Previous studies have mainly focused on the individual role of comorbidities, which is counterintuitive, as risk factors cluster. Therefore, in this chapter, we aimed to predict the drop-outs and treatment outcomes by pre-treatment patient characteristics extended with cardiometabolic comorbidities (individually and in total), leptin and adiponectin.

Methods: Both in- and outpatient participants were measured before treatment (n=144 and n=100) and after 12 months of treatment (n= 87 and n=70). Additionally, inpatient participants were measured six months after leaving the treatment center (n=43) and outpatient participants were measured after 24 months of treatment (n=43). At every visit, anthropometric data, a fasting venous blood sample and body composition measurements were obtained in addition to endothelial function measurements. Endpoints of the study were drop-out and change in BMI SDS.

Results: In inpatient treatment, we recruited 144 children (mean age of 14.3 $\pm$ 2.2 years, mean BMI 2.7 $\pm$ 0.4 SDS). The 57 patients dropping out during treatment and the 44 patients dropping out during aftercare had a higher pretreatment BMI compared to the patients completing treatment (mean BMI 38.3 $\pm$ 6.8 kg/m^2 vs 35.7 $\pm$ 5.5 kg/m^2) and those completing aftercare (mean BMI 34.6 $\pm$ 5.3 kg/m^2 vs 37.7 $\pm$ 6.3 kg/m^2), all $p<0.05$. A logistic regression indicated that pretreatment weight (B=-0.016, S.E. 0.008, p=0.043) and adiponectin (B=0.088, S.E. 0.032, p=0.006) were predictive for drop-out during inpatient treatment, (Nagelkerke R^2 0.15), whereas drop-out during aftercare was only predicted by age (B=-0.29, S.E.=0.09, p=0.01, Nagelkerke R^2 0.11) with aftercare attenders being younger than non-attenders (mean age 13.4 $\pm$ 2.3 years vs 14.9 $\pm$ 2.0, $p<0.05$).

Patients lost on average 1.0 ± 0.4 SDS during treatment and regained 0.4 ± 0.3 SDS posttreatment corresponding to regain of 43 ± 27% (calculated as the increase in BMI SDS posttreatment over the BMI SDS lost during treatment). A higher BMI and more comorbidities inversely predicted BMI SDS reduction during treatment, with r=-0.29, and r=-0.24, both p<0.05, explaining 12.0% of the variance. The absolute BMI SDS increase after returning home, was predicted by pretreatment leptin (r=-0.66, p=0.02) and systolic blood pressure (r=0.39, p=0.01), adjusted R^2 0.39 , whereas posttreatment BMI SDS regain was predicted by pretreatment age (r=0.5, p<0.01), leptin (r=-0.67, p<0.001) and adiponectin (r=-0.46, p=0.02), in multivariate linear regressions (adj. R^2 0.57).

In outpatient treatment, we recruited 100 children (mean age 12.0 ± 2.2, mean BMI 2.4 ± 0.4 SDS). There were no differences between the 70 children attending the one year follow-up visit and the 30 children that dropped out and drop-out during the first treatment year was only predicted by BMI reduction during the first six months (B=-0.44, S.E.= 0.21, p=0.03), (Nagelkerke R^2 0.12). Sixty children were included in the extended follow-up as 10 wished not to participate in this part of the study. Drop-out during the second year by pretreatment BMI (B=0.17, S.E.=0.07, p=0.017), (Nagelkerke R^2 0.11) with the treatment completers having a significantly lower BMI compared to the participants dropping out, e.g. 33.7 ± 5.1 kg/m^2 compared to 30.3 ± 4.1, p<0.05). Patients had a BMI that was on average 0.2 ± 0.3 SDS lower than baseline at the end of the first year and 0.3 ± 0.4 SDS lower than baseline at the end of the second year. The one- and two-year BMI SDS change was not importantly predicted by pretreatment patient or metabolic characteristics.

Conclusion: Pretreatment weight status importantly influences long-term treatment results. Metabolic comorbidities, including adipokines, seem to predict inpatient treatment outcome, however more research is needed to understand how they mediate BMI reduction. For outpatient treatment outcome, non-physical features seem to contribute more significantly.

6.2 Introduction

As indicated in **Chapter 1**, obesity tends to persist from childhood into adulthood (32) and treatment at a young age is crucial to tackle the growing obesity burden. For children, a family-centered lifestyle modification is recommended either as outpatient or in some cases residential care. Although scientific guidance on which patient performs best in which treatment setting is missing (115).

Cost effectiveness of health care expenses gains importance, as the financial sustainability of the health care systems is under pressure (257). Currently, only 5-10% of the children with obesity are referred to inpatient treatment (12). Data on inpatient care in Belgium from 2006 indicate a low cost for the families with >95% of costs covered by health insurance. Additionally, outpatient follow-up after ending residential treatment is required so expenses continue thereafter. For outpatient care, costs are lower, but patients might be faced with more direct costs depending on the number of care providers involved and the frequency of visits. Nevertheless, all the above made expenses are ineffective in reducing the long-term health expenditure if long-term treatment results are absent.

Currently, (pediatric) obesity programs are faced with two major challenges that limit long-term treatment results. A first challenge is retaining patients within the treatment program, as early drop-out is common (116,128) and premature treatment cessation lowers the chance to achieve or maintain a satisfying weight reduction (258,259). Research on predictors of drop-out in children undergoing obesity treatment varies in the predictors studied and the findings between different studies are often inconsistent. It is uncertain whether these inconsistent findings result from population or treatment differences or result from another definition or measurement method of drop-out (260). A second commonly encountered challenge is the problem of weight regain during or after outpatient treatment or after discharge from the inpatient center (130). A previous study in the Netherlands found no significant difference in BMI SDS after 2 years follow-

up between a group of children with obesity treated in residential care versus a group treated by an outpatient lifestyle intervention, even though the inpatient group lost more weight initially (117). As many studies regarding inpatient treatment outcome focus on predicting (short-term) weight loss during treatment, rather than exploring what happens after treatment cessation, evidence on predictive factors for long-term outcome is scarce.

Besides the standard patient characteristics, such as age, sex and BMI, some studies indicate a role for metabolic comorbidities as predictors of treatment outcome in children with obesity. Insulin resistance has been mostly described (261–263) and a single study has broadened the question to the predictive value of all metabolic components (264). However, to the best of our knowledge, there are no studies investigating whether the cumulative number of cardiometabolic comorbidities, for example the metabolic syndrome components, influences treatment outcome in these children.

Lastly, some adipocyte hormones such as leptin and adiponectin might have a role in predicting weight outcome as well (265–267). In **chapter 1.2.1.2.1 and 1.2.1.2.2** the physiologic actions of leptin and adiponectin have already been described. Obesity is generally characterized by hyperleptinemia and hypoadiponectinemia (67,75,76). Previous research has demonstrated the predictive potential of leptin and adiponectin regarding future BMI changes in 9-10 year old children measured three years later (265) and to short-term weight loss during treatment in children with excess weight (266,267).

Interestingly, all previous studies focused on the metabolic comorbidities and adipokines as stand-alone factors that might impact treatment outcome. This feels counterintuitive as these risk factors tend to cluster (63). Therefore, in this study we determined the predictive value of baseline patient characteristics (age, sex, adiposity) extended with cardiometabolic comorbidities, leptin and adiponectin on drop-out and short- and long-term treatment outcome in children with obesity. Predictive parameters were explored in an inpatient pediatric rehabilitation center and a tertiary outpatient pediatric obesity treatment center.

6.3 Methodology

6.3.1 Study design and participants

A pretreatment baseline assessment was planned for all patients, after which 2 follow-up visits were planned for the patients from residential care (12 months and 18 months from baseline). The patients following treatment in an outpatient setting received a follow-up visit at 3 different time points (6, 12 and 24 months from baseline). A detailed overview of the study visits by setting and the measurements conducted is depicted in **figure 6.1**.

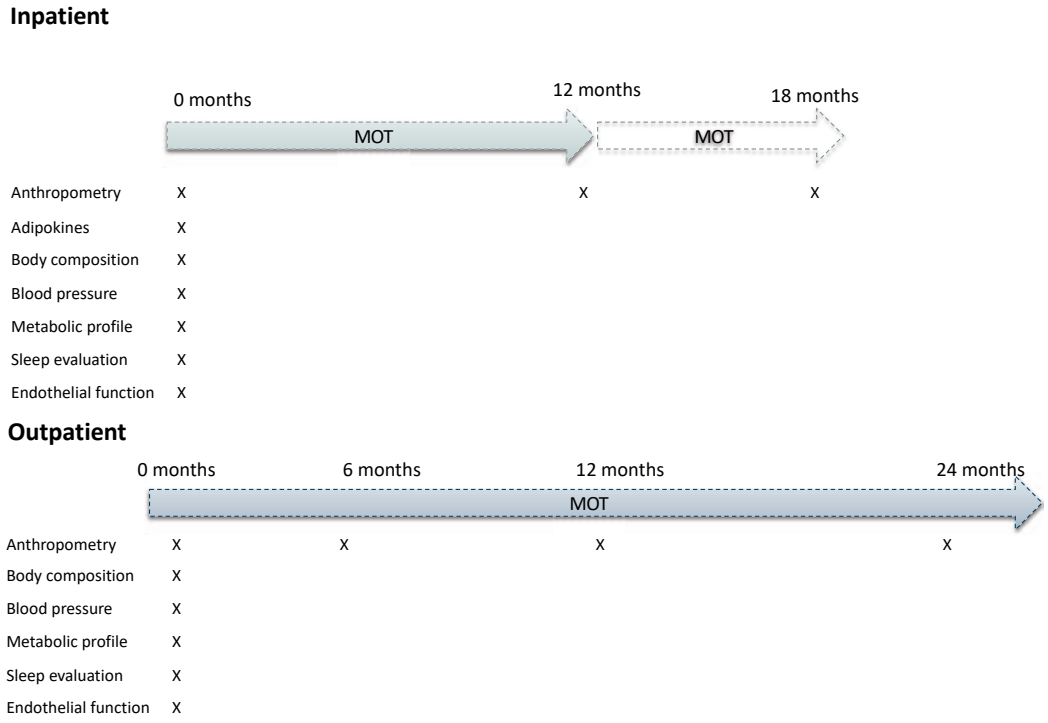

Figure 6.1: Visual representation of the study design. MOT = multidisciplinary obesity treatment.

The inclusion criteria were previously described in **chapter 3.2** and the obesity treatment programs in **chapter 3.3**.

6.3.2 Clinical evaluation

As described in **chapter 3**, anthropometric data, blood pressure, body composition, metabolic profile and endothelial function were measured. For endothelial function, parameters of interest were the maximal dilatation and the time to maximal dilatation.

The sleep evaluation of our inpatient participants was performed using a portable device, the ApneaLink air®, a reliable screening tool for sleep-disordered breathing (268). In our outpatient cohort, a one-night in-hospital polysomnography was performed, which is the golden standard for the diagnosis of sleep-disordered breathing. Parameters of interest were similar for both sleep evaluations: the obstructive apnea hypopnea index (oAHI) and the oxygen desaturation index (ODI).

6.3.2.1 Adipokines

Leptin and adiponectin were determined by a human adiponectin and leptin enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's guidelines (Invitrogen, Life Technologies, Waltham, MA, USA) on a fasting venous blood sample drawn before treatment start. The detection limit of the assay was 15.6 pg/ml for leptin and 0.5 ng/ml for adiponectin. The inter-assay coefficient of variation was 14.2% for leptin and 10.5% for adiponectin. The intra-assay coefficient of variation was <10% for all samples. Adipokines were only determined for the inpatient cohort.

6.3.2.2 Metabolic profile

Besides each risk factor separately, as described in **chapter 3.4.4**, we also determined the influence of the cumulative number of comorbidities by categorizing each of the five components of the metabolic syndrome, i.e. abdominal obesity (waist circumference), hypertriglyceridemia, lowered HDL-cholesterol, increased fasting glucose and arterial hypertension, as 'present' or 'not present' and added up the number of comorbidities present, resulting in a score for each patient ranging from 0 to 5.

Cut-off values were determined as follows:

- Triglycerides ≥ 130 mg/dl (269)
- HDL-cholesterol < 40 mg/dl (269)
- Waist circumference ≥ 90th percentile (270)
- Fasting glucose ≥ 100 mg/dl (271)
- Arterial hypertension: systolic or diastolic blood pressure ≥ 90th percentile (171)

6.3.3 Evaluation of treatment outcome

The following endpoints to assess treatment outcome were defined for inpatient care:

- drop-out during treatment and aftercare
- the BMI SDS loss during inpatient treatment
- the absolute BMI SDS change (in most cases increase) after discharge from the inpatient treatment center to six months follow-up
- the relative BMI SDS change, expressed as the percentage of lost BMI SDS points regained – six months after treatment. This relative increase was calculated as: (BMI in SDS at the second follow-up – BMI in SDS at the end of treatment)/ (BMI in SDS at baseline – BMI in SDS at the end of treatment).

The following endpoints to assess treatment outcome were defined for outpatient care:

- drop-out after one and two years of treatment
- the BMI SDS change between baseline and one year of multidisciplinary obesity treatment.
- the BMI SDS change between baseline and two years of multidisciplinary obesity treatment.

However, BMI SDS has some limitations in children and adolescents with severe obesity. Therefore, it is recommended to report more BMI derived measures (231), so therefore supplementary analyses were done with BMI (in kg/m^2) as outcome variable.

6.3.4 Statistical analysis

First, baseline patient characteristics of the patients who dropped out prematurely were compared to the group that completed the entire treatment program using the appropriate statistical tests (see **chapter 3.5**). The independent predictive values of these variables were tested using backward logistic regression. The same approach was applied to compare the baseline patient characteristics of the aftercare drop-out cases to aftercare completers.

Second, possible baseline predictors (patient characteristics, metabolic comorbidities, and adipokines) of BMI SDS change during treatment were identified by including each predictor as an independent variable in a univariate model (including the intercept) and the difference between baseline and end-of-treatment BMI SDS as the dependent variable. Significant associations are shown, and non-significant data are mentioned but not presented in a table. Subsequently, all significant univariate predictors ($p<0.05$) were combined into a multivariate linear regression model to identify independent predictors. Multicollinearity was checked by examining the variance inflation factor.

6.4 Results inpatient care

6.4.1 Study population

A total of 141 patients were included with a mean age of 14.3 $\pm$ 2.2 years and mean BMI of 36.7 $\pm$ 6.2 kg/m^2, corresponding to a mean BMI SDS of 2.7 $\pm$ 0.4. The baseline patient characteristics are depicted in **Table 6.1.**

Patients had a median of two metabolic risk factors (range 1–4) based on the cut-off values described above. All patients had a high waist circumference, 46 were hypertensive, 36 had low HDL-cholesterol, 4 had impaired glucose tolerance (based on fasting glucose), and 30 patients fulfilled the criteria of hypertriglyceridema. The number of metabolic comorbidities was associated with baseline weight ($r=0.27$, $p=0.002$), BMI ($r=0.30$, $p<0.001$), and BMI SDS ($r=0.30$, $p<0.001$) but not with age ($p=0.40$).

Pre-treatment age was significantly associated with baseline weight (r=0.61, p<0.001), BMI (r=0.53, p<0.001), and BMI SDS (r=0.40, p<0.001). Boys had a higher weight than girls (109.9 ± 28.2 kg vs 98.6 ± 20.2 kg, p=0.009), but no sex differences were found in BMI or BMI SDS (p>0.05).

Table 6.1: Baseline characteristics and comparison between patients that have completed the treatment program and follow-up and those who have not.

	Baseline	During treatment (n=144)		During aftercare (n=87 [e.g., all patients with complete treatment])	
	All	Drop-out	Complete treatment	Drop-out	Complete aftercare
N	144	57	87	44	43
Age (years)	14.3 ± 2.2	14.5 ± 2.0	14.2 ± 2.3	**14.9 ± 2.0**	**13.4 ± 2.3*****
♂/♀ ratio	60/84	28/29	32/55	14/28	18/27
Weight (kg)	103.3 ± 24.6	**109.8 ± 25.9**	**99.1 ± 22.6****	**104.5 ± 22.8**	**93.5 ± 21.1***
BMI (kg/m^2)	36.7 ± 6.2	**38.3 ± 6.8**	**35.7 ± 5.5****	**36.9 ± 5.5***	**34.4 ± 5.2***
BMI SDS (SDS)	2.7 ± 0.4	**2.8 ± 0.4**	**2.6 ± 0.4***	2.7 ± 0.4	2.6 ± 0.4
Waist (cm)	115.7 ± 14.3	**119.1 ± 14.9**	**113.4 ± 13.7***	115.3 ± 13.5	111.6 ± 14.0
Hip (cm)	119.2 ± 12.5	121.3 ± 13.1	117.8 ± 12.1	**121 ± 12.1**	**114.5 ± 11.2***
Waist-to-hip ratio	0.97 ± 0.06	0.98 ± 0.05	0.96 ± 0.06	0.96 ± 0.06	0.97 ± 0.06
Fat mass (kg)	43.3 (14.4–93.8)	46.5 (20.6–93.8)	41.8 (14.4–78.1)	**46.5 (14.4–78.1)**	**35.6 (20.5–71.4)****
Fat% (%)	44.0 ± 5.7	44.4 ± 6.0	43.7 ± 5.6	**45.0 ± 5.4**	**42.2 ± 5.5***
Lean mass (kg)	41.8 (24.9–67.9)	**44.2 ± 7.2**	**41.6 ± 8.0***	42.1 ± 7.4	41.3 ± 8.8
Lean% (%)	42.4 ± 7.5	41.9 ± 7.7	42.7 ± 7.4	**40.8 ± 7.1**	**45.0 ± 7.2***
Leptin (μg/L)	31.98 (6.33–81.26)	28.9 (6.3–81.3)	34.0 (7.7–70.6)	34.1 (9.4–66.0)	29.9 (7.7–70.6)
Adiponectin (μg/mL)	11.9 (1.47–41.87)	**10.7 (4.4–27.5)**	**14.3 (1.5–30.7)***	15.9 (5.4–41.9)	12.4 (1.5–41.0)
Systolic BP (SDS)	0.97 ± 0.87	0.94 ± 1.04	1.0 ± 0.7	0.9 ± 0.8	1.0 ± 0.7
Diastolic BP (SDS)	0.27 ± 0.71	0.23 ± 0.78	0.30 ± 0.66	0.3 ± 0.6	0.3 ± 0.7
Glucose (mg/dL)	86 ± 7	**85 ± 7**	**88 ± 7***	87 ± 8	88 ± 6
Insulin (pmol/L)	162.9 ± 72.1	166.8 ± 78.5	159.3 ± 68.0	146.4 ± 62.4	173.2 ± 71.6
HOMA-IR (mass units)	5.4 (1.2–16.2)	5.4 (1.2–16.1)	5.4 (1.5–14.1)	4.8 (1.5–11.0)	5.9 (2.2–14.1)

Table 6.1 *continued*	Baseline	During treatment (n=144)		During aftercare (n=87 [e.g., all patients with complete treatment])	
	All	Drop-out (n=57)	Complete treatment (n=87)	Drop-out (n=44)	Complete aftercare (n=43)
Total cholesterol (mg/dL)	154 ± 30	153 ± 33	155 ± 28	156 ± 25	155 ± 31
HDL-cholesterol (mg/dL)	47 ± 10	47 ± 11	47 ± 10	48 ± 11	46 ± 8
LDL-cholesterol (mg/dL)	87 ± 27	86 ± 29	88 ± 26	88 ± 24	88 ± 29
Triglycerides (mg/dl)	90 (39–263)	88 (39–263)	92.5 (49–245)	85 (49–209)	99 (52–245)
Metabolic risk factors (n)	2 (1–4)	2(1–4)	2(1–3)	2 (1–3)	1 (1–3)
Hs-CRP (mg/L)	4.6 (0.3–40.2)	3.5 (0.3–40.2)	3.3 (0.3–21.8)	2.6 (0.3–18.7)	3.7 (0.3–21.8)
AST (U/L)	25 (13–110)	27 (13–100)	25 (14–110)	24 (14–110)	25 (16–95)
ALT (U/L)	22 (5–64)	**27 (11–64)**	**21 (5–47)***	18 (5–47)	21 (12–45)
AST/ALT	0.98 ± 0.30	**0.91 ± 0.29**	**1.03 ± 0.30***	0.99 ± 0.32	1.07 ± 0.27
OAHI (/h)	2.7 (0.4–56.9)	2.8 (0.5–12.7)	2.5 (0.4–56.9)	2.3 (0.5–56.9)	3.0 (0.4–31.8)
ODI (/h)	3.0 (0.1–47.3)	2.35 (0.1–47.3)	1.8 (0.1–11.2)	1.3 (0.1–11.2)	2.1 (0.3–8.3)
Maximal dilatation of the endothelium	1.30 ± 0.27	1.29 ± 0.28	1.30 ± 0.27	1.30 ± 0.29	1.30 ± 0.26
Endothelial time to maximal dilatation (s)	181.6 ± 59.7	170 ± 56	188 ± 61	178 ± 68	199 ± 52

The parameters in bold are significantly different between groups. *significantly different between groups p≤0.05, ** significantly different between groups p≤0.01, *** significantly different between groups p≤0.001. AST = aspartate aminotransferase; ALT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; HOMA-IR = homeostatic model for the assessment of insulin resistance; hs-CRP = high-sensitivity C-reactive protein; LDL =low-density lipoprotein; OAHI = obstructive apnea–hypopnea index; ODI = oxygen desaturation index; SDS = standard deviation score.

6.4.2 Predictors of drop-out during inpatient treatment and aftercare

Of the 144 patients included at baseline, 87 completed the 12-month inpatient treatment program, corresponding to a dropout rate of 40% (every patient who did not complete the entire treatment was considered a dropout, independent of their duration of stay). Patients who prematurely left the treatment center had a higher weight, BMI, BMI SDS, and waist circumference at baseline than those who completed the entire program as shown in **Table 6.1.** Additionally, a higher ALT (median, 27 U/L (11–64) vs 21 U/L (5–47); p=0.017), lower AST/ALT ratio (mean, 0.91 $\pm$ 0.29 vs 1.03 $\pm$ 0.30; p=0.021), and lower adiponectin levels (median, 10.7 (4.4–27.5) μg/mL vs median, 14.3 (1.5–30.7) μg/mL; p=0.021) were found in the group that dropped out before treatment was completed.

A logistic regression predicting **dropout during inpatient treatment** was built, including weight, AST/ALT ratio, fasting glucose, and adiponectin. As a representation of the anthropometric variables, weight was included as a predictor in the model, as this anthropometric variable most significantly differed between completers and dropouts based on the p-value and model fit (Nagelkerke R Square). For the same reason, the AST/ALT ratio was included in the model instead of AST or ALT values. After backward elimination of non-significant terms, only **weight and adiponectin** were retained with a p-value of 0.04 and 0.006, respectively (Nagelkerke R^2 0.15).

Six months after discharge from the inpatient treatment center, 43 of the 87 patients participated in the follow-up visit (49.4%). The patients who attended the follow-up visit were generally younger than those who did not attend the last visit (13.4 $\pm$ 2.3 years vs 14.9 $\pm$ 2.0 years respectively; p=0.001) and had a lower weight and BMI before treatment initiation (**Table 6.1**). There were no differences in sex (p=0.7) or in any cardiometabolic parameters between those attending aftercare and those who did not (all p>0.05). In a logistic regression predicting **dropout during aftercare** by pre-treatment age and weight, only **age** was significant (B=0.29, S.E. 0.09, p=0.01 and Nagelkerke R^2 0.11).

6.4.3 BMI evolution during and after inpatient treatment

The 87 patients who completed the entire treatment program reduced their BMI by 8.6 ± 2.9 kg/m^2 corresponding to 1.0 ± 0.4 SDS, p<0.001. The 43 patients attending the follow-up visit 6 months after ending treatment regained on average 3.3 ± 2.2 kg/m^2 corresponding to 0.4 ± 0.3 SDS compared to the end of treatment (p<0.001)**.** When correcting for lost weight during treatment, a relative BMI regain of 43 ± 27% was found. Nevertheless, there was high interindividual variability ranging from an additional loss of 27% to a complete regain of 102% relative to the previous BMI SDS reduction. On average, patients had lost 5.3 ± 3.2 kg/m^2 corresponding to 0.6 ± 0.4 SDS from baseline. The evolution of the other anthropometric variables is presented in **Table 6.2**

Table 6.2: Evolution of anthropometric and body composition parameters during and after treatment

Parameter	Baseline	After treatment (12 months)	Follow-up visit (18 months)
N	144	87	43
Weight (kg)	103.3 ± 24.6	77.2 ± 16.0*	82 ± 18.2*,#
BMI (kg/m^2)	36.7 ± 6.2	27.1 ± 4.2*	29.1 ± 5.5*,#
BMI SDS	2.7 ± 0.4	1.7 ± 0.6*	1.9 ± 0.6*,#
Fat mass (kg)	43.3 (14.4–93.8)	24.4 (8.1–53.8)*	29.4 (12.5–59.2)*,#
Fat% (%)	44.0 ± 5.7	32.6 ± 8.2*	36.4 ± 7.6*,#
Lean mass (kg)	41.8 (24.9–67.9)	41.3 (27.4–71.4)*	38.5 (25.9–70.0)
Lean% (%)	42.4 ± 7.5	56.3 ± 10.7*	51.7 ± 9.7*,#

*Significantly different from baseline; #significantly different from 12 months. Analyses were performed using a linear mixed model. For pairwise comparisons, post hoc Bonferroni correction was used. BMI = body mass index; SDS =standard deviation.

6.4.4 Predictors of BMI SDS change during and after inpatient treatment

The BMI SDS decrease during inpatient treatment was inversely associated with baseline weight status, cumulative number of metabolic risk factors and AST/ALT ratio). The absolute change in BMI SDS (in case of most patients, an increase) after inpatient treatment was positively associated with systolic blood pressure and inversely with baseline leptin and total cholesterol and the relative BMI SDS regained 6 months after treatment was associated with age, systolic blood pressure, number of metabolic comorbidities, leptin level, and adiponectin level. No sex differences were found for BMI change during or after inpatient treatment. All correlations are depicted in **Table 6.3**

Table 6.3. Partial correlation coefficients from univariate linear regressions between baseline variables and treatment outcome

	BMI SDS reduction during treatment	**Absolute BMI SDS change post-treatment**	**Relative BMI SDS change post-treatment**
Age	n.s.	n.s.	r= 0.33*
Weight	r=-0.25*	n.s.	n.s.
BMI	r=-0.31**	n.s.	n.s.
BMI SDS	n.s.	n.s.	n.s.
Waist	r=-0.24*	n.s.	n.s.
Hip	r=-0.25*	n.s.	n.s.
Fat mass	r=-0.27*	n.s.	n.s.
Fat%	n.s.	n.s.	n.s.
Lean mass	n.s.	n.s.	n.s.
Lean%	n.s.	n.s.	n.s.
Systolic BP (SDS)	n.s.	r=0.36*	r=0.43**
AST/ALT	r=0.26*	n.s.	n.s.
Total cholesterol	n.s.	r=-0.33 *	n.s.
Metabolic risk factors (n)	r=-0.26*	n.s.	r=0.39*
Leptin	n.s.	r=-0.54**	r=-0.45**
Adiponectin	n.s.	n.s.	r=-0.43*

*significant with p<0.05. **significant with p<0.01Metabolic variables not mentioned in the table did not correlate significantly with any of the three outcome variables. AST = aspartate aminotransferase; ALT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; SDS = standard deviation score; n. s. = non-significant

A linear regression model to predict **BMI SDS reduction during inpatient treatment** was created with pre-treatment BMI, number of metabolic risk factors and AST/ALT ratio as independent predictors. After removing non-significant terms, only **BMI and the number of metabolic risk factors** were retained, explaining 12.0% of the variance (**Table 6.4A**).

In the model for **absolute BMI SDS change after treatment** systolic blood pressure, total cholesterol and leptin were included. After removing non-significant terms, the model revealed a significant effect of **leptin level** (p=0.02) and **systolic blood pressure** (p=0.01), which explained 38% of the total variance (**Table 6.4B**).

Lastly, age, number of metabolic risk factors, leptin and adiponectin were tested as predictors of the **relative BMI SDS change after treatment**. Systolic blood pressure was not included, as this variable was already incorporated into the number of metabolic comorbidities, and the latter correlated more strongly and significantly. **Age, leptin, and adiponectin** were found significant predictors of this relative BMI SDS increase after non-significant terms were removed. This model explained 57% of the variance (**Table 6.4C**).

Table 6.4. Linear regressions after removal of non-significant terms identifying pre-treatment factors predictive for BMI SDS loss during inpatient treatment (n=87) and for absolute BMI SDS change (B) and BMI SDS regain (C) after inpatient treatment (n=43).

	r	p-value	Adj. R^2
A)			0.12
Intercept		<0.001	
BMI (kg/m^2)	-0.29	**0.01**	
Metabolic risk factors	-0.24	**0.04**	
B)			0.39
Intercept		0.003	
Leptin	-0.66	**0.02**	
SBP (SDS)	0.39	**0.01**	
C)			0.57
Intercept		0.2	
Age (years)	0.50	**0.01**	
Adiponectin (μg/mL)	-0.67	**0.02**	
Leptin (μg/L)	-0.46	**<0.001**	

Using the same approach, the analyses were repeated but with BMI change instead of BMI SDS change. **Table 6.5** depicts the final results. **Figure 6.2** compares the findings on BMI SDS change with those on BMI change for patients in inpatient care.

Table 6.5: Final linear regression models to identify predictors of BMI (in kg/m^2) decrease during inpatient treatment (A), of absolute BMI (in kg/m^2) change 6 months after treatment (B) and relative BMI change (in %) 6 months after treatment (C).

	r	p-value	Adj. R^2
A)			0.525
Intercept		0.076	
Age at baseline	-0.26	**0.018**	
Male sex	0.34	**0.001**	
Pretreatment BMI	0.68	**<0.001**	
B)			0.575
Intercept		0.3	
Age at baseline	0.56	**0.002**	
Leptin	-0.64	**<0.001**	
Adiponectin	-0.47	**0.014**	
C)			0.529
Intercept		0.4	
Age at baseline	0.56	**0.008**	
Leptin	-0.64	**0.001**	
Adiponectin	-0.47	**0.016**	

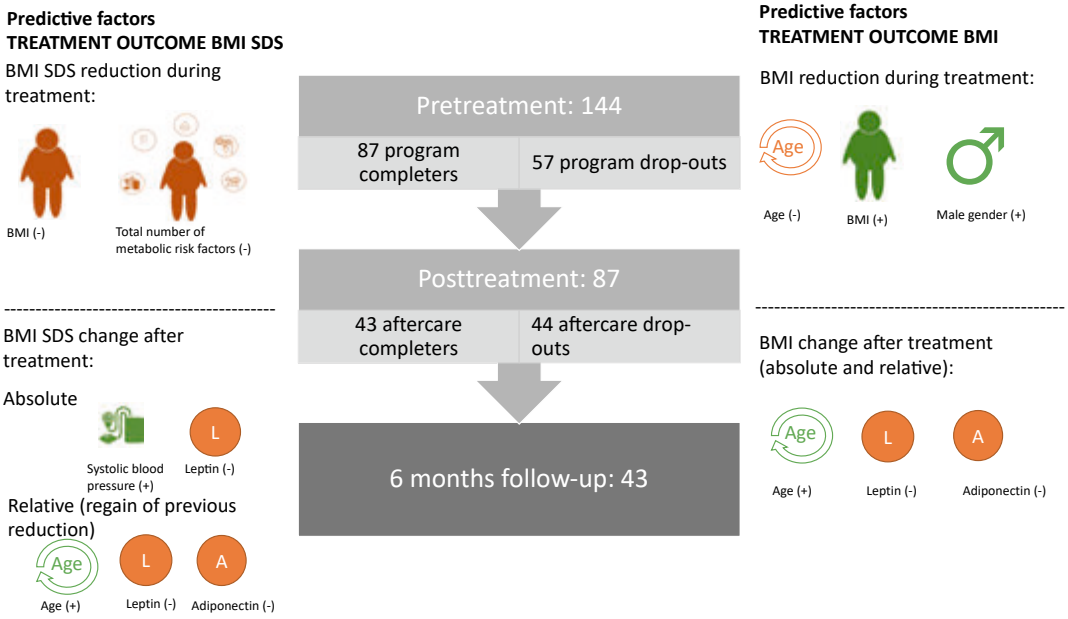

Figure 6.2: The middle panel represents the number of study patients at every visit. The left side depicts the factors predictive of the treatment outcomes in BMI SDS whereas the right side indicates the factors predictive of treatment outcomes in BMI. + (green) or – (orange) indicates whether the factor is positively or inversely predictive of treatment outcome.

6.5 Results outpatient care

6.5.1 Study population

One hundred participants were included with a mean age of 12.0 ± 2.2 years, a mean BMI of 31.6 ± 4.7 kg/m^2, corresponding to a mean BMI SDS of 2.4 ± 0.4. Baseline patient characteristics are depicted in **Table 6.6**.

Patients had a median of 2 metabolic risk factors (range 0 - 5). All participants but one had an increased waist circumference, 25 were hypertensive, 19 had a lowered HDL-cholesterol, 5 an impaired glucose tolerance (based on fasting glucose) and 31 patients suffered from hypertriglyceridemia. The number of metabolic comorbidities related significantly with baseline weight (r=0.20, p=0.047), BMI (r=0.24, p=0.017) and BMI SDS (r=0.22, p=0.032), but not with age (p=0.3). Treatment with metformin for increased glucose or insulin values was started in 86 of the 100 participants.

Older participants had more severe obesity, witnessed by associations between age and baseline weight (r=0.77, p<0.001), BMI (r=0.58, p<0.001) and a borderline non-significant correlation with BMI SDS (r=0.19, p=0.07), but no sex differences were found.

Table 6.6: Baseline characteristics and comparison between patients that have completed the follow-up visits at 12 and 24 months and those who have not.

	Baseline	12 months		24 months	
	All	Drop-out	Complete treatment	Drop-out	Complete treatment
N	100	30	70	17	43
Age (years)	12.0 ± 2.2	12.0 ± 2.0	12.0 ± 2.2	12.4 ± 2.5	11.7 ± 2.0
♂/♀ ratio	49/51	12/18	37/33	12/5	22/21
Weight (kg)	81.0 ± 20.7	80.8 ± 16.7	81.1 ± 22.3	89.2 ± 22.4	77.9 ± 20.2
BMI (kg/m^2)	31.6 ± 4.7	31.8 ± 3.6	31.5 ± 5.2	**33.7 ± 5.1**	**30.3 ± 4.1**
BMI SDS (SDS)	2.4 ± 0.4	2.4 ± 0.4	2.4 ± 0.4	**2.6 ± 0.4**	**2.4 ± 0.3**
Waist (cm)	92.5 ± 11.6	92.5 ± 9.0	92.5 ± 12.6	98 (65 – 118)	91.0 (75.5 – 115.0)
Hip (cm)	106.3 ± 13.0	106.6 ± 14.0	105.6 ± 10.4	111.7 ± 13.7	104.6 ± 12.5
Waist-to-hip ratio	0.87 ± 0.06	0.88 ± 0.07	0.87 ± 0.06	0.86 ± 0.08	0.87 ± 0.05
Fat mass (kg)	33.8 ± 11.9	33.0 ± 9.2	34.1 ± 13.0	**39.9 ± 13.1**	**31.4 ± 10.6**
Fat% (%)	40.7 ± 5.3	40.4 ± 4.8	40.8 ± 5.5	**43.8 ± 5.2**	**39.6 ± 4.7**
Lean mass (kg)	37.1 ± 7.3	37.9 ± 6.9	36.8 ± 7.5	37.1 ± 7.6	36.7 ± 7.7
Lean% (%)	46.8 ± 6.8	47.4 ± 6.2	46.5 ± 7.0	**42.8 ± 6.6**	**48.1 ± 6.0**
Systolic BP (%)	69 (3 – 99)	58 (3 – 98)	72 (3 – 99)	78 (8 – 99)	70 (8 – 99)
Diastolic BP (%)	54 (4 – 99)	47 (4 – 92)	50 (6 – 99)	74 (21 – 99)	47 (6 – 99)
Glucose (mg/dl)	88 ± 7	89 ± 8	87 ± 7	86 ± 6	86 ± 7
Insulin (pmol/l)	183 (37 – 533)	191 (65 – 533)	178.5 (37 – 526)	179 (75 – 363)	183 (37 – 526)
HOMA-IR	5.5 (1.0 – 19.3)	5.8 (2.0 – 18.0)	5.4 (1.1 – 19.3)	5.6 (2.0 – 11.0)	5.6 (1.1 – 19.3)
Total cholesterol (mg/dl	165 ± 31	166 ± 32	164 ± 31	170 ± 30	161 ± 31
HDL-cholesterol (mg/dl)	48 ± 11	49 ± 13	48 ± 9	47 ± 9	48 ± 9
LDL-cholesterol (mg/dl)	93 ± 26	93 ± 27	94 ± 26	89 (59 – 151)	94 (31 – 149)
Triglycerides (mg/dl)	92 (29 – 284)	79 (43 – 236)	87 (35 – 305)	104 (57 – 217)	89 (38 – 239)
Metabolic risk factors (n°)	2 (0 – 5)	1 (1 - 4)	2 (0 - 5)	2 (0 – 4)	1 (1 – 5)

Table 6.6 *continued*	Baseline	12 months		24 months	
	All (n=100)	Drop-out (n=30)	Complete Treatment (n=70)	Drop-out (n=17)	Complete Treatment (n=43)
Hs-CRP (mg/l)	2.1 (0.2 – 12.0)	2.6 (0.3 – 9.5)	2.0 (0.2 -12.0)	3.6 (0.3 – 12.0)	1.5 (0.2 – 7.0)
AST (U/l)	21 (11 - 53)	20 (11 – 53)	22 (11-43)	23 ± 6	22 ± 7
ALT (U/l)	27 (12 – 68)	26 (12 – 63)	27 (15 – 68)	33 (15 – 54)	26 (15 – 68)
AST/ALT	0.74 (0.39 - 1.77)	0.68 (0.44 – 1.77)	0.77 (0.39 – 1.34)	0.78 ± 0.29	0.81 ± 0.22
OAHI (/hour)	0.6 (0.0 – 14.4)	0.3 (0.0 – 5.6)	0.6 (0.0 -14.4)	**1.0 (0.1 – 14.4)**	**0.5 (0.0 – 6.1)**
ODI (/hour)	0.4 (0.0 – 6.9)	0.4 (0.0 – 5.1)	0.3 (0.0 – 6.9)	0.5 (0.0 – 6.9)	0.3 (0.0 – 4.4)
Maximal dilatation	1.4 ± 0.4	1.5 ± 0.4	1.4 ± 0.3	1.4 (1.1 – 2.3)	1.3 (1.1 – 2.5)
Time to maximal dilatation (s)	195 (45 - 285)	195 (45 – 285)	165 (45 – 285)	165 (135 – 285)	195 (45 – 285)

Parameters in bold are significantly different between groups. *significantly different between groups p≤0.05, **significantly different between groups p≤0.01, ***significantly different between groups p≤0.001. BP = blood pressure. 70 patients completed one year of outpatient treatment, but only 60 are analyzed for the second year of outpatient treatment since 10 patients had not signed the informed consent for the extended follow-up.

6.5.2 Drop-out during the first and second year of outpatient treatment

As visually depicted in the flowchart of **Figure 6.3**, 70 patients attended the 12-months follow-up visit, corresponding to a drop-out rate of 30%. Sixty participants were included for the two year follow-up, as 10 patients did not sign the informed consent for the extension study. Of the 60 participants, 17 participants ended treatment and 43 completed the entire 2-year follow-up. Motives for dropping out are listed in **Table 6.7** Interestingly, whereas initially loss of motivation is an important motive in the first year of treatment, we see that during in the second year of treatment motivational drop-out is only found in a minority of the participants and social motives are attributed to half of the drop-outs.

Table 6.7: overview of motives for dropping out of treatment in outpatient care

First year	N	Second year	N
Loss of motivation	21	Loss of motivation	6
Start inpatient treatment	3	Start of inpatient treatment	3
Travel distance	2	Social motives (i.e. changes	6
Endocrinopathy	1	In family situation,	
Reached normal weight	1	financial…)	
Parental health problems	1	Transition to adult clinic	1
Other	1	Unknown	1

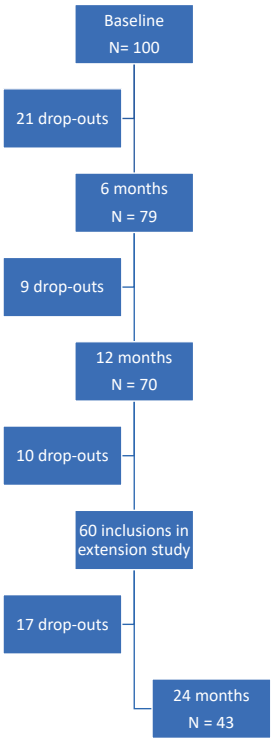

Figure 6.3: Flowchart showing participant flow throughout the study. The extension study refers to the extended follow-up for the cohort in the Antwerp University Hospital as written in **Chapter 3.1.**

No differences were found in any of the patient characteristics or metabolic risk factors between the 30 participants that dropped out before 12 months of treatment and those that retained in treatment for at least one year, as can be seen in **Table 6.6**. Analyses were repeated comparing only the 21 motivational drop-outs with the participants that completed the program, but results remained unchanged. Although not our original intent, we further explored whether the treatment success during the first 6 months of treatment had an impact on the drop-out at 12 months.

Our results showed that the 70 participants completing the one-year follow-up had more reduction in BMI in the initial 6 months compared to the 9 participants attending the 6 months follow-up but dropping out by 12 months, i.e. a BMI reduction of -1.3 ± 1.9 kg/m^2 compared to + 0.2 ± 0.8 kg/m^2, p=0.006 and p<0.001 respectively. A logistic regression with **drop-out after one year** as outcome, revealed a significant effect for **BMI reduction during the first six months** (p=0.03), Nagelkerke R^2 0.12.

The 17 participants that dropped out during the second year of treatment had generally more severe obesity and had a higher oAHI measured by polysomnography at baseline compared to those that were retained in treatment, see **Table 6.6**. No difference was found in initial reduction between the participants dropping out by 24 months compared to those completing the second year of treatment (p=0.075). In a logistic regression predicting **drop-out in the second year** by pretreatment BMI (in kg/m^2) and oAHI on polysomnography, only **BMI** remained significant (p=0.017), Nagelkerke R^2 0.11.

6.5.3 Predictors of BMI (SDS) reduction during the first and second year of outpatient treatment

The 70 participants who completed the one-year follow-up visit significantly reduced their BMI by 0.8 ± 2.5 kg/m^2, corresponding to 0.2 ± 0.3 SDS and the 43 remaining patients by 1.0 ± 3.3 kg/m^2 after 2 years corresponding to 0.3 ± 0.4 SDS compared by baseline. The evolution in other anthropometric variables is depicted in **Table 6.8**.

Table 6.8: evolution of anthropometry and body composition during treatment

Parameter	Baseline	After 12 months	After 24 months
N	100	70	43
Weight (kg)	81.0 ± 20.7	83.6 ± 20.9*	82.4 ± 15.4
BMI (kg/m^2)	31.6 ± 4.7	30.7 ± 5.5*	29.3 ± 4.4
BMI SDS	2.4 ± 0.4	2.2 ± 0.5*	2.1 ± 0.5
Fat mass (kg)	33.8 ± 11.9	34.1 ± 13.0	31.4 ± 10.6
Fat% (%)	40.7 ± 5.3	40.8 ± 5.5	39.6 ± 4.7
Lean mass (kg)	37.1 ± 7.3	36.8 ± 7.5	36.7 ± 7.7
Lean% (%)	46.8 ± 6.8	46.5 ± 7.0	48.1 ± 6.0

* significantly different from baseline, # significantly different from 12 months

The **BMI SDS decrease after one year of outpatient treatment** was only found to be predicted by **baseline HDL-cholesterol** as tested in univariate models, with r=0.26 and p=0.03 resulting in an explained proportion of the variance of 2.1%. None of the other patient characteristics or metabolic comorbidities related significantly to the decrease in BMI SDS.

The overall difference in **BMI SDS after 2 years of treatment** was **not associated with any of the patient characteristics or metabolic comorbidities** (p>0.05).

These analyses were repeated but with change in BMI as outcome variable instead of change in BMI SDS. The **BMI change during the first year** of treatment was only associated with pretreatment **lean mass** (r=0.28, p=0.02) in a univariate linear regression accounting for 6.6% of the explained variance. A borderline non-significant difference in BMI was found between the 59 patients who received treatment with metformin for deregulations in their glucose metabolism compared to the 11 participants who did not receive metformin (p=0.054). The **BMI difference between baseline and 24 months** of treatment was significantly predicted by **gender, waist and number of metabolic risk factors**, as depicted in **Table 6.9**.

Figure 6.4 compares the findings on BMI SDS change with those on BMI change for patients in outpatient care.

Table 6.9: Final linear regression models to identify predictors of BMI (in kg/m^2) decrease during two years of outpatient treatment.

	r	p-value	Adj. R^2
			0.362
Intercept		<0.001	
Waist	0.53	**<0.001**	
Male sex	0.42	**0.009**	
Number of metabolic risk factors	0.32	**0.05**	

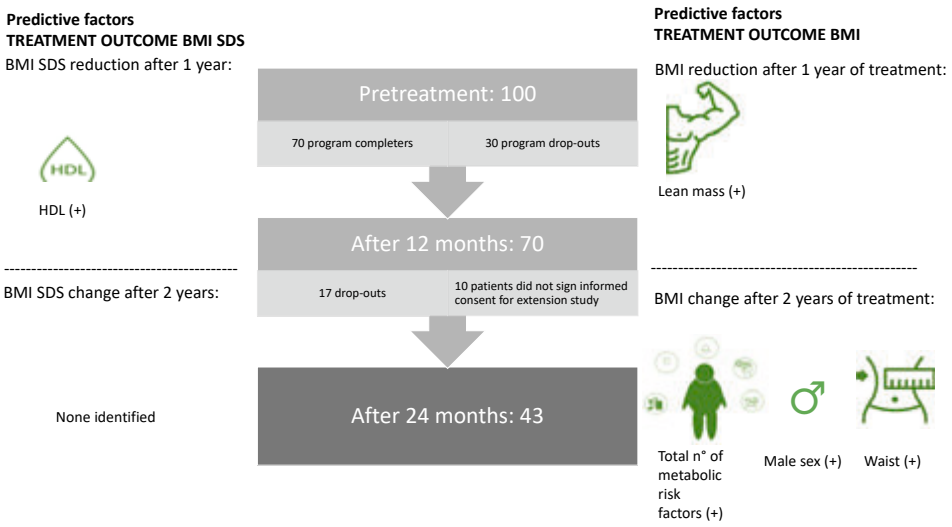

Figure 6.4: The middle panel represents the number of study patients at every visit. The left side depicts the factors predictive of the treatment outcome in BMI SDS whereas the right side indicates the factors predictive of treatment outcomes in BMI. All factors were positively predictive of treatment outcome.

6.6 Discussion

The present study explored the predictive value of baseline patient characteristics, pretreatment comorbidities for treatment drop-out, as well as short- and long-term treatment outcome in a large cohort of Belgian children with obesity treated in either a pediatric rehabilitation center or a tertiary outpatient obesity treatment center.

6.6.1 Drop-out

First, we have identified factors predictive for drop-out. An overview of our findings is presented in **Table 6.10.**

Table 6.10: overview of the predictive factors identified by logistic regression for drop-out in each setting

Inpatient	Difference drop-out group with non-drop-out	Significant in logistic regression (0 = complete treatment, 1 = drop-out)	Nagelkerke R^2
During treatment	Higher weight, BMI, BMI SDS, waist circumference, high ALT, lower AST/ALT ratio and adiponectin	Weight (+) Adiponectin (-)	0.15
During aftercare	Older, higher weight and BMI	Age (+)	0.11
Outpatient			
1 year reduction	/	Initial BMI loss (-)	0.12
2 year reduction	Higher BMI, BMI SDS, fat mass and %, lean mass and OAHI	BMI (+)	0.11

Our study showed that children with more severe obesity had a higher risk of drop-out during inpatient treatment and during the residential aftercare program (as age was related to higher BMI), as well as during the second year of outpatient treatment. A previous study conducted 6 years earlier in the same inpatient facility described a higher fat% in patients dropping out (272) and another inpatient study in 7-13 year old children identified initial weight status and weight loss as predictive for drop-out after 6 and 12 months (273), explaining 14-16% of the variance. Also in outpatient programs, obesity severity was previously documented to affect drop-out. For instance a previous RCT in 6-9 year old children reported a higher BMI SDS, waist circumference and older age in children dropping out after 1 year (274), similar to another RCT where children aged 5 – 10 years old dropping out by 9 months had higher pretreatment BMIs (275).

The finding that those most in need of treatment have the highest risk of drop-out has been described as the 'attrition paradox' (276). As premature treatment cessation and drop-out during aftercare are risk factors for poorer treatment outcome (116,258,259,277,278), our results indicate a pessimistic future for patients with the most severe form of obesity. Therefore, strategies focused on retaining these at-risk individuals during treatment and aftercare should urgently be developed. For inpatient settings, no studies on preventive interventions to retain individuals during treatment and aftercare have been conducted. In contrast, outpatient some successes have been booked (279), by implementing reminder phone calls, offering an orientation session before treatment start or sending goal-setting text messages (280–282). In future research, it would be interesting to study whether these interventions could be successfully implemented to improve aftercare attendance after inpatient treatment as well. Furthermore, due to COVID-19, online health care is rapidly evolving and might overcome commonly experienced barriers related to physical distance, (travel) time, or missed work/school (283). Positive results with online provided care in the context of pediatric obesity have been previously reported for communities facing difficulties with health care access (284,285). As the inpatient treatment center in our study was situated in a remote corner of the country, online interventions could improve aftercare attendance here and are in fact currently being used due to the COVID-19 pandemic.

Interestingly, opposed to the above-named risk factors for drop-out, none of the patient characteristics was predictive of one-year treatment drop-out in the outpatient setting. Although this was not part of the original research question, we found that the participants still participating in treatment after 1 year of outpatient obesity treatment were those with a greater BMI reduction during the first six months. These findings confirm the results of the DIRECT trial in adults with obesity stating that initial 6-month reduction in weight is the main predictor of long-term retention in weight programs (286). Other adult studies also report that the preceding weight loss is a risk factor for drop-out, for example weight-loss failure after 1 month predicted 2 month drop-out in the study by Alexander and co-workers (287).

Similarly, Perna *et al*. found that weight loss during the first 3 months was the main predictor of drop-out at 6 and 12 months for adults treated in an outpatient endocrinology department (288). In a 2011 review, 5 out of 6 studies associated lower early weight loss to higher drop-out rates (129). All of these findings above indicate that early weight loss importantly predicts long-term retention and indicates why retaining participants previously treated in inpatient care after their transition to outpatient (after)care is so difficult, as they are known to generally experience weight re-increase after returning home (117). These data illustrate the complexity of the interplay between treatment drop-out and treatment response in outpatient centers. On one hand, a low response to treatment seems a risk factor for drop-out, and on the other hand non-attendance is associated with a poorer weight outcome (289–291) creating a vicious cycle. Therefore, early treatment redirection should be considered if treatment is unsuccessful (292), for example by referring to an inpatient center, by changing the dietetic approach or by providing additional pharmacologic support with some of the newly emerging therapies.

Lastly, we have provided an overview of the reasons causing drop-out in our outpatient cohort. During the first year of treatment, we found that 70% of the drop-outs was reported to be due to a loss of motivation, which might be related to initial treatment success in some participants as discussed above. Interestingly, during the second year of treatment, only 6 out of 17 participants dropped out due to motivational issues and equally as many participants dropped out due to social reasons (family situation, conviction, financial reasons). As drop-out from obesity treatment is often thought to result simply from a lack of motivation, our data indicate that often social motives contribute. As our data are coming only from a small group of outpatient participants, they should only serve to raise awareness and encourage other researchers to keep track of the reasons for premature termination of treatment programs as with this knowledge effective preventive strategies or useful program modifications could be developed.

6.6.2 Predictors of BMI evolution

Second, we identified factors predictive for BMI SDS change during and after treatment. An overview of our findings is presented in **Table 6.11.**

Table 6.11: overview of the predictive factors identified for BMI evolution by setting and outcome measure.

Inpatient		Adj. R^2		Adj. R^2
	BMI SDS		BMI	
Reduction	Pretreatment BMI (-) N° of metabolic risk factors (-)	0.12	Age (-) Male gender (+) Pretreatment BMI (+)	0.53
Absolute re-increase	Systolic blood pressure (+) Leptin (-)	0.39	Age (+) Leptin (-) Adiponectin (-)	0.58
Relative regain (%)	Age (+) Leptin (-) Adiponectin (-)	0.57	Age (+) Leptin (-) Adiponectin (-)	0.53
Outpatient				
1 year reduction	HDL-cholesterol (+)	0.02	Lean mass (+)	0.07
2 year reduction	/		Waist (+) Male gender (+) N° metabolic risk factors (+)	0.36

This is the first study to report the influence of the total number of weight-related comorbidities on BMI reduction. Interestingly, we see a negative effect of the number of metabolic comorbidities on BMI SDS reduction during inpatient treatment, whereas we see more BMI reduction in the outpatient cohort. For the outpatient group, this can be partly explained by the treatment goals set. For younger children with only a mild-to-moderate form of obesity in absence of coexisting comorbidities, the treatment can be targeted at BMI stabilization, whereas in those with a more severe form of obesity (especially when accompanied with comorbidities) the focus of treatment will be on losing weight (24).

Therefore, the finding that a higher initial BMI and more metabolic comorbidities are associated with more BMI reduction might indicate that our outpatient treatment is successful in obtaining weight loss in those that need it most if they are retained in treatment. Contrarily, our inpatient data indicate that a worse pretreatment metabolic profile relates to less BMI reduction during stay and more posttreatment BMI regain, supporting a previous study reporting individual negative associations between metabolic syndrome markers and treatment outcome (264), indicating again that current pediatric obesity treatment is unfeasible for the patients most in need of treatment.

Regarding BMI, some studies confirm that a higher initial weight status negatively impacts weight loss (293–295), whereas others report an opposite association (296–300). A possible explanation for these conflicting findings is the observed drop-out of patients with most severe obesity, creating a bias in the population available for analysis. Otherwise, studies with discrepant findings often used other BMI metrics such as kg, BMI or adjusted BMI which might change the observed findings, as pointed out previously (231). Indeed, when analyzing the data on BMI (instead of BMI SDS) the exact opposite is found (more weight loss for those with a higher BMI), as can be seen in **Table 6.11** and these findings contribute to the ongoing discussion on which outcome measure to use.

Besides BMI and metabolic comorbidities, age was found as an independent positive predictor of posttreatment relative BMI SDS regain. These findings can be explained by the hypothesis that patients with the most comorbidities and highest BMI at baseline come from the most obesogenic environment with a more sedentary lifestyle. As a better cardiorespiratory fitness has been associated with more weight loss during treatment (293), this outlines why they would lose less weight during treatment and explains why older age positively predicts posttreatment weight regain, as physical activity decreases with increasing age (301–303). This could indicate that older participants need even more physical training during the inpatient program or that a treatment preparation program might be useful to already improve cardiorespiratory fitness, lower pretreatment metabolic comorbidities and pretreatment BMI.

Similarly, in outpatient care, the one-year treatment outcome is positively predicted by pretreatment HDL and lean mass, which could support the same hypothesis in the outpatient population, i.e. more pretreatment exercise associates with better outcomes. One previous study by Uysal and co-workers could not find an association between baseline HDL and weight reduction (264), however their population was generally younger than our study population. When following the hypothesis above on physical activity with younger aged individuals being more active, this might explain why HDL-cholesterol did not predict weight loss in this younger – possibly more active – population. Nevertheless, as the explained proportion of the variance in our findings was low, these findings could also be chance findings caused by multiple testing.

In conclusion, the above findings again point at the pessimistic prognosis of those subjects in the highest need for treatment, even if they complete the entire inpatient treatment and aftercare, and emphasizes the importance of program modifications, guiding these patients and their families to make and maintain changes in the home environment as well.

6.6.3 Predictive role of adipokines

Lastly, we studied the predictive ability of leptin and adiponectin on weight outcome during and after inpatient treatment. Neither leptin nor adiponectin predicted weight loss, however both were inversely predictive of weight regain during aftercare.

The finding that a high baseline leptin was associated with less weight regain was unexpected when considering leptin resistance. Here, it should be noted that we only gathered follow-up data of a limited sample of inpatient children that were generally younger with less severe obesity compared to the inpatient group that was lost to follow-up. Therefore, these children might have not yet developed a resistance to the actions of leptin as was previously hypothesized by Murer *et al.* who studied baseline leptin levels and its changes in relation to weight loss in a similar population of children with obesity

(304). As a result, a higher leptin level would promote satiety, hereby counteracting weight regain.

Next, a higher adiponectin was also found to be predictive of less weight regain after inpatient treatment. Adiponectin enhances the body's insulin sensitivity of the peripheral tissues hereby stimulating glucose transport and fatty acid oxidation (72) and subsequently promoting weight loss (73). Centrally, it acts upon the body's energy expenditure by increasing oxygen consumption and thermogenesis, again promoting weight loss (74). By these same mechanisms, adiponectin might counteract weight regain. An alternative explanation on the inverse association between adiponectin and weight regain can be found in the adipose tissue. Adiponectin production tends to be lower in the visceral abdominal adipose tissue compared to the subcutaneous adipose tissue (305). Therefore, it could be hypothesized that subjects with obesity and a lower adiponectin level have more visceral adipose tissue than those with a higher adiponectin level. As weight loss and weight regain tend to alter the visceral adipose stores favorably, subjects with a low adiponectin (so more visceral adipose tissue) would therefore be expected to lose weight more easily, but consequently also be more vulnerable to weight regain (306). Thus, a lower adiponectin could also reflect a higher obesity severity and fit into the previously discussed worse prognosis for the youngsters with the highest weight status. As this is one of the first studies describing the predictive potential of leptin and adiponectin regarding posttreatment weight regain in children with obesity, further research needs to confirm these findings.

6.6.4 Limitations

Despite adding a new perspective, our results should be seen with the following limitations.

A first limitation is that these data are coming from a previously conducted randomized controlled trial. Within this trial, additional efforts were made to minimize drop-out, especially outpatient. Therefore, this might have lowered the observed drop-out rate

when no additional efforts for patient retention are made. Nevertheless, even despite these efforts a one-year drop-out rate of 30% in the outpatient setting was observed, which is consistent with other studies (128).

Second, our residential population differed from our outpatient group with those treated residentially being generally older and having more severe obesity. Our results show the least favorable prognosis after inpatient treatment for subjects suffering from the most severe form of obesity. Although, since our outpatient population had a generally lower body weight, it remains difficult to predict how these inpatient subjects would respond when placed in an outpatient setting. Therefore, it would be interesting in future research to follow populations comparable in age, sex and obesity severity in each setting.

Third, the group attending the last follow-up visit in both settings, i.e. 43 participants in either setting, and this should be kept in mind when reading these results. However, this limitation inversely provided us with a sufficiently large group for the analyses of drop-out cases.

Fourth, although we were able to identify some contributors to treatment outcome, the explained proportion of the variance in our drop-out analyses and the outpatient analyses was rather low although in line with other studies (273) This underpins the importance of many 'non-medical' factors in the determination of short- and long-term outcome.

Last, we have focused on BMI status as outcome variable, whereas in obesity treatment the focus was on improving health. When focusing on the health benefits of treatment, this might change the point of view, as the health benefits obtained from obesity treatment (and the resulting BMI reduction) remain present for a longer period of time despite weight regain (107,307) and sometimes improvements in health can already be achieved for example by stabilizing the amount of body weight. Nevertheless, this state of metabolic healthy obesity is rather a temporal stage before obesity-related comorbidities develop (308).

6.7 Conclusion

In conclusion, children with more severe obesity and more metabolic comorbidities are at increased risk for early drop-out during inpatient obesity treatment and late drop-out during the inpatient aftercare sessions or during outpatient treatment. Furthermore, they have an unfavorable outcome during in- and outpatient treatment and are prone to regain more of their lost body weight after returning home. Therefore, successful strategies to reduce drop-out and to prevent posttreatment weight regain are urgently needed. With the knowledge that younger patients with less severe obesity have better long-term results after inpatient treatment, physicians should consider an early referral of these patients to an inpatient treatment setting when outpatient results are insufficient. Additionally, this study identified baseline leptin and adiponectin levels as independent predictors of posttreatment weight regain in children with (previous) obesity. Further research on how adipokines mediate the relation between adipose tissue and body weight is therefore needed.

Chapter 7: The effect of BMI regain on cardiometabolic health in children with obesity: a systematic review of clinical studies

Parts of this chapter are adapted from:

The effect of weight regain on cardiometabolic health in children with obesity: a systematic review of clinical studies

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7.1 Abstract

Aims: Children with obesity are treated by a lifestyle intervention to obtain weight loss. Nevertheless, weight regain often occurs. This systematic review examines the effect of weight regain on cardiometabolic health with the prevalence of the metabolic syndrome as integrated endpoint.

Data synthesis: A literature search was performed in PubMed and Web of Science. Studies were selected if they included participants aged <18 years with obesity and presented data before and after weight loss and after weight regain hereby reporting minimally 1 cardiovascular risk factor at every assessment. After screening, nine articles remained.

Results: Generally, the diastolic BP re-increased after weight regain, whereas for systolic BP a sustained result for 6 months was reported with an increase during longer follow-up. No significant changes in fasting glucose were reported after weight regain compared to baseline. Regarding triglycerides, a complete weight regain re-increased the lowered values to baseline, whereas a partial regain resulted in a sustained decrease in triglycerides in 2 studies and an increase to intermediate levels in 1 paper. HDL-cholesterol only rose several months after initiating treatment. Hs-CRP remained lowered for a longer period than the moment where the weight loss nadir was achieved.

Conclusion: Research on weight regain and cardiometabolic health in children with obesity is scarce. No convincing evidence was found for a worsening of the cardiometabolic profile after weight regain. Some benefits even persisted despite weight recovery. Subsequently, the metabolic syndrome prevalence seems temporarily lowered after weight loss, despite weight regain.

7.2 Introduction

Anno 2016, worldwide 124 million children aged 5 to 19 years old were diagnosed with obesity (11). Up to 70-90% of these children with obesity have at least one cardiovascular risk factor (309) and a clustering of multiple risk factors was previously referred to as 'the metabolic syndrome'. The metabolic syndrome has already been discussed in the introduction chapter under **chapter 1.2.1.1**, including its 5 key features (central obesity, hypertriglyceridemia, a low HDL-cholesterol, hypertension and hyperglycemia) and the population specificity leading to a large variation of the definitions currently used (52–54,61).

Recently, the diagnostic value of the metabolic syndrome in pediatrics has been questioned. The reasons are the missing of one universally accepted definition, the criteria relying on a categorical (yes/no) fulfillment whereas the clinical risk factors are continuous variables, the instability of the diagnosis throughout development to adulthood despite consistent clustering of risk factors and lastly, the conflicting results regarding the predictive potential towards adult metabolic syndrome and adverse health consequences (57–59,310–312). Furthermore, more recently discovered risk factors, such as hs-CRP, are not incorporated in the metabolic syndrome definition. Nevertheless, hs-CRP is an independent predictor of cardiovascular disease and mortality (313). Therefore, the American Academy of Pediatrics recommends to 'shift the focus to cardiometabolic risk factor clustering'. Hereby, they advise to focus more on screening of individual risk factors and to be aware that the presence of one cardiometabolic risk factor is often accompanied by the presence of other risk factors (63). Like excess body weight, also the clustering of cardiometabolic derangements often tracks from childhood to adulthood (314–316) as pointed out previously in **chapter 1.2.1.1**.

In **chapter 1.3.4**, we previously outlined a lifestyle intervention as the standard of care for children with obesity despite the modest long-term results and frequent relapses (131–134,295,317), including the relation between weight fluctuations and adverse cardiometabolic outcomes reported in some adult studies (160,161,166).

Conclusive pediatric data on this topic is missing. Therefore, we have reviewed the existing literature on the influence of weight loss and weight regain on the different cardiovascular risk factors separately. Secondly, we have provided a general synthesis by discussing the influence of these weight changes on the metabolic syndrome, as a surrogate endpoint for the combined cardiometabolic risk profile.

7.3 Methodology

We performed a systematic review according to the recommendations of the PRISMA guidelines (318).

7.3.1 Eligibility criteria

Studies were included if the following criteria were met:

- mean age < 18 years old
- mean BMI defined as obese by recognized international criteria
- research reporting data before and after weight loss, followed by a period of longitudinal follow-up in which any form of BMI regain occurred
- information on at least 1 cardiometabolic risk factor at every time point
- written in English, French, Dutch or German

Only original clinical studies were included. Publications were excluded if they consisted of literature reviews, if only adults or animal models were included, and/or if an endogenous cause for obesity was studied.

7.3.2 Search strategy

A literature research was performed in Pubmed and Web of Science using the following search strategy: ((("obese children" or "obese adolescents" or "pediatric obesity" or "obese teenagers")) AND (“body weight trajectory” or “body mass index trajectory” or “body mass index change” or “body weight change” or “weight cycling” or “weight regain” or “body mass index regain” or “body mass index cycling” or “yoyo-dieting” or “post-dieting weight regain” or “body mass index variability” or “weight variability” or “weight maintenance”)) AND ("cardiovascular diseases" or “cardiovascular risk” or "hypertension" or “blood pressure” or "vascular function" or "endothelial dysfunction" or "vessel disease" or "cardiovascular risk" or "cardiovascular health" or "inflammation" or “hs-CRP” or "cholesterol" or “triglycerides” or “HOMA-IR” or “endothelial function” or “EndoPAT” or “reactive hyperemia index” or “cardiac” or “insulin resistance” or “impaired glucose tolerance” or "fasting glucose" or "fasting insulin" or "HDL-cholesterol" or "LDL-cholesterol" or "total cholesterol" or “diabetes type 2” or “IL-6” or “IL-10” or “inflammatory cytokines”). This search was last repeated on March-9-2020. When a reference in a selected paper pointed to another relevant study, these references were searched manually (snowball effect).

7.3.3 Study selection

The ‘template for study selection’ created by the ‘KCE - Belgian Health Care Knowledge Centre’ was used for synthesizing the result of the selection process. Relevant studies were selected in 3 stages. First, duplicates were removed. Second, publications were screened on title and abstract. Then, when the paper was found relevant and met the eligibility criteria, the full text version was screened and, if it fulfilled the criteria, included in the systematic review. If there was doubt over the eligibility of a publication, a second reviewer was consulted.

7.3.4 Data extraction

The following information was extracted from each paper: patient characteristics (e.g. number of patients, patient eligibility criteria), study design, the amount of weight regained and the cardiometabolic risk factors studied.

7.3.5 Risk of bias

The risk of bias in each individual study was assessed by the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed by the National Institutes of Health (NIH) (319). Based on a list of 14 items, this tool evaluates the following parameters: the study objective and population, the study design, the statistical analysis and power of the study and the risk of bias. At the end of the checklist, the overall quality of the study was rated as good, fair or poor based on the 14 items by the rater. Only one rater was involved in assessing the risk of bias.

7.4 Results

7.4.1 Literature search

A systematic search in Pubmed and Web of Science resulted in 93 articles. Eleven studies were found eligible and another 3 studies were added by hand searching the reference lists of the selected papers. As depicted in **Figure 7.1**, eighty-two articles were excluded based on title and abstract of which thirty-nine papers were excluded because of their design, as they were reviews or based on cross-sectional research. The interventional papers excluded showed a longitudinal follow-up, but did not report weight regain data. Finally, 15 articles were evaluated in full text. Additionally, 5 studies were excluded after full reading for the following reasons: two studies did not report a cardiovascular risk factor at follow-up and three studies only reported weight loss, but no weight regain. At the end of the selection process, 9 articles met the eligibility criteria as presented in **Figure 7.1**.

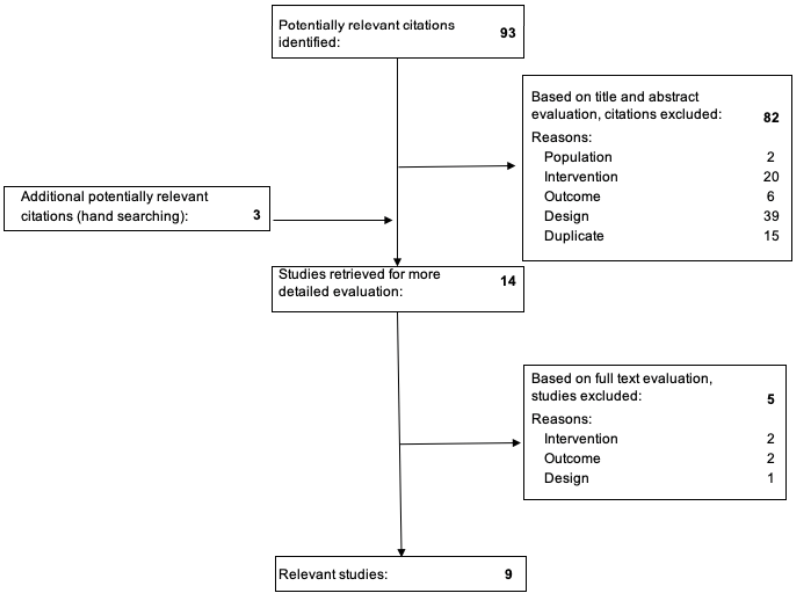

Figure 7.2: Flowchart of the study selection for inclusion in the review.

7.4.2 Study characteristics

Of the 9 selected studies, 4 were randomized controlled trials (RCT) comparing two treatments (320–322) or a treatment with a control group (323). Four studies were prospective observational studies (132,324–326) and one was a retrospective descriptive case series (327). An overview of the extracted information can be found in **Table 7.1**.

First author (year)	Patient characteristics (n, age, girls, obesity definition)	Design (study type, intervention, follow-up assessments*)	Cardiovascular risk factors studied
Holm (2012)	N=115 8-15 years 62 girls, obesity defined based on BMI SDS	Prospective observational study 3-month inpatient weight-reduction program Follow-up at 7, 13 and 25 months after intervention	Blood pressure
Lausten-Thomsen (2015)	Cfr. Study of Holm *et al.*	Cfr. Study of Holm *et al.*	Hs-CRP
Chang (2007)	N=49 12-14 years 16 girls BMI $\geq 95^{th}$ percentile	Randomized controlled trial 9-month supervised exercise intervention vs control group Follow-up 3 months post-intervention	Fasting glucose and insulin, HOMA-IR Triglycerides Cholesterol (total, HDL and LDL)
Franco (2017)	N=22 14-19 years 16 girls BMI$\geq$40 kg/m^2 or $\geq$35 kg/m^2 with co-morbidities	Retrospective descriptive case series Laparoscopic sleeve gastrectomy Follow-up at 6, 12, 18 and 24 months after surgery	Blood pressure/ hypertension, Fasting glucose and insulin/Insulin resistance/impaired glucose tolerance/ type 2 diabetes Triglycerides Cholesterol (total, HDL and LDL)/dyslipidemia Metabolic syndrome
Sachdev (2018)	N=12 Adolescents with tanner stage $\geq$4 7 girls BMI SDS >3.5	Feasibility study 6 months of intragastric balloon placement as additive to a lifestyle intervention Follow-up at 24 months (18 months after balloon removal)	Blood pressure Fasting glucose and insulin, HOMA-IR, insulin area under the curve following an OGTT Triglycerides Cholesterol (total)

Table 7.1
continued

First author (year)	Patient characteristics (n, age, girls, obesity definition)	Design (study type, intervention, follow-up assessments*)	Cardiovascular risk factors studied
Lazzer (2005)	N=26 aged 12-16 years 14 girls BMI>99th percentile for age and gender	Prospective observational study 9 months personalized inpatient weight reduction program Follow-up 4 months after ending the program	Fasting glucose and insulin, Triglycerides Cholesterol (total, HDL and LDL, LDL/HDL ratio)
Shalitin (2009)	N=162 aged 6-11 years old with Tanner stage 1 81 girls BMI >95th percentile	Randomized controlled trial 12-week intervention of exercise, diet or both Follow-up 9 months post intervention	Blood pressure CRP and IL-6 Fasting glucose and insulin, HOMA-IR Triglycerides Cholesterol (total, HDL and LDL)
Kelishadi (2008)	N=100 aged 7-9 years with Tanner stage 1 number of girls not reported BMI ≥95th percentile	Randomized controlled trial 6-month lifestyle intervention targeted at diet or exercise. Follow-up visit 6 months after ending the intervention	Blood pressure Fasting glucose and insulin, HOMA-IR, QUICKI Triglycerides Cholesterol (total, HDL and LDL)
Okely (2010)	N=165 aged 5.5-9.9 years with Tanner stage 1 68 girls BMI defined as overweight or obese by the IOTF criteria but BMI SDS ≤4.0	Randomized controlled trial 10-weeks face-to-face session followed by 3 monthly relapse-prevention phone calls. The intervention was focused on a parent-centered dietary program, a child-centered physical activity program activity or both. Follow-up 6 months after the intervention	Blood pressure Hs-CRP Fasting glucose and insulin Triglycerides Cholesterol (total, HDL and LDL)

*Every study included had assessments at baseline and at the end of the intervention.

A total of 651 children and adolescents with obesity were included in this review. The mean age was 9.8 years. Two papers comprised the same patient cohort, so these patients were only counted once (324,325). Kelishadi *et al.* did not report the male-to-female ratio (320). Of the remaining 551 participants, 264 were female (48%). The study of Holm *et al.* comprising 115 patients only reported BMI SDS, which was 3.0 SDS (324). The average BMI of the other 536 patients was 26.5 kg/m^2. Three studies were performed in pre-pubertal children with obesity, with one including also children with overweight. Two studies included both children and adolescents aged 8 – 15 years old. Four studies were conducted in adolescents, age ranging from 12 to 19 years, with two studies reporting only on adolescents with severe obesity.

Only 3 papers focused specifically on the influence of weight regain after weight loss (132,324,325), whereas the remaining 6 papers presented these data, without weight regain being one of the primary or secondary outcomes of that particular study. Most studies focused on lifestyle interventions for obtaining weight loss. The lifestyle intervention studies consisted of an outpatient setting in 4 studies (320–323) and an inpatient setting in 3 studies (132,324,325). Just two studies discussed the influence of a surgical weight loss intervention (326,327). Six papers reported information on blood pressure (320–322,324,326,327), 7 on the metabolic profile (cholesterol, lipids, glucose, insulin) (132,320–323,326,327) and 3 on the inflammatory profile (321,322,325).

7.4.3 Quality of the evidence

An overview of the quality assessments of the studies can be found in **Table 7.2**. Most studies included showed a suboptimal quality. The most common limitations were small sample sizes and high or unreported drop-out rates. Additionally, some studies made no statistical comparison between the baseline and follow-up data. A control group with maintained weight loss was only present in 1 study (132).

Table 7.2: Risk of bias assessment of studies included, based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed by the National Institutes of Health (NIH).

Validity Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality
Holm (2009)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA	No	Yes	Fair
Lausten-Thomsen (2015)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA	No	Yes	Fair
Chang (2007)	Yes	Yes	NR	Yes	No	Yes	Yes	NA	Yes	Yes	Yes	NR	NR	Yes	Fair
Franco (2017)	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	Yes	Yes	NA	No	No	Fair
Sachdev (2018)	Yes	Yes	NR	NR	Yes	Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	Yes	Fair
Lazzer (2005)	Yes	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Good
Shalitin (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NR	No	CD	Fair
Kelishadi (2008)	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NA	Yes	NR	Yes	No	Fair
Okely (2010)	Yes	Yes	Yes	NR	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	No	Yes	Fair

NR = not reported, NA = not applicable, CD = cannot determine

(1) Clear objective; (2) Clearly defined study population; (3) Participation rate ≥ 50%; (4) Subjects from similar populations; (5) Calculation of sample size, power or variance and effect estimates; (6) Exposure measured before outcome; (7) Sufficient timeframe for association between exposure and outcome; (8) Examine different levels of exposure; (9) Exposure measures valid and consistent across participants; (10) Exposure measured >1 time; (11) Outcome measures valid and consistent across participants; (12) Blinded outcome assessors; (13) Loss to follow-up ≤20%; (14) Adjusted for confounders.

7.4.4 Summary of the results

Due to the heterogeneity of the included studies, a meta-analysis could not be performed. Therefore, a qualitative synthesis of the main results is given structured by the cardiometabolic outcome parameters as summarized in **Table 7.3**.

Table 7.3: overview of the reported results by outcome parameter

First author	(Sub)-group	Average BMI lost	Time of BMI loss	Effect of BMI loss vs baseline	Average BMI regained	Time of BMI regain	Effect of BMI regain vs BMI nadir	Effect of BMI regain vs baseline
Waist circumference								
Kelishadi		1.0-1.1 kg/m^2	6 mo	↓	0.5-0.7 kg/m^2	6 mo	=	n.r.
Shalitin		1.6 kg/m^2	3 mo	↓	1.9 kg/m^2	9 mo	↑	↑
Okely		0.6 kg/m^2	6 mo	↓	0.5 kg/m^2	6 mo	n.r.	=
Sachdev		2.53 kg/m^2	6 mo	↓	5.43 kg/m^2	18 mo	n.r.	=
Franco		12.3 kg/m^2	12 mo	↓	4.7 kg/m^2	12 mo	↑	↓
Systolic blood pressure								
Kelishadi		1.0-1.1 kg/m^2	6 mo	↓	0.5-0.7 kg/m^2	6 mo	=	n.r.
Shalitin								
	Overall	1.6 kg/m^2	3 mo	=	1.9 kg/m^2	9 mo	=	=
	Exercise	1.0 kg/m^2		=	1.5 kg/m^2		=	↑
Okely		0.6 kg/m^2	6 mo	=	0.5 kg/m^2	6 mo	n.r.	=
Holm		0.9-1.0 SDS	3 mo	↓*	0.6-0.8 SDS	25 mo	↑*	↓*
Sachdev		2.53 kg/m^2	6 mo	=	5.43 kg/m^2	18 mo	n.r.	=
Franco		12.3 kg/m^2	12 mo	↓	4.7 kg/m^2	12 mo	↑	n.r.
Diastolic blood pressure								
Kelishadi		1.04-1.1 kg/m^2	6 mo	=	0.5-0.7 kg/m^2	6 mo	=	n.r.
Shalitin		1.6 kg/m^2	3 mo	↓	1.9 kg/m^2	9 mo	↑	=
Okely		0.6 kg/m^2	6 mo	=	0.5 kg/m^2	6 mo	n.r.	=
Holm		0.9-1.0 SDS	3 mo	↓*	0.6-0.8 SDS	25 mo	↑*	↓*
Sachdev		2.5 kg/m^2	6 mo	=	5.43 kg/m^2	18 mo	n.r.	=
Franco		12.3 kg/m^2	12 mo	=	4.7 kg/m^2	12 mo	n.r.	n.r.
Pro-inflammatory profile								
Lausten-Thomsen								
	Hs-CRP	0.9-1.0 SDS	3 mo	↓*	0.6-0.8 SDS	25 mo	↑*	n.r.
Shalitin								
	CRP	1.6 kg/m^2	3 mo	=	1.9 kg/m^2	9 mo	=	=
	IL-6			=			=	=
Okely								
	Hs-CRP	0.6 kg/m^2	6 mo	=	0.5 kg/m^2	6 mo	n.r.	=

Table 7.3 *continued*

First author	Study group	Average BMI lost	Time of BMI loss	Effect of BMI loss vs base-line	Average BMI regained	Time of BMI re-gain	Effect of BMI regain vs BMI nadir	Effect of BMI regain vs baseline
Fasting glucose								
Kelishadi		1.0-1.1 kg/m^2	6 mo	=	0.5-0.7 kg/m^2	6 mo	=	n.r.
Shalitin		1.6 kg/m^2	3 mo	↓	1.9 kg/m^2	9 mo	=	=
Okely		0.6 kg/m^2	6 mo	=	0.5 kg/m^2	6 mo	n.r.	=
Chang		0.6 kg/m^2	9 mo	↓	1.2 kg/m^2	3 mo	↑	=
Sachdev		2.5 kg/m^2	6 mo	=	5.43 kg/m^2	18 mo	n.r.	=
Lazzer	*Boys*	8.1 kg/m^2	9 mo	↓	2.4 kg/m^2	4 mo	↑	=*
	Girls	6.3 kg/m^2						
Franco		12.3 kg/m^2	12 mo	=	4.7 kg/m^2	12 mo	=	=
Fasting insulin (ins.)								
Kelishadi		1.0-1.1 kg/m^2	6 mo	=	0.5-0.7 kg/m^2	6 mo	=	n.r.
Shalitin		1.6 kg/m^2	3 mo	=	1.9 kg/m^2	9 mo	↑	↑
Okely		0.6 kg/m^2	6 mo	↓	0.5 kg/m^2	6 mo	n.r.	↓
Chang		0.6 kg/m^2	9 mo	↓	1.2 kg/m^2	3 mo	↑	=
Sachdev								
Fasting ins.		2.5 kg/m^2	6 mo	=	5.43 kg/m^2	18 mo	n.r.	=
Ins. AUC				↓			n.r.	=
OGTT$^+$								
Lazzer	*Boys*	8.1 kg/m^2	9 mo	↓	2.4 kg/m^2	4 mo	↑	=*
	Girls	6.3 kg/m^2						
Franco		12.3 kg/m^2	12 mo	↓	4.7 kg/m^2	12 mo	=	=
Insulin resistance indices								
Kelishadi								
HOMA-IR		1.0-1.1	6 mo	=	0.5-0.7	6 mo	=	n.r.
QUICKI		kg/m^2		=	kg/m^2		=	n.r.
Shalitin								
HOMA-IR		1.6 kg/m^2	3 mo	=	1.9 kg/m^2	9 mo	↑	↑
Chang								
HOMA-IR		0.6 kg/m^2	9 mo	↓	1.2 kg/m^2	3 mo	↑	=
Sachdev								
HOMA-IR		2.5 kg/m^2	6 mo	=	5.4 kg/m^2	18 mo	n.r.	=
Franco								
HOMA-IR>2.5		12.3 kg/m^2	12 mo	↓	4.7 kg/m^2	12 mo	n.r.	n.r.

Table 7.3 continued

First author	Study group	Average BMI lost	Time of BMI loss	Effect of BMI loss vs base-line	Average BMI regained	Time of BMI regain	Effect of BMI regain vs BMI nadir	Effect of BMI regain vs baseline BMI
Triglycerides								
Kelishadi								
	Diet	1.1 kg/m^2	6 mo	↓	0.7 kg/m^2	6 mo	=	n.r.
	Exercise	1.0 kg/m^2		=	0.5 kg/m^2		=	n.r.
Shalitin		1.6 kg/m^2	3 mo	↓	1.9 kg/m^2	9 mo	↑	=
Okely		0.6 kg/m^2	6 mo	=	0.5 kg/m^2	6 mo	n.r.	=
Chang		0.6 kg/m^2	9 mo	↓	1.2 kg/m^2	3 mo	↑	=
Sachdev		2.5 kg/m^2	6 mo	=	5.43 kg/m^2	18 mo	n.r.	=
Lazzer	*Boys*	8.1 kg/m^2	9 mo	↓	2.4 kg/m^2	4 mo	↑	↓*
	Girls	6.3 kg/m^2						
Franco		12.3 kg/m^2	12 mo	↓	4.7 kg/m^2	12 mo	n.r.	n.r.
LDL-cholesterol								
Kelishadi		1.0-1.1 kg/m^2	6 mo	=	0.5-0.7 kg/m^2	6 mo	=	n.r.
Shalitin		1.6 kg/m^2	3 mo	=	1.9 kg/m^2	9 mo	=	↓
Okely		0.6 kg/m^2	6 mo	=	0.5 kg/m^2	6 mo	n.r.	↑
Chang		0.6 kg/m^2	9 mo	=	1.2 kg/m^2	3 mo	=	=
Lazzer	*Boys*	8.1 kg/m^2	9 mo	↓	2.4 kg/m^2	4 mo	↑	=*
	Girls	6.3 kg/m^2						
Franco		12.3 kg/m^2	12 mo	=	4.7 kg/m^2	12 mo	n.r.	n.r.
HDL-cholesterol								
Kelishadi		1.0-1.1 kg/m^2	6 mo	=	0.5-0.7 kg/m^2	6 mo	=	n.r.
Shalitin		1.6 kg/m^2	3 mo	↓	1.9 kg/m^2	9 mo	↑	=
Okely		0.6 kg/m^2	6 mo	=	0.5 kg/m^2	6 mo	n.r.	=
Chang		0.6 kg/m^2	9 mo	=	1.2 kg/m^2	3 mo	↑*	↑*
Lazzer	*Boys*	8.1 kg/m^2	9 mo	=	2.4 kg/m^2	4 mo	↑	n.r.
	Girls	6.3 kg/m^2						
Franco		12.3 kg/m^2	12 mo	↑	4.7 kg/m^2	12 mo	↑	↑

= : no significant difference, ↓: significantly decreased (p<0.05), ↑: significantly increased (p<0.05), n.r.: not reported: data are presented, but stat
* reported to change, but no p-value was provided by the authors+: AUC is area under the curve, OGTT is oral glucose tolerance test

7.4.4.1 ***Body composition***

Three studies reported information on body composition (132,321,326). Two studies reported on fat% as a parameter for body composition (321,326), whereas Lazzer and colleagues reported the fat and fat-free mass, but this allows to calculate fat% indirectly (132).

The fat% decreased significantly by all three interventions and increased thereafter. In two out of three studies - where patients partially and completely recovered their lost weight - the fat% remained significantly under baseline levels (132,321). In the study of Sachdev *et al.* the fat% recovered to a non-significant difference with baseline levels (p=0.5), however here patients regained more than double of their initially lost BMI points (326).

7.4.4.2 ***Waist circumference***

Five studies reported on waist circumference (320–322,326,327) and all reported a significant decrease in waist circumference after treatment (320–322,326,327).

A near complete weight regain and more than complete weight regain was observed in the studies Okely *et al.* and Shalitin *et al*., with a difference from baseline of 0.1 kg/m^2 decrease and +0.3 kg/m^2 increase in BMI, respectively (321,322). The waist circumference equaled pretreatment circumference in the first study, whereas it exceeded the initial measurement in the second study. The sample size of 10 participants (that regained double of their lost BMI) in the study of Sachdev and colleagues might have been too low to detect a statistically significant increase in the waist circumference, however a clear trend is found with an average increase in waist circumference of 10.4 cm from baseline (p=0.3).

A partial weight regain, observed by Kelishadi *et al.* did not significantly increase waist circumference compared with the waist circumference measured right after treatment (320). In the study of Franco *et al.*, patients with a sleeve gastrectomy lost 60% of their excess weight but regained 15% after 24 months. The waist circumference remained lower than baseline, but was significantly higher than the point with a 60% excess weight loss (327). The average post-treatment BMI increase was more pronounced in the group of patients that underwent a sleeve gastrectomy than in the prepubescent children treated by a lifestyle intervention as described by Kelishadi *et al.* This difference in BMI increase after treatment provides an explanation for the difference in results regarding the effect of partial weight regain.

Waist circumference generally seems to parallel the amount of regain.

7.4.4.3 ***Blood pressure***

Six studies investigated the effect of weight changes on blood pressure (320–322,324,326,327), whereas two studies did not report a change in blood pressure (322,326).

Kelishadi *et al.* reported a significant decrease in SBP by -1.7 $\pm$ 0.5 mm Hg in prepubertal children after a 6-month weight loss program in both a diet and an exercise group with a weight loss of 1.1 and 1.04 kg/m^2. This benefit was sustained 6-months after the intervention, despite that half of the lost weight was regained. The DBP did not change significantly throughout this study (320).

The study of Holm *et al*. was designed specifically to assess the effect of weight loss followed by weight regain on blood pressure. They described a divergent response for DBP and SBP SDS after weight regain studied in children with obesity aged 8 – 15 years old after a 3-month inpatient weight loss program (324). The lowest DBP was measured at the end of the treatment program and DBP started to increase immediately and proportional to the increasing BMI. Contrarily, the lowest SBP was found 13 months after ending the program, despite a weight regain of 0.5 BMI SDS at that time. SBP increased between 13 months and 2 years after ending the weight reduction program, but 2 years after treatment, both DBP and SBP did not reach the hypertensive values as seen at baseline, although the participants' weight was exceeding baseline weight (324).

In a sleeve-gastrectomy study performed in adolescents with severe obesity, the number of patients with arterial hypertension decreased from 59.1% (13/22) to 17.6% (3/17) 1 year after surgical intervention. Two years after gastric sleeve 21.4% of the patients, corresponding to 3 out of 14, were diagnosed as hypertensive, however it was not stated whether these 3 patients were the same as the 3 hypertensive patients reported 1 year post-gastrectomy (327).

In the study of Shalitin *et al.* the DBP evolution followed the BMI evolution, with a significant decrease during treatment and a reincrease to baseline thereafter. In this study conducted in prepubertal children, the SBP was not initially lowered by the 3-month intervention. Remarkably, in the exercise-only group was reported to have a significant increase between the SBP values 9 months post-intervention compared with those at baseline ($p<0.05$), with an SBP of 114 ± 2.7 mm Hg at follow-up compared to 110 ± 2.2 mm Hg at baseline. The DBP did not change significantly throughout the study (321). It has to be noted that both age and height increased as well by the last study visit, which are known confounders of blood pressure (171). Secondly, diet can also influence blood pressure, for example by salt or protein intake or energy drinks (328) and since the exercise group was not provided with any dietary advice, this might contribute to the increased blood pressure registered at follow-up.

In summary, the three studies reporting a decrease in SBP after weight loss, all found a sustained benefit 6 months after the intervention (320,324,327). Although, two studies reported a re-increase during a longer follow-up of 12 and 25 months compared to the blood pressure at the weight loss nadir (324,327). Regarding DBP, two studies reported a weight loss induced lowering, that increased with weight regain compared to the weight loss nadir. Shalitin *et al.* reported that the DBP returned to baseline levels after complete weight regain, whereas Holm *et al.* reported that the percentage of subjects with a SBP or DBP SDS above the 90th centile was still lower than measured initially despite full weight recovery (321,324). Neither systolic nor diastolic blood pressure were found to overshoot baseline values, even when weight was fully regained. Furthermore, evidence even seems to indicate a potential prolonged benefit on the systolic blood pressure.

7.4.4.4 Inflammatory profile

Only 3 studies reported on the inflammatory profile, with all including data on hs-CRP (321,322,325). Two studies reported no significant changes in hs-CRP by weight loss or regain (321,322).

Lausten-Thomson *et al.* focused specifically on the influence of weight loss and weight regain on hs-CRP. They found that hs-CRP tended to decrease during a 3-month inpatient weight loss program and increased again after weight regain. However, the concentrations of hs-CRP measured roughly 6 and 12 months after inpatient treatment were comparable to those measured at the end of the weight loss program, despite that the patients' BMI had already increased by that time. The authors hypothesized that the body might require some time after weight regain before the baseline inflammatory state is restored. Nevertheless, the concentration of hs-CRP was associated with BMI SDS during the period of weight regain, with an increase of 1 BMI SDS being associated with an increase of 60% in hs-CRP in boys and 88% in girls (325).

7.4.4.5 Insulin and glucose metabolism

Four studies found a beneficial effect of weight reduction on fasting insulin, fasting glucose and/or insulin (resistance indices) (132,322,323,327), while two did not (320,326). One study reported a beneficial effect only on fasting blood glucose, but not on fasting insulin or HOMA-IR (321).

In the studies of Chang *et al.* and Shalitin *et al.*, all the lost weight was completely regained (321,323). Chang *et al.* studied 49 children with a mean BMI reduction of 0.6 kg/m^2 after a 9-month supervised exercise intervention. BMI increased significantly over baseline values 3 months after the intervention with the fasting insulin, fasting glucose and the HOMA-IR returning to baseline levels (323). The RCT of Shalitin *et al.* found a significant decrease of blood glucose levels after the weight loss intervention, that returned to baseline values at follow-up, but with no significant difference between the different RCT-groups, e.g., diet, exercise or the combination of both. The fasting insulin levels and HOMA-IR did not improve during weight loss intervention, but after weight regain, a significant increase above baseline values was reported (321). However, this latter study was conducted in pre-adolescent children, and at follow-up 26 of the children had entered puberty. Since in puberty, all children develop some insulin resistance (56), this might have contributed to the increased fasting insulin and HOMA-IR measured at follow-up.

In two studies, patients partially regained their lost weight after a lifestyle intervention. The RCT of Okely *et al.* consisted of a parent-centered dietary program, a child-centered physical activity program or both offered face-to-face for 10 weeks extended with a relapse prevention program for 3 months provided telephonically. The first follow-up visit was planned immediately after the relapse prevention program (so 6 months from baseline) and the second visit 6 months after ending the telephonic follow-up (so 12 months from baseline). Patients lost on average 0.6 kg/m^2 at 6 months and regained 0.5 kg/m^2 by 12 months, which caused no significant changes in fasting glucose, but resulted in an improved fasting insulin 6 months from baseline, which was sustained until 12 months from treatment start, despite weight regain (322). A 9-month inpatient weight reduction program, as described by Lazzer *et al.,* that resulted in an average weight loss of 6.3 kg/m^2, significantly improved the patients' fasting glucose and insulin levels (132). However, in both groups, e.g. patients that maintained the weight loss and in those that regained weight, an increase in fasting glucose to baseline levels and insulin to intermediate levels was registered after 4 months follow-up.

The highest weight loss was obtained by a sleeve gastrectomy. On average, patients lost 34.5 kg or 12.3 kg/m^2. Despite a partial weight regain of 39%, the improved metabolic profile was maintained at least up to 2 years after surgery. One patient with type 2 diabetes reached remission and 2/3 of the insulin resistant patients (defined as HOMA-IR>2.5) normalized their insulin values (327).

Altogether, none of the studies reported a significant difference in fasting glucose after weight regain compared with baseline. Regarding fasting insulin, one study where weight was completely restored, reported no difference with baseline after weight regain (323). Two out of three studies with a partial weight regain reported a sustained ameliorated insulin sensitivity (322,327) and one mentioned an increase to intermediate levels (132).

7.4.4.5 Lipid and cholesterol disturbances

Regarding triglycerides, 2 studies found no changes after weight loss or weight regain (322,326), however 5 other studies reported a significant decrease of triglyceride levels after weight loss (132,320,321,323,327). This improved lipid profile was maintained despite a partial weight regain in the studies of Kelishadi *et al.* and Franco *et al.,* measured 6 months after a lifestyle intervention and 24 months after sleeve gastrectomy compared to the moment with the lowest BMI, e.g. at the end of the lifestyle intervention and 6 months after surgery (132,320). In contrast, Lazzer *et al.* reported that the triglycerides significantly increased to intermediate levels in 10 patients who partially regained weight after an inpatient weight loss program (132). A complete weight regain measured 3 and 9 months post-intervention, returned the triglycerides to baseline levels in the RCT's of Chang *et al.* and Shalitin and co-workers (321,323). Therefore, the BMI difference from baseline seems an important determinant of (longer term) triglyceride profile.

Two studies found no effect on LDL-cholesterol in response to weight loss or weight regain (320,323). In contrast, an inpatient intervention did lower the LDL concentrations significantly, but this reduction was not maintained after partial weight regain and returned to initial values. Furthermore, the changes in LDL-cholesterol were related with the changes in BMI and fat mass during the period that the weight was regained ($r=0.6$ and $r=0.57$, $p<0.05$) (132). Okely *et al.* reported a significant increase in LDL-cholesterol 6 months after their weight loss intervention, targeted at diet, exercise or both, compared to baseline ($p=0.02$), although the change was small, e.g. 0.17 mmol/l (0.02-0.31). At this moment, patients had almost completely recovered their lost weight (322). A 12-week intervention consisting of exercise, diet or the combination, did not lower significantly the LDL-cholesterol, although a non-significant diminishment in the cholesterol values was yet observed. At 9 months follow-up, a further decrease in LDL-levels was observed resulting in a significant difference from baseline ($p<0.01$). The decrease in BMI SDS during the entire study related significantly to the change in LDL-cholesterol ($r=0.281$, $p=0.037$) (321).

In summary, a highly heterogenic response of LDL-cholesterol in reaction to weight changes is seen across the cited studies. Although the correlations found by Lazzer and Shalitin between BMI and LDL-cholesterol suggest a role for overall weight reduction of regained body weight from the weight loss nadir.

HDL was not increased by any of the lifestyle interventions immediately after ending treatment. Surprisingly, three studies found an increase in HDL levels 12 months after starting the weight loss intervention compared to the end-intervention levels despite a partial or complete weight regain (132,321,323). Franco *et al.* described the effect of a sleeve gastrectomy and found an increase in HDL, already starting 6 months after surgery. This significant improvement in HDL was sustained for at least 24 months (327). As HDL-cholesterol is said to 'typical respond slowly to body weight changes'(323), these results confirm this hypothesis, despite the occurrence of weight regain.

7.5 Discussion

This systematic review summarizes the current literature on the effects of weight regain after weight loss on different the components of the metabolic and cardiovascular risk profile in children with obesity. There is no clear evidence pointing towards a harmful effect of weight regain after weight loss. Whereas certain risk factors increase in line with the weight recovered, others seem to experience a prolonged benefit of the preceding weight loss. Although based on the current evidence, we cannot determine how long this benefit persists and what happens in the long term by weight regain.

Since the metabolic syndrome represents a common clustering of all these separate risk factors, except for the pro-inflammatory status, this is an interesting surrogate endpoint to estimate the influence on the combined cardiometabolic risk profile. A recent review reported a metabolic syndrome prevalence in children and adolescents ranging from 0.3 – 26.4% depending on the definition used and the population studied (329).

Miller *et al.* reported that 73.2% of the US adolescents had at least one cardiometabolic risk factor (330), with central obesity and dyslipidemia (low HDL or high triglycerides) being the most prevalent features (329,331). As the increase in HDL seems to be sustained for a longer period after weight regain, this sustained benefit could result in a decreased prevalence of the metabolic syndrome despite weight regain – independent of the definition used. This delayed response to weight regain was also observed for hs-CRP both in a pediatric and an adult study (325,332). Both, HDL and hs-CRP are secreted by the liver and response to changes in the adipose tissue, although indirectly (333,334). Therefore, when weight regain leads to a complete restoration of the lost visceral adipose tissue, a period of time exists between the weight recovery and the changes in hs-CRP and HDL. An additional explanation for the late response of HDL to weight changes can be found in the hypothesis that weight loss and weight regain favor the visceral adipose tissue depot (306), whereas subcutaneous tissue is likely the most important contributor to the circulating HDL-cholesterol concentrations (334). This might explain the different reaction to weight changes compared to the other risk factors that are more directly influenced by the visceral adipose tissue, for example blood pressure by the adipocytes producing leptin and angiotensinogen (335).

Our results are consistent with findings in adults with obesity. Li *et al.* reported that patients that restarted a weight loss program had a lower blood pressure and lower triglycerides than the first time they participated, despite they regained 73% of their lost BMI at that time (336). Graci and co-workers, studying weight cycling in adults with obesity, stated that it is more the accumulation of body fat over several years rather than the weight cycling or weight regain that negatively affects cardiovascular health and body composition (337). This is in line with the findings of Wing *et al.* that it is rather the net weight loss or weight gain than the trajectory taken that determines the cardiovascular profile (338).

It should be noted that children with obesity often already have one or more cardiovascular risk factors. Therefore, weight reduction might temporarily improve their health status, independent of the weight regained. This is an important difference with their normal-weight counterparts that are in good cardiovascular health and subsequently an important difference with the population included in the large cohort studies describing an adverse effect of weight regain on cardiovascular health.

BMI vs BMI SDS: which outcome measure to use for evaluating weight regain?

There is no straightforward definition of weight regain available in children, as multiple authors use different definitions (136,339). In this review, we have used absolute BMI change as a reference. Although BMI is the most used metric in weight-related research, it has limitations in children, as does not give any information on what is normal in function of age. For example, a BMI of 21 kg/m^2 corresponds to obesity at the age of 6 years, whereas this is a normal BMI at the age of 14 years (10). Furthermore, BMI increases over time in normal development (10). This means that when BMI increases (after a preceding BMI loss), it is impossible to determine by BMI alone, whether this is an increase more than would be expected in normal growth. Therefore, using BMI forms a major limitation of our research. BMI SDS however can easily distinguish these two situations from each other.

Unfortunately, previous research indicates that BMI SDS might not reliably report the influence on the true BMI trajectory and has limitations in children with severe obesity, as pointed out previously (231,340). A good example hereof is the study by Okely *et al.*, where both BMI and BMI SDS are reported. When studying the results as BMI data, a weight regain is seen between 6 and 12 months. However, studying the same data as BMI SDS shows a stable or even a decrease in weight trajectory (322). Furthermore, it should be noted that SDS depends on charts derived from cross-sectional research (341). Therefore, these SDS might not be suitable for longitudinal pediatric studies as this was not their intended use (341).

Berkey and colleagues demonstrated that the use of BMI SDS in longitudinal pediatric studies can negatively impact its power and can even complicate the interpretation of results. Therefore, in the study by Berkey *et al.* the change in absolute BMI with incorporation of an age-variable in the statistical model is recommended in longitudinal research in adolescents rather than BMI SDS (341), which supports the choice for BMI as outcome variable in this review.

However, BMI SDS maintains its value as a cross-sectional parameter to determine the weight category of a child at a certain moment in time and can provide supplementary information to determine whether BMI regain takes place in function of normal growth. In the three out of four included studies that reported both BMI and BMI SDS, both BMI and BMI SDS increased, indicating a regain by more than one could expect of normal growth (320,321,326). As there is no consensus on which outcome measure to use, Kelly *et al*. advised to report multiple BMI-derived outcome measures in future research, as was done for example in the recently published liraglutide trial where BMI SDS, absolute BMI and BMI as percentage of the 95th percentile were all reported (121,231).

Limitations

Although our results are consistent with those reported in adults, the following limitations should be considered. First, all included studies had a rather low sample size ranging from 12 to 162 subjects. Additionally, high drop-out rates were often present without a clear description of the population that dropped-out. Secondly, a high heterogeneity was found between studies for the type of intervention, the duration of the intervention and subsequent follow-up, the amount of weight loss and weight regain, and the evaluated outcome measures.

Thirdly, we have only looked into the effect of weight variability, although many cardiometabolic risk factors may also experience influence of other factors, for example nutritional habits, physical activity, puberty and ethnicity (329,342,343), as well as other obesity-related comorbidities. For example obstructive sleep apnea and non-alcoholic fatty liver disease might unfavorably alter the cardiometabolic risk profile as well and can be seen as cardiometabolic risk factors themselves (344,345). However, the complex interplay of these comorbidities, the cardiometabolic risk factors and weight status were not the intended scope of this review. Lastly, weight regain after a weight loss intervention is a negative outcome. Therefore, authors may choose not to report these findings, creating a publication bias in the existing literature and providing an explanation for the low number of studies eligible for inclusion in this review.

Recommendations for future research

Overall, future researchers should be encouraged to conduct prospective studies with a longer follow-up to determine the longevity of the benefits resulting from the initial weight loss. Secondly, we advise besides reporting the separate risk factors (which is important as they all evolve differently but contribute to cardiometabolic risk), to also combine these into one comprehensive endpoint to allow a more definite conclusion on the overall cardiovascular health. As the use of the metabolic syndrome is currently discussed, endothelial function could serve as another surrogate endpoint, combining the influences of all these separate cardiometabolic risk factors (63,95).

Lastly, making a statistical comparison between all the separate timepoints might aid the interpretation of the reader, as this was a difficulty faced when interpreting the results of the currently included studies. Additionally, a comparison with a BMI stable group (as done by Wing *et al.)* or a group that only reduced their BMI without weight regain (as done by Lazzer *et al.)* can provide complementary valuable information (132,346).

7.6 Conclusion

In conclusion, weight loss can improve the metabolic and cardiovascular profile in children with obesity. In the short term, the benefit of the initial weight loss on the risk factors seems of more importance than the potential weight regain. It seems that the benefit on certain risk factors such as HDL and hs-CRP might be sustained longer than the initial weight loss itself. Nevertheless, caution is warranted with interpretation of these results, since this conclusion is based on a limited number of studies with low sample sizes. Based on the available literature, no conclusions can be drawn on the long term cardiometabolic effects of weight regain after weight loss.

Chapter 8: The influence of BMI fluctuations in children during obesity treatment on improvement in cardiovascular risk and endothelial function

8.1 Abstract

Introduction: BMI fluctuations have been associated with increased cardiometabolic risk in adults. Children with obesity commonly undergo BMI fluctuations during treatment, but pediatric studies on how this affects cardiometabolic health are scarce (see **chapter 7**). Therefore, we have studied the effect of the BMI trend and variability during pediatric obesity treatment on the changes in cardiometabolic health and endothelial function.

Methods: Children aged 8-18 years, participating in a 12-month inpatient or 18-month outpatient obesity treatment, had their BMI, body composition, blood pressure, hs-CRP, lipid profile, insulin sensitivity and endothelial function (as overall cardiovascular endpoint) recorded at baseline and again each three months (outpatient group) or at baseline and after 12 and 18 months (inpatient group).

For each patient, an individual linear regression model predicting the BMI evolution over time was created. The slope (reflects BMI evolution) and root mean squared error ((RMSE), reflects variability) of this regression were correlated with the change (Δ) in risk factors between the first and last study visit.

Results: Eighty-three patients were included (mean age 12.8 $\pm$ 2.4 years, mean BMI 32.8 $\pm$ 5.5 kg/m^2, 36 boys, 45 inpatient). By 18 months, BMI significantly lowered by 3.5 $\pm$ 3.6 kg/m^2, resulting in an average BMI slope of -0.19 $\pm$ 0.21 kg/m^2/month and a median RMSE of 2.79 (0.29 – 9.44). The slope significantly related (all $p<0.05$) to the changes in body composition, insulin sensitivity, hs-CRP, HDL-cholesterol and endothelial function over a period of 18 months, whereas for the RMSE only a relation with Δlean% ($r=-0.75$) and ΔHDL ($r=-0.44$) was found, both $p<0.001$.

Conclusion: The overall trend, but not the variability, of BMI trajectories related significantly to changes in cardiometabolic health and endothelial function. This indicates that reducing BMI prioritizes over how (the variability) this reduction is achieved.

8.2 Introduction

As previously pointed out in **chapter 1**, attempting to control or reduce excess body weight in children with obesity is necessary from a young age to prevent cardiometabolic complications or to tackle them at an early and still reversible stage. Controlling the excess weight and its associated comorbidities can be very challenging, especially on the long term. As a result, children with obesity often experience a BMI reduction initially during treatment, but regain BMI eventually.

The effect of weight variability on cardiovascular morbidity has already been examined in numerous large epidemiological adult studies as pointed out in **chapter 1.3.4** and **chapter 7**. Several limitations were present in these studies such as no distinction between intentional and unintentional weight loss; not taking into account the number of weight loss and weight regain periods, and the assessments being often widespread in time (160,161,166,347–349). Additionally, in most studies, patients had a normal BMI. Therefore, these results should not be applied on subjects with obesity, as in 90% of children with obesity one or multiple harmful cardiovascular risk factors are already present. If we examine the studies in adults with obesity, weight cycling per se was not found to increase the blood pressure, lipid or insulin values (136,336–338,350). Interestingly, in adults with type 2 diabetes, certain risk factors even seemed to improve in the 'weight loss and weight regain' group, compared with those that never lost weight (346,351). As indicated in **chapter 7**, studies in a pediatric cohort with obesity that investigated the effect of weight variability on cardiometabolic risk factors are scarce, often have a small sample size and only report on individual cardiovascular risk factors without providing an overall endpoint (132,324,352). Although the benefits of the initial weight loss generally seem to outweigh the potential of weight regain in children with obesity, well-developed studies on the impact of weight fluctuations on the cardiometabolic health in children with obesity are missing (307).

In adults, commonly used cardiovascular endpoints are stroke or myocardial infarction, but fortunately these are rare in children. Interestingly, endothelial function adds up the impact of the different individual cardiovascular risk factors, and functional changes at the endothelial level have been demonstrated to precede the occurrence of structural vascular disease. Therefore, it is an interesting all-encompassing surrogate endpoint for the estimation of the overall cardiovascular health in the pediatric age range (88,89,353). Furthermore, endothelial dysfunction has repeatedly and consistently been found to independently predict later cardiovascular events (88), resulting in cardiovascular morbidity and mortality.

As the number of children with obesity is growing every year and this group is at increased risk for repeated episodes of weight loss followed by weight regain, the influence of a patient's BMI trajectory (considering the overall evolution and the variability) on cardiometabolic health should urgently be studied. The present study is the first to explore the effect of BMI fluctuations on the different cardiovascular risk factors separately (blood pressure, dyslipidemia, glucose metabolism and pro-inflammatory profile) and on endothelial function (reflecting the overall cardiovascular health) in children with obesity.

Within this study, two questions were addressed:

1) Do BMI fluctuations during treatment in children with obesity adversely affect patients their cardiometabolic health and endothelial function? Or is the general BMI evolution more important?
2) What is the effect of BMI re-increase after initial BMI reduction on the cardiometabolic health and endothelial function in children with obesity?

8.3 Methods

8.3.1 Study design

The study population was included via a larger randomized controlled trial (the WELCOME trial: n°ISRCTN14722584) of which the design and eligibility criteria and the content of the obesity treatment are reported in **chapter 3**. Patients were followed over a period of 18 months and only those completing at least the baseline, 12- and 18-month visit were included in our analyses. A general overview of the study design is depicted in **Figure 8.1.**

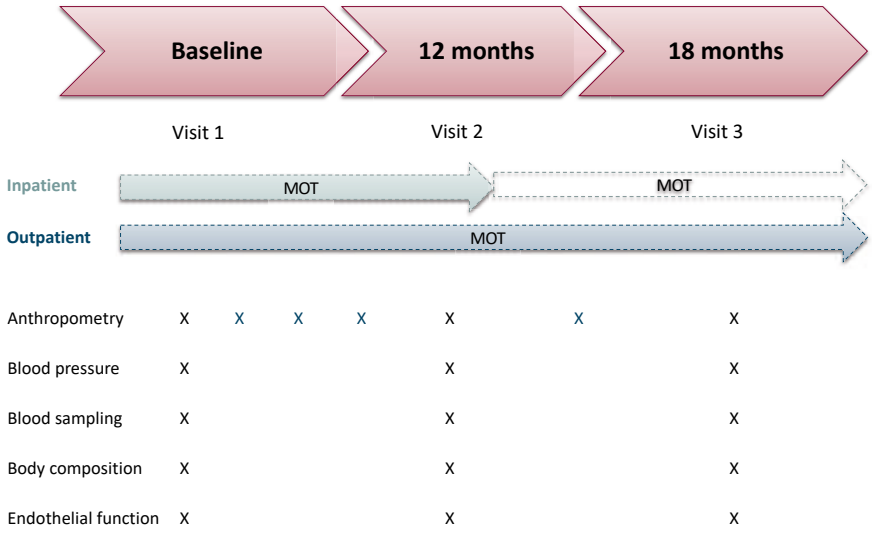

Figure 8.1: visual representation of the study design. For the outpatient setting, anthropometric data were collected additionally each three months, which is indicated by the blue X.

Patients were evaluated at baseline, 12 and 18 months, where all assessments were completed. For the residential group, only the data of the visits at baseline, 12 and 18 months were collected for analysis as these included the BMI peak and nadir of the patients' trajectory. For the outpatient participants, additionally all available BMI data of the three-monthly evaluations were included as their BMI trajectories were more variable. In contrast with the inpatient treatment, the obesity treatment in the outpatient group continued until the last evaluation moment.

8.3.2 Clinical evaluation

All assessments were performed as described in **chapter 3** and will only briefly be described here.

8.3.2.1 *Anthropometry*

Anthropometric data (height, weight, BMI) were collected at each study visit. The BMI in kg/m^2 was further used as a determinant of a patient's individual BMI trajectory. Corresponding BMI standard deviation scores (SDS) were determined using the Flemish growth charts as a reference population (10) to allow classification of patients as overweight or obese according to the definitions of the International Obesity Task Force criteria (9,10). Waist and hip circumference were measured and the waist-to-hip ratio was calculated.

8.3.2.2 Blood sampling

A venous blood sample was drawn at every visit after an overnight fast. The fasting glucose and insulin were determined, as well as the total and HDL-cholesterol, triglycerides and high-sensitivity CRP (hs-CRP). The LDL-cholesterol was determined based on the total and HDL-cholesterol and the triglycerides based on Friedewald's formula (174): LDL-cholesterol = total cholesterol – HDL-cholesterol – triglycerides/5. Before applying this formula, it was checked that none of the participants had triglycerides >400 mg/dl. All analyses were performed in the central laboratory of the Antwerp University Hospital or "Het Zeepreventorium".

8.3.2.3 Blood pressure, body composition & endothelial function

The measurements of blood pressure, body composition and endothelial function were performed as described in **chapter 3**. The blood pressure was analysed as percentile corrected for age, sex and height (354). For body composition, data on fat- and fat-free mass and fat- and fat-free% were collected. For endothelial function, the outcome parameters of interest were the maximal dilatation during the hyperemic period, the time to maximal dilatation and the reactive hyperemia index (RHI).

8.3.3 Statistical analysis

The general statistical approach was already described in **chapter 3**. Additionally, we have assessed the influence of the individual BMI trajectory on the evolution in cardiometabolic risk factors over time. To represent a patients' BMI trajectory, two variables were used: the trend over time and the variability (RMSE), as depicted in **Fig 8.2**.

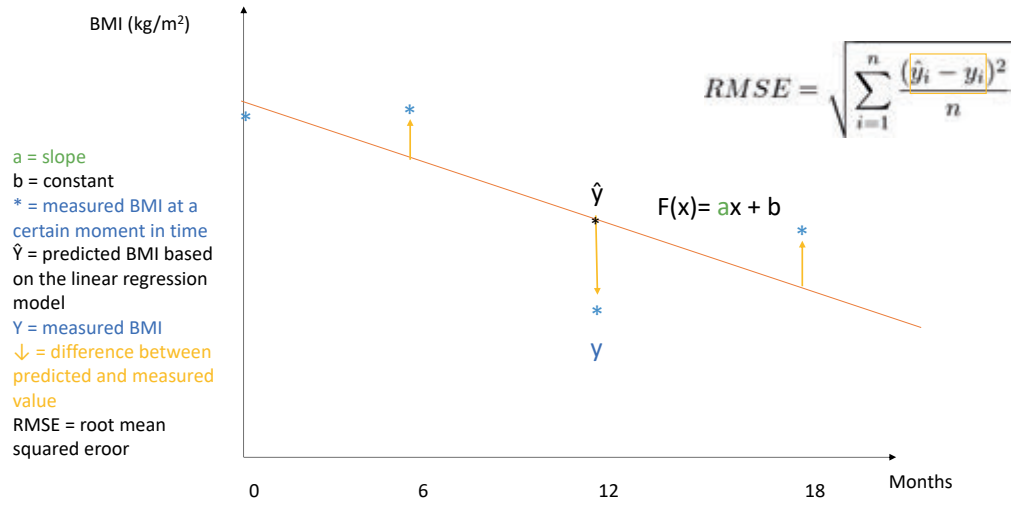

Figure 8.2 represents an individual linear regression predicting a patient's BMI evolution over time based on his actual BMI at certain timepoints. The slope of this linear regression is further used as a measure of the general trend over time, whereas the root mean squared error (RMSE) is used as a measure of the patient's variability in subsequent analyses.

The general trend per patient over time was calculated by fitting a time-dependent linear regression through the measured BMIs. The slope coefficient was used as the variable representing the trend over time, here average BMI decrease per month. Additionally, the root mean squared error (RMSE) was determined as a parameter to measure the variability around the created linear regression. These determinants for a patients' trajectory were correlated with the change (Δ) in each individual cardiovascular risk factor from baseline to 18 months. If a significant correlation was found with both the slope and variability, a linear regression model was created with the change in the cardiovascular risk factor as dependent variable and the slope and variability as independent variables with age, gender and pretreatment BMI as confounders.

Furthermore, we aimed to determine the effect of BMI re-increase compared to the BMI nadir by comparing data at the different visits (baseline, 12 months, 18 months) in a population reaching their BMI nadir at 12 months and re-increasing BMI by 18 months. The minimal required BMI reduction by 12 months and the minimal required increase between 12 and 18 months was 1 kg/m^2. This cut-off was chosen as this prevented inclusion of subjects where the observed BMI change resulted from measurement variability between weighing scales and yard sticks and to allow inclusion of outpatient participants as well (where the average BMI reduction was solely 1.2 $\pm$ 2.4 kg/m^2). Furthermore, by using this cut-off, all of the participants reduced their BMI by $\geq$0.1 SDS, which has been shown to have beneficial effects on cardiovascular risk factors in previous research (355).

For normal distributed data, a repeated measures ANOVA with post hoc Bonferroni comparison was conducted to detect changes in body composition and cardiovascular risk factors over time. In case of skewed data, a Friedman test was used, followed by a Wilcoxon signed rank test to allow pairwise comparisons.

8.4 Results

8.4.1 Patient characteristics

In total, 83 patients (mean age 12.8 ± 2.4 years, mean BMI 32.8 ± 5.5 kg/m^2 corresponding to a BMI SDS of 2.5 ± 0.4, 36 boys) were analysed of which 45 came from an inpatient and 38 from an outpatient treatment program. **Table 8.1** provides an overview of the patient characteristics of the overall population and the two subgroups based on the treatment center, including the differences between the in- and outpatient population such as age, obesity severity and blood pressure.

Table 8.1: Baseline patient characteristics

	Inpatient	Outpatient	Overall
Male/female	18/27	18/20	36/47
Age (years)	**13.5 ± 2.4**	**11.9 ± 2.2***	12.8 ± 2.4
BMI (kg/m^2)	**34.6 ± 5.3**	**30.8 ± 5.1****	32.8 ± 5.5
BMI SDS	**2.6 ± 0.4**	**2.4 ± 0.4***	2.5 ± 0.4
Waist (cm)	**111.6 ± 13.8**	**90.6 ± 10.7****	102.0 ± 16.3
Hip (cm)	**115.1 ± 11.4**	**106.3 ± 13.5***	111.0 ± 13.1
Waist-to-hip ratio	**0.97 ± 0.06**	**0.86 ± 0.05****	0.92 ± 0.08
Fat mass (kg)	**40.5 ± 13.6**	**32.6 ± 12.5***	36.5 ± 13.5
Fat % (%)	42.4 ± 5.5	40.1 ± 5.5	41.2 ± 5.5
Lean mass (kg)	**41.1 ± 8.7**	**36.6 ± 8.2***	38.8 ± 8.7
Lean % (%)	44.7 ± 7.2	47.4 ± 7.0	46.1 ± 7.2
Systolic BP (%)	**90 (39 – 99)**	**66 (8 – 97)****	82 (8 – 99)
Diastolic BP (%)	**60 (21 – 98)**	**46 (6 – 98)***	55 (6 – 98)
Hs-CRP	3.6 (0.3 – 21.8)	1.3 (0.16-9.5)	2.6 (0.16 – 21.8)
HDL-cholesterol (mg/dl)	46 ± 8	48 ± 8	47 ± 8
LDL-cholesterol (mg/dl)	88 ± 28	95 ± 26	91 ± 27
Triglycerides (mg/dl)	98 (52 – 245)	91 (38 – 239)	93 (38 – 245)
Fasting glucose (mg/dl)	89 ± 6	86 ± 7	88 ± 7
Fasting insulin (pmol/l)	162.4 (61.4 – 341.8)	174 (87 – 282)	170 ± 63
HOMA-IR	5.5 ± 2.4	5.2 ± 1.7	5.3 ± 2.1
Maximal dilatation	1.25 (1.04 – 2.39)	1.27 (1.09 – 2.46)	1.26 (1.04 – 2.46)
Time to maximal dilatation (s)	195 (105 – 285)	195 (45 – 285)	195 (45 – 285)
RHI	1.39 (1.00 – 2.89)	1.57 (1.06 – 3.03)	1.41 (1.00 – 3.03)

*= significantly different between in- and outpatient at the 0.05 level, ** = significantly different between in- and outpatient at the 0.001 level. BP=blood pressure. RHI = reactive hyperemia index.

8.4.2 Effects of treatment on BMI

Figure 8.3 visually represents the BMI evolution by setting.

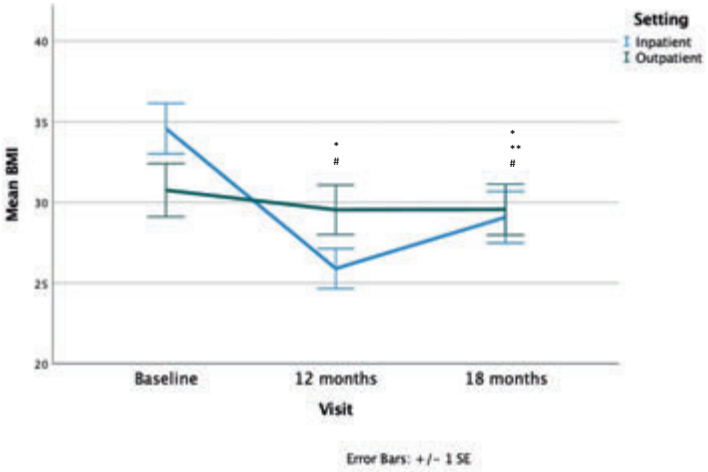

Figure 8.3 depicts the BMI evolution of the in- and outpatient group over time. * indicates a significant difference compared with baseline for inpatients, ** indicates a significant difference compared with 12 months for inpatients and # indicates a significant difference compared with baseline for outpatients.

The 45 patients from inpatient care significantly reduced their BMI by 8.7 ± 2.5 kg/m^2 by the end of inpatient treatment, at 12 months ($p<0.001$). Subsequently, overall these patients significantly regained weight, resulting in an average BMI increase of 3.2 ± 2.3 kg/m^2 six months after ending inpatient treatment compared to their posttreatment BMI ($p<0.001$). This corresponds to a mean regain of 40 ± 30% of their lost BMI points. However, there was a high interindividual variability within the BMI regain ranging from -15 to +115%. Over the entire study period, patients from inpatient care had reduced their BMI significantly by 5.5 ± 3.3 kg/m^2 between the treatment start and the last follow-up visit six months after inpatient treatment ($p<0.001$). By this last study visit, 22 inpatients still had obesity based on their BMI SDS, 17 had overweight and 6 had reached a normal BMI.

Children in outpatient care also significantly reduced their BMI by 1.2 ± 2.4 kg/m^2 after 12 months of treatment (p=0.003), whereafter the BMI stabilized between 12 and 18 months (p=0.9) with a difference in BMI of -1.2 ± 2.4 kg/m^2 at 18 months compared to baseline BMI (p=0.004). Again, there was a high heterogeneity in the BMI evolution during outpatient care ranging from a BMI reduction of 6.1 kg/m^2 to a BMI increase of 4.4 kg/m^2. Of the 38 patients, 2 reached a normal weight at the last follow-up visit, 15 were overweight and 21 still had obesity after 18 months of outpatient treatment.

The BMI trajectory indices, i.e. slope and RMSE, are shown in **Table 8.2**. As one could expect, the average slope and variability were larger in the population treated in inpatient care compared to the outpatient group (both p<0.001). The slope and RMSE were inversely related to each other, r=-0.63 and p<0.001.

Table 8.2: BMI trajectory indices

	Inpatient	**Outpatient**	**Overall**
BMI slope (/month)	**-0.33 ± 0.18**	**-0.03 ± 0.11**[*]	-0.19 ± 0.21
BMI variability (RMSE)	**4.33 (2.19 – 9.44)**	**0.94 (0.29 – 2.26)**[*]	2.79 (0.29 – 9.44)

[*] = significantly different between in- and outpatient care, both at the 0.001 level. RMSE = root mean squared error.

8.4.3 Effect of treatment on cardiovascular risk factors

After 18 months of treatment, an overall improvement in cardiometabolic risk factors including endothelial function was found, as presented in **Table 8.3**. Only blood pressure, HDL-cholesterol and fasting glucose had not significantly improved.

Table 8.3: comparison for each cardiovascular between baseline and 18 months.

	Baseline	18 months	p
Waist (cm)	102.0 ± 16.3	87.8 ± 11.8	**<0.001**
Hip (cm)	111.0 ± 13.1	105.0 ± 11.1	**0.001**
Waist-to-hip ratio	0.92 ± 0.08	0.84 ± 0.07	**<0.001**
Fat mass (kg)	36.5 ± 13.5	31.1 ± 11.6	**0.005**
Fat % (%)	41.2 ± 5.5	38.1 ± 7.4	**0.009**
Lean mass (kg)	38.8 ± 8.7	38.7 ± 9.0	0.8
Lean % (%)	46.1 ± 7.2	49.5 ± 9.5	**0.038**
Systolic BP (%)	82 (8 – 99)	81 (2 – 99)	0.9
Diastolic BP (%)	55 (6 – 98)	58 (8 – 99**)**	0.2
Hs-CRP	2.6 (0.16 – 21.8)	0.49 (0.16 – 2.5)	**<0.001**
HDL-cholesterol (mg/dl)	47 ± 8	48 ± 10	0.1
LDL-cholesterol (mg/dl)	91 ± 27	80 ± 23	**<0.001**
Triglycerides (mg/dl)	93 (38 – 245)	69 (37 – 242)	**<0.001**
Fasting glucose (mg/dl)	88 ± 7	87 ± 8	0.5
Fasting insulin (pmol/l)	170 ± 63	93 ± 44	**<0.001**
HOMA-IR	5.3 ± 2.1	2.9 ± 1.5	**<0.001**
Maximal dilatation	1.26 (1.04 – 2.46)	1.44 (1.02 – 3.98)	**0.008**
Time to maximal dilatation (s)	195 (45 – 285)	165 (45 – 285)	**0.003**
RHI	1.41 (1.00 – 3.03)	1.74 (1.05 – 3.87)	**<0.001**

BP = blood pressure, RHI = reactive hyperemia index, HOMA-IR: homeaostasis model assessment for insulin resistance.

8.4.4 Effect of BMI trajectory on the cardiometabolic profile

Correlations between the change in each individual cardiovascular risk factor and the BMI trajectory indices are presented in **Table 8.4**. Whereas the improvement in most cardiovascular risk factors related significantly to the slope of the patients' BMI trajectory, only the change in anthropometric data, HDL-cholesterol, hs-CRP, RHI and time to maximal dilatation related significantly to the BMI variability. Some factors however do not relate to the slope or variability, which we presumed to be due to these factors being more related to body composition or central obesity rather than BMI trajectory.

Table 8.4: correlations between the change in cardiovascular risk factors and the slope and variability of the patients' BMI trajectory.

	Slope	Variability (RMSE)
Δ fat mass (kg)	-0.89***	0.58***
Δ fat% (%)	-0.73***	0.40**
Δ lean mass (kg)	n.s.	n.s.
Δ lean% (%)	0.68***	-0.78***
Δ waist (cm)	-0.87***	0.59***
Δ waist-to-hip ratio	-0.41***	n.s.
Δ glucose (mg/dl)	n.s.	n.s.
Δ insulin (pmol/l)	-0.35**	n.s.
Δ HOMA-IR	-0.27*	n.s.
Δ hs-CRP (mg/l)	-0.46***	0.38**
Δ triglycerides (mg/dl)	n.s.	n.s.
Δ HDL-cholesterol (mg/dl)	0.65***	-0.61***
Δ LDL-cholesterol (mg/dl)	-0.25*	n.s.
Δ diastolic blood pressure (%)	-0.28*	n.s.
Δ systolic blood pressure (%)	n.s.	n.s.
Δ maximal dilatation	n.s.	n.s.
Δ time to maximal dilatation	-0.31*	0.37*
Δ reactive hyperemia index	0.31*	-0.26*

n.s.: not significant, *significant at the p<0.05 level, ** significant with p<0.01, *** significant with p<0.001, ****significant with p<0.0001

Furthermore, after correction for age, gender, pretreatment BMI and slope in a multiple linear regression model, only the association between the variability and Δlean% and the variability and ΔHDL-cholesterol remained significant, as shown in **Table 8.5**.

Table 8.5: Results of multiple linear regression analyses (expressed as partial correlation coefficients) to examine the association between the change in cardiovascular risk factors and the slope and variability of patients' BMI trajectory corrected for setting.

	Age	Gender	BMI	Slope	Variability	Adj. R^2
Δ fat mass (kg)	-0.02	**0.36****	0.17	**-0.82*****	-0.053	0.801
Δ fat% (%)	**-0.40****	**0.42*****	0.05	**-0.68*****	0.08	0.671
Δ lean% (%)	-0.21	**-0.32****	**0.47*****	**0.57*****	**-0.75*****	0.776
Δ waist (cm)	0.11	**-0.35****	0.06	**-0.80*****	0.06	0.769
Δ hs-CRP	0.18	-0.06	**-0.03***	**-0.33***	0.24	0.244
Δ HDL-cholesterol	-0.11	**0.36****	**0.32***	**0.56*****	**-0.44*****	0.572
Δ time to maximal dilatation#	0.04	-0.19	-0.02	-0.12	0.21	0.081
Δ RHI#	-0.09	0.008	0.03	0.20	-0.14	0.098

RHI = reactive hyperemia index, *significant at the p≤0.05 level, ** significant with p<0.01, *** significant with p<0.001. #Regression model is non-significant.

8.4.5 Clinical population of interest

Lastly, we aimed to study how the degree of BMI regain after initial BMI loss impacts the cardiovascular risk factor evolution. Therefore, we selected a clinical group of interest from the entire population, as described above. This group consisted of those participants who reached their BMI nadir at 12 months and had a partial or complete relapse by 18 months. A subgroup of 47 participants (39 from inpatient and 8 from outpatient care) fulfilling these criteria was selected. These patients reduced their BMI by an average of 7.8 $\pm$ 3.1 kg/m^2 during the first year and thereafter had a median BMI increase of 3.3 kg/m^2 (1.1 – 10.9) between 12 and 18 months, corresponding to a median regain of 44 % (12 – 115).

Most parameters improved significantly during treatment as can be seen in **Table 8.6**. After treatment, similar to the increase in BMI, the body composition parameters such as fat mass and fat% and lean% were again altered. The BMI increase favored regain of fat mass, as by 18 months the participants had already regained 70 $\pm$ 28% of their previously lost fat mass (in kg).

Table 8.6: Evolution of body composition and cardiovascular risk factors between baseline, 12 (BMI nadir) and 18 months (BMI regain) in the selected subgroup (n=47).

	Baseline	12 months	18 months	p-value
Fat mass (kg)	37.1 ± 12.8	23.1 ± 9.4*	32.9 ± 10.7**	<0.001
Fat% (%)	40.8 ± 5.5	30.9 ± 8.0*	39.2 ± 6.9**	<0.001
Lean mass (kg)	40.7 ± 8.2	42.0 ± 9.5	39.3 ± 8.8**	0.016
Lean% (%)	46.7 ± 7.1	58.6 ± 10.5*	48.4 ± 9.0**	<0.001
Waist (cm)	106.5 ± 14.7	91.0 ± 10.5*	91.8 ± 11.6#	<0.001
HOMA-IR	5.9 (2.2 – 12.9)	2.4 (0.9 – 5.9)*	2.5 (1.1 – 7.4)#	<0.001
Hs-CRP (mg/l)	3.6 (0.16 – 11.3)	0.5 (0.16 – 5.9)*	0.7 (0.16 – 16)#	<0.001
Triglycerides (mg/dl)	90 (42 – 196)	64 (29 – 185)*	62 (41 – 242)#	<0.001
HDL-cholesterol (mg/dl)	47 ± 9	50 ± 9	52 ± 10#	0.002
LDL-cholesterol (mg/dl)	85 ± 23	67 ± 23*	77 ± 20**,#	<0.001
Diastolic blood pressure (percentile)	58 ± 22	44 ± 23*	60 ± 25**	<0.001
Systolic blood pressure (percentile)	90 (35 – 99)	66 (24 – 98)*	87 (2 – 99)	0.018
Maximal dilatation	1.25 (1.04 – 1.83)	1.45 (1.10 – 2.52)	1.45 (1.02 – 3.98)#	0.018
Time to maximal dilatation	195 (135 – 255)	105 (45 – 285)*	135 (45 – 225)#	0.005
Reactive hyperemia index	1.35 (1.07 – 2.11)	1.54 (1.08 – 3.58)*	1.79 (1.17 – 3.87)**,#	0.001

*significantly different between baseline and 12 months, *significantly different between 12 and 18 months, #significantly different between baseline and 18 months by pairwise comparisons.

Remarkably, despite this considerable amount of BMI regain, many risk factors remained stable between 12 and 18 months such as the HOMA-IR, the pro-inflammatory status, triglycerides and time to maximal dilatation, as shown in **Table 8.6**. The HDL-cholesterol, maximal dilatation and reactive hyperemia index even further improved, resulting in a significant difference from baseline only after 18 months. Unfortunately, some risk factors, including blood pressure and LDL-cholesterol, worsened again (see **Table 8.6**).

Next, the alterations in those risk factors were correlated to the changes in BMI and fat mass (absolute increase and relative regain) between 12 and 18 months in **Table 8.7**.

Table 8.7: correlations between the change in cardiovascular risk factors between 12 and 18 months and the change in BMI and fat mass (absolute and relative to the previous reduction).

	ΔBMI	BMI regain	Δfat mass	Fat regain
ΔHDL-cholesterol	n.s.	**-0.59**	n.s.	n.s.
ΔLDL-cholesterol	n.s.	n.s.	**0.48**	n.s.
ΔDiastolic blood pressure (%)	**0.45**	n.s.	n.s.	n.s.
ΔSystolic blood pressure (%)	n.s.	n.s.	n.s.	n.s.
ΔMaximal dilatation	n.s.	n.s.	n.s.	n.s.
ΔReactive hyperemia index	n.s.	n.s.	n.s.	n.s.

Parameters in bold indicate a significant correlation, defined as $p<0.05$.

More BMI regain resulted in less increase in HDL-cholesterol between 12 and 18 months, while a larger increase in BMI was associated with a higher increase in the diastolic blood pressure. The increase in LDL-cholesterol during weight regain related to the increase in fat mass rather than the increase in BMI. Endothelial function was not related to the amount of BMI or fat increase, however significant correlations were found between the difference in time to maximal dilatation during BMI regain and the increase in systolic and diastolic blood pressure in that same period with $r=0.67$, $p<0.001$ and $r=0.48$, $p<0.017$.

8.5 Discussion

This is the first study assessing the influence of the variability in a patients' BMI trajectory on the overall cardiometabolic risk factors in a pediatric population with obesity. Apart from all the separate individual cardiovascular risk factors, we have also included an all-encompassing endpoint: endothelial function. Providing this comprehensive endpoint allows us to draw an overall conclusion of general cardiometabolic health. This addresses an important limitation of previous (in)direct research on this topic (307), where all risk factors were treated as stand-alone items without providing one single surrogate endpoint.

Question 1: Does BMI variability during weight loss treatment negatively affect the improvement in the cardiometabolic risk factors (and endothelial function) in children with obesity? (Or is the overall evolution more important?)

Our results suggest that the overall BMI slope, representing the overall BMI evolution (increase, decrease, stabilization) is the most important factor for improving the cardiometabolic health, rather than how this BMI reduction was achieved (measured by the amount of variability over time). These findings confirm previous research in adults reporting that the effect of the BMI evolution outweighs the effect of variability. Indeed, our results add up to a 2017 review concluding that there is little detrimental effect of weight fluctuations and therefore treatment should keep targeting weight loss, despite the risk of weight regain (337,338,356–359).

One recent, very interesting study has addressed the question regarding BMI variability and the development of adult type 2 diabetes in a large cohort of 1718 participants followed from childhood to adulthood over a period of 20 years (167). They report that a high BMI variability during childhood was an independent risk factor for developing type 2 diabetes. We like to highlight a few differences with our study: first, their population comprised healthy children with a normal BMI, an important difference with our population of which most participants already had one or multiple cardiovascular risk factors resulting from their excess body weight. Therefore, in our group, reducing BMI might have restored these initially increased risk factors and hereby, outweighed any potential detrimental effect of BMI variability that might have been detected if the same study was performed in healthy children without any cardiovascular risk factor. This would mean that healthy people without cardiovascular risk factors are more likely to be exposed to the detrimental impact of weight cycling, as previously hypothesized by Montani and colleagues (165).

Second, in our population an overall BMI decrease was found as our population was intentionally undertaking weight loss efforts. In the cohort study by Du *et al.* (167), the overall BMI evolution and intentionality of the weight loss is unknown. This is an important aspect as a high variability can occur around a stable BMI, but can also represent an increasing or decreasing trend over time. As many studies have reported an effect on later cardiovascular and metabolic end points based on the general BMI evolution, e.g. increase or decrease, this would provide additional valuable information for comparison of these data (360–362). A last difference is that the cohort of Du et al. comprises a very large population followed over a long period of 20 years, which therefore increases the power to detect significant effects that might not be found in our smaller cohort or with a shorter (although clinically relevant) follow-up.

Question 2: What is the effect of BMI re-increase after initial BMI reduction on the cardiometabolic health and endothelial function in children with obesity?

For this question, a subgroup analysis was conducted to detect the effect of BMI regain on the cardiovascular risk factors compared to the moment where the lowest BMI had been recorded. Despite a significant BMI regain at that time, many risk factors, including endothelial function, were still improved compared with baseline. This indicates that the benefits of the initial BMI reduction remained present for a longer period despite BMI regain, as expected based on our previous written review (307). However, some risk factors and endothelial function deserve to be discussed in more detail.

First, HDL-cholesterol further increased between 12 and 18 months, which is not surprising as this compound typically lags behind the initial BMI reduction (323). However, this is the first study showing that BMI regain slows the improvement of HDL resulting from the preceding weight loss.

For LDL-cholesterol, we found a recovery to intermediate levels associated with the re-increase in fat mass, which is in line with the findings of Lazzer *et al.* (132). The importance of a net fat mass reduction compared to baseline should be emphasized when studying LDL-cholesterol, as this will probably determine whether an improvement in LDL-cholesterol remains after BMI is regained.

Second, regarding the blood pressure evolution some critical remarks should be made on our findings. Diastolic blood pressure increased significantly at 18 months compared to 12 months and this increase was related to the increase in BMI, which is consistent with previous research by Holm and colleagues (324). Similar to this previous study, the systolic blood pressure was not found to differ significantly at 18 months compared to the values measured at the BMI nadir (12 months), corresponding to previous indications that the effect of a preceding BMI reduction might remain present for a period of at least 6 months after the BMI nadir has been achieved. However, both - systolic and diastolic blood pressure - at 18 months were no longer different from baseline, despite only partial BMI recovery. Whereas this recovery to baseline values can be explained by the repeated overshoot theory, stating that during weight regain risk factors increase disproportional to the amount of weight regained, it must be noted that blood pressure measurements at the 18 months follow-up visit in the inpatient center were not measured early in the morning in a fasting state as opposed to the preceding measurements at baseline and 12 months. Therefore, diurnal variation or intake of certain foods or drinks might have exaggerated the blood pressure trends found.

Lastly, an interesting finding is that the benefits on the endothelial level remained present 6 months after the BMI nadir was achieved, despite considerable BMI regain at that time. As endothelial function results from a summation of all risk factors, it is therefore rather indirectly influenced by BMI explaining the absent correlations between the changes in endothelial function and the BMI changes on one hand and the present correlations between endothelial variables and the changes in blood pressure during weight regain on the other hand.

As in our study most cardiometabolic risk factors remained stable (or – in case of HDL - even further improved), this most likely explains why endothelial function was not significantly altered at follow-up. Altogether, despite the overall cardiovascular benefits (endothelial function) of the initial BMI loss still being present 6 months later, BMI maintenance at the BMI nadir should of course remain the aimed treatment goal.

Limitations

A longitudinal and multicenter design, the measurement of anthropometric variables by the research team (rather than self-reported weight data), the multiple cardiometabolic risk factors evaluated (including endothelial function as an all-encompassing endpoint) and the separation of the BMI trajectory in slope and variability constitute important strengths of the present study, however some limitations are present.

First, as our population consists of children with obesity intentionally trying to lose weight, our results should not be broadened to a general normal-weight pediatric population. Second, for the present study the BMI measured at every study visit was used to further determine each person's individual trajectory over time, instead of e.g. body composition that might be more related to cardiometabolic health. Nevertheless, this choice allows us to additionally study the impact of BMI fluctuations on body composition and fat distribution (waist circumference and waist-to-hip ratio) and increases the comparability with previously conducted adult studies (356–358). Third, several months were situated between the study measurements, which might (similar as in previous studies) lead to an underestimation of the actual weight variability during the 18-month duration of the entire study. However, it should be noted that in previous research there were often many years between observations (166,167,356,363). Fourth, although the effects of an overall BMI reduction seemed to overrule the effects of BMI variability and regain, we cannot exclude a long-term effect of BMI variability or predict how long these benefits will remain after the BMI has been fully recovered.

Last, we looked at increases or decreases of cardiometabolic risk factors, but not at clinically relevant changes as for some parameters such as endothelial function the cut-off value of what is healthy or unhealthy is not yet identified in children, as also pointed out in **chapter 9.1.3**.

Future perspectives

As (short-term) effective - surgical and pharmacotherapeutic - obesity treatments are becoming increasingly available for use in children, the question on whether and how BMI fluctuations contribute to the cardiometabolic health of children and adolescents with obesity will probably gain more importance in the future. Researchers could further extend the knowledge on this topic by focusing on children with obesity as a separate entity in prospective large cohort studies as they might behave differently than their normal-weight peers due to the possible presence of cardiovascular risk factors. Additionally, the slope should preferably be separated from the variability to exclude a confounding effect of slope with variability in subjects undergoing large weight changes. In future research, it might be interesting to compare different clinically relevant subgroups (for example large BMI decrease with high vs. low variability). Unfortunately, this was not possible in our cohort as our population only consisted of 83 participants. Finally, expansion of the follow-up period in patients undergoing BMI regain after BMI loss might help to determine how long initial benefits of weight loss remain present.

8.6 Conclusion

Overall, the general BMI evolution over time (increase or decrease) was found to significantly alter the cardiometabolic risk and endothelial function in children with obesity, whereas the variability did not. Therefore, achieving a BMI reduction in children with obesity remains the absolute priority. Although, most of the risk factors were still ameliorated 6 months after the BMI nadir was achieved despite a partial BMI recovery, we must consider that BMI regain (after initial BMI reduction) might negatively impact specific cardiovascular risk factors (diastolic blood pressure, HDL- and LDL-cholesterol).

Chapter 9: General discussion

Currently, 2 out of 3 children with obesity ultimately become adults with obesity, indicating that treatment fails in achieving long-term results (130,131). The consequences of the current obesity pandemic are reflected at the societal level through the high healthcare costs associated with obesity-related comorbidities (as described in **chapter 1**) (2), but also individually in the physical and emotional wellbeing of the affected people (111). Therefore, current research is challenged to identify new strategies that improve treatment outcomes of the pediatric obesity programs. With this thesis, we investigated different aspects of the clinical trajectory that children with obesity go through. By adding new insights, we aimed to broaden current knowledge on pediatric obesity and assist future researchers in the development of feasible and effective treatment strategies.

9.1 Which outcome measure should be used to evaluate treatment effect in children with obesity?

To determine the effectiveness of an intervention, the choice of outcome measures in scientific research is of paramount importance. As mentioned earlier, there is ongoing debate about which outcome measure to use in pediatric obesity research.

9.1.1 BMI SDS

BMI SDS is the most used outcome measure in pediatric weight-related research, but a 2017 paper was critical of its shortcomings, especially in children with severe obesity (231). Limitations named are the modest correlations with BMI percent of the 95th percentile, Δ BMI percent of the 95th percentile or measures of body fatness (233,364). Moreover, using BMI SDS in longitudinal research may bias results compared to those in BMI, since BMI SDS was never intended to be used for longitudinal evaluation (364). Kelly *et al.* recommend against using BMI SDS in research involving children with severe obesity and against using it as a metric to evaluate individual children with high BMIs in the clinical setting.

A suggested solution is to report more than one outcome measure to help the reader interpret the data. The authors suggested BMI percent of the 95th percentile and Δ BMI percent of the 95th percentile as alternative outcome measures (233,364,365). However, further research is needed to evaluate their correlation with changes in body composition and to determine the amount of reduction needed to improve cardiometabolic health. Kelly and colleagues call for a general scientific and clinical consensus on BMI measures to be used, but unfortunately this is not yet available today.

In conclusion, **BMI-derived outcome measures can be used but it is advised to report more than one outcome measure, with a preference towards BMI percent of the 95th percentile and Δ BMI of the 95th percentile.**

9.1.2 Body composition

Evaluating body composition could be an alternative to using BMI-derived metrics. However, as written in **chapter 4**, an ideal technique is missing (366). Whereas MRI, CT and DEXA scanning are quite precise, they are time-consuming, high in cost and therefore unfeasible for daily practice, especially for repeated measurements (367).

The bioimpedance devices have benefits in terms of bed-side availability, cost and measurement time (189). They are feasible for repeated measurements in children and our study in **chapter 4** revealed the potential of the Body Composition Monitor (BCM) to detect trends at a group level in clinical research populations. Unfortunately, currently none of the available devices has been found sufficiently reliable at the individual level compared with the conventional methods to recommend routine clinical use in children with obesity.

Our research shows that patient characteristics such as age, gender and a higher BMI SDS contribute to the observed differences in body composition measurements between DEXA and BIS. One could have expected these results, because these characteristics determine the body's hydration constant and it is the incorporation of a fixed hydration constant in the adult bioimpedance devices that complicates their use in children. In children, there is no fixed hydration constant as this varies throughout growth (and with different body compositions), so using a fixed hydration constant will always create some bias in the BIS measurements.

Interestingly, a much better agreement was seen after BMI reduction, indicating that especially the excess body weight augments the bias between BIS and DEXA, which confirms previous findings (368). Ideally, a specific equation should be developed for children with obesity, not relying on a fixed hydration constant. This was recently done for the octopolar TANITA BC-418MA device in a group of Spanish children with obesity (369). For the BCM, a 2021 study of our own research group provided reference values that can be used to facilitate future research on this topic (173).

In conclusion, **conscious use of the bioimpedance devices is recommended acknowledging their possibility for detecting changes on a group level, but being aware of their limitations on an individual level.**

9.1.3 Cardiometabolic health

The main treatment goal of obesity treatment is improving health or preventing health problems from arising. This is achieved by reducing BMI, that is correlated to cardiometabolic health, and represents a surrogate outcome marker for a person's health. However, directly measuring an individual's health would be the preferred way for evaluating treatment effectiveness. Nevertheless, many cardiometabolic risk factors are present and - as indicated in **chapter 7** and **8** - they all respond differently to BMI changes. This complicates the identification of a single parameter that can be used as a universal golden standard to reflect a child's overall cardiometabolic health.

In the earlier days, the metabolic syndrome was a commonly used umbrella-term for different metabolic derangements. However recently, the limitations of the metabolic syndrome as a diagnosis (discussed in **chapter 7**) have led to abandoning this term. Instead, this is replaced by 'being-conscious' that risk factors tend to cluster, so that if one is present, one should be encouraged to search for the others as well (63).

In this thesis, we have used microvascular endothelial function as endpoint (89). This was chosen as it sums up all individual influences of separate cardiovascular risk factors and therefore has the potential to serve as a surrogate marker of cardiovascular risk. However, measuring microvascular endothelial function by peripheral arterial tonometry (PAT) is also time-consuming (20 minutes per patient), and rather expensive to use as a standardized test in clinical routine. Additionally, many confounders have to be taken into account when using PAT, such as room temperature, fasting, the effect of exercise or psychological stress (176). Furthermore, our results in **chapter 8** indicate that microvascular endothelial function responds late to cardiometabolic alterations. **The delayed response of microvascular endothelial function limits its use for short-term treatment effect evaluation, but makes it a suitable evaluation tool for cardiometabolic health over a longer period of time.**

Alternatively, one could measure macrovascular endothelial function by flow-mediated dilatation (FMD), as this shows a treatment response already after 6-12 weeks (370). Although noninvasive, FMD also suffers limitations in clinical feasibility as it is equally time consuming. Additionally, it requires the presence of a trained technician as measurements are more user dependent compared with PAT (95).

Pediatric reference values for endothelial function are still missing today, but the Youth Vascular Consortium is currently working on this topic to provide normative data (371).

9.2 Is there a role for e-health in pediatric obesity treatment?

9.2.1 New e-health interventions

As e-health could overcome factors associated with attrition, such as travel time or school absences, the role of e-health in pediatric obesity should be explored (128). In **chapter 5,** we have studied the effect of an online self-control training added to existing obesity treatment programs (372). Previous pilot studies (158,159) already demonstrated the potential of computer-delivered self-control trainings in children with obesity, but translation into applications available at home was lacking at the start of this project.

Our results show a potential effect for the younger, inpatient participants. These findings were contributed to more environmental control and supervision inpatient and the effect of puberty or more completed trainings in the younger participants. More focus on the psychologic aspects of the training was provided in the PhD of Dr. Tiffany Naets (373).

Motivating participants to start and continue trainings was an important challenge, leading to an average completion of only 35% of the sessions. While studies in a controlled environment report high feasibility, outpatient studies report drop-out rates up to 78% and planned intervention exposure of 19% (238,245,374). These results should push researchers to identify the underlying barriers. In our project, practical obstacles complicated training completion at home in the previous inpatients (238). Addressing motivations behind non-completion would help to achieve successful implementation.

A 2020 systematic review on engaging youngsters in digital mental health interventions (375) reported a preference for videos, limited text, the possibility of personalization (251) and connecting with peers (376), as well as text message reminders. Other previous reported alternatives are gamification (237) and smart-phone availability (156). However, it should be noted that before testing the effect of smartphone applications, usability should be evaluated. In 2022, Arthurs *et al.* reviewed usability and engagement testing of mobile health applications in pediatric obesity (377).

Surprisingly, they found only seven studies using all different tests (378–382). This underpins the current knowledge gap on how to perform usability testing of mobile (and more widely e-health) interventions in children with obesity, including the need for a standardized, validated usability tool.

In conclusion, a large gap was found between in-lab and real-world feasibility of online interventions. **In the future, the role for e-health interventions in pediatric obesity should be reassessed, but first the challenges,** such as participation, **complicating real-world implementation should be addressed.** Therefore, we advise future researchers to first optimize the implementation strategy (including mode of delivery, usability and identification of treatment barriers), whereafter scientific evaluation of the treatment in well-organized randomized controlled trials can be undertaken.

9.2.2 E-health instead of face-to-face usual care

Although the impact of online consultations on drop-out was not part of our research questions, we reflect shortly on this for two reasons. First, the inpatient center was on an outer border of the country, which possibly enlarged the aftercare drop-out. Second, during the COVID-19 lockdowns telemedicine was used to follow our participants.

Interestingly, previous research indicated positive results for online provided care in those with difficult health care access (284,285) with similar attrition and BMI reduction reported in children receiving the telemedicine follow-up compared to conventionally treated children (284). A 2012 review concluded that telemedicine was the preferred method for treating patients living far from the treatment center (285). More recently, a 2021 review on pediatric obesity confirms noninferiority when comparing the telehealth to in-person cohorts in clinical efficacy and attrition (383). Evidence from during the pandemic concludes the same, but points at a beneficial effect of the combined use of face-to-face and online visits (384). Thus, despite the long way to go in new therapeutic e-health interventions, **literature indicates that (partially switching to) online-delivered routine care seems promising in pediatric obesity**.

9.3 Should we change our point of view on a patient's BMI trajectory?

Clinical experience and scientific research, including our own data, demonstrate that initial treatment success is often followed by a relapse on the long-term. Interestingly, few pediatric data on the health consequences of this relapse have been found in literature.

In **chapter 7** we have reviewed this topic and we found no arguments that a new increase in BMI (after an initial decrease) led to a disproportionate increase in cardiometabolic risk factors. In fact, the benefit on some risk factors, such as hs-CRP and HDL-cholesterol, even persisted over a longer period, despite a return to a higher BMI (307). The same conclusion was also drawn from our own data in **chapter 8** by studying the participants who reached a BMI low point at 12 months and had regained several BMI points by 18 months. Our data showed that most risk factors were unchanged from the BMI nadir 6 months before, despite weight regain. Endothelial function and HDL-cholesterol had even further improved. It should be mentioned that these findings cover only a 6-month period in a population with a rather large average BMI decrease of 8.7 kg/m^2. Therefore, in the long-term those risk factors are likely to deteriorate again knowing that metabolic healthy obesity is only a transient phase in the progression to metabolic unhealthy obesity (308). Transitions between metabolic healthy and unhealthy obesity have been described in children and adolescents as well (385).

However, for most of the children with excess body weight, repeated cycles of losing and regaining weight follow one another. Therefore, in **chapter 8**, we also investigated the effect of BMI variability during weight loss treatment on cardiometabolic risk factors, including endothelial function as a comprehensive endpoint. Our findings stated that an overall reduction in BMI over time took precedence over how this reduction was achieved, as variability had no impact on most risk factors.

The cardiometabolic impact of weight regain seems to be rather reassuring, at least during the first six months after the initial BMI decrease. But one should not forget to talk about the personal impact regarding the decision for treatment (dis)continuation. For example, in **chapter 6** our data demonstrated that BMI decrease during the first 6 months predicted treatment drop-out at one year and that a higher BMI in general, especially in co-occurrence with more metabolic deregulations, predestines a patient to drop-out and complicates BMI reduction.

Therefore, early treatment change or intensification should be considered if treatment is unsuccessful. Referral to an inpatient center could be a solution for those treated in outpatient care, although long waiting lists complicate transition. Another option in adolescents is to switch to an intensive diet with more rapid weight loss such as a very low energy diet, low carbohydrate diet or intermittent fasting. Good results have been described with short-term improvement, but long-term outcomes are unknown (386). Similarly, association of liraglutide (a GLP-1 agonist) provides additional BMI reduction of -0.22 SDS, but a re-increase was seen after withdrawal (121). Finally, despite bariatric surgery being very effective in BMI reduction with average reductions of 26-28% in the body weight of the participating adolescents (124,387), this option is not reimbursed for minors in Belgium, so is financially unavailable for most patients. Interestingly, our study indicated that socio-economic arguments were a frequent reason for drop-out in outpatient treatment, emphasizing the need for addressing social problems as well in outpatient obesity teams.

Ideally, an individualized plan would be designed with involvement of specialties based on individual needs (e.g. pediatrician, psychologist, dietician, physiotherapist, social worker, psychiatrist). As involvement of all these specialties would mean a significant increase in treatment costs, a convention (as with diabetic patients) would be a valuable step to optimize pediatric obesity care. This option was reviewed in Belgium and has led to the introduction of a new carepath in Belgium since December 1st 2023 including the recognition of specialized pediatric multidisciplinary obesity centers.

In conclusion, treatment should be targeted at BMI reduction in children with obesity and the lowering of BMI should prioritize over how this is achieved, i.e. slow and steady vs faster with partial relapse. A relapse seems to not immediately impact cardiometabolic health as there is a time window where the child still benefits from the previous BMI loss. **BMI regain should therefore be seen in relation to the pretreatment BMI. And if BMI regain occurs, it should be perceived as a period wherein treatment changes should be considered to retain cardiometabolic benefits**.

9.4 Critical remarks

In this dissertation, we investigated different aspects of evaluation, treatment and outcome of children with obesity. Although different limitations were identified for each study individually, we would like to highlight some general limitations.

Our study population across chapters was included through the WELCOME trial. Although our cohort was quite large and ethnically diverse, most of the participants lived in Belgium. Therefore, these data might show some bias compared with other international cohorts due to the rather small area where all participants were recruited.

Second, there is no set protocol for a multidisciplinary obesity treatment and practices vary between centers. The centers participating in our study all had a specialized treatment program, so our treatment results are likely to change if children were recruited at centers where limited resources are devoted to pediatric obesity care.

Finally, COVID-19 broke out in the middle of our study. For some participants, the lockdown helped them to lower their BMI through fewer restaurant visits or more time to exercise, while in others the opposite evolution was seen by the financial consequences prioritizing over investing in healthy food. Therefore, the effect of COVID-19 on a patient's treatment result is difficult to correct from our data. Internationally, a doubling of prepandemic rates of BMI increase was reported in children aged 2-19 years that was more pronounced in those with pre-existent overweight (388).

9.5 Future perspectives

This thesis provides insights on various aspects of the clinical trajectory of children with obesity. New emerging therapies that can be added to the current treatment offer interesting possibilities, but as with any new therapy, long-term results must be evaluated. Obesity treatment is not a one-size-fits-all approach. This was demonstrated by the results of the WELCOME trial (**chapter 5**), where a treatment effect was found only among younger participants in residential care. Another example was found in the results of our study exploring baseline predictors for treatment outcome of patients in an in- or outpatient treatment program (**chapter 6**). Therefore, research questions should generally be changed from 'Is this treatment effective for every child with obesity?' to 'In which child with obesity would this treatment be effective?'

Treatment drop-out and non-adherence have been named in most pediatric obesity research, but a thorough understanding of the motives behind drop-out or treatment failure is a crucial next step towards improvement. We therefore advocate for more research on this topic, as this would provide valuable insights for ameliorating treatment adherence and participation in any type of intervention. For example, in our outpatient cohort, drop-out stemmed from social motives in half of the cases, indicating the need for a social worker in outpatient obesity treatment teams. In case of the online self-control training, participants frequently perceived practical obstacles, so addressing these would likely improve adherence (238). As previously stated, the development of a standardized, validated usability tool would be of added value to evaluate new e-health interventions.

Our data demonstrated that an overall BMI reduction overrules the way it is achieved (i.e. the variability in the trajectory) in cardiometabolic benefits at least during the first 1.5 years. Although, BMI maintenance after BMI loss must remain the primary treatment goal, this knowledge should change the view on interventions that lead to rapid short-term BMI loss but lead to some BMI re-increase afterwards, for example very strict diets, GLP-1 analogues…

BMI regain should be viewed as a normal occurrence in obesity treatment and future researchers should be encouraged to study and report BMI regain, including (other) cardiometabolic health markers, for example macrovascular endothelial function, to gather information on how long the physical health benefits persist and what influences them. Our suggestions for future research are listed in **table 9.1**

Table 9.1: overview of questions for future research.

Evaluation
Body composition • Are the measurements of the BCM interchangeable with those of the 4-C model and if not, what determines this bias? Cardiometabolic endpoints • How rapid does flow mediated dilatation responds to BMI fluctuations and could it be a surrogate endpoint to measure the evolution of overall cardiometabolic health in children with obesity?
Management
E-health • Which delivery mode is most suited for offering an e-health intervention to children with obesity (e.g. a website, mobile app, YouTube tutorials…) and what are the perceived barriers with each of them? • How can we reliably evaluate and compare usability of these online interventions?
Treatment outcome
Drop-out and treatment outcome • What are the motives behind dropping out from pediatric inpatient obesity treatment? • Can a (parent and patient) pretreatment preparation program limit drop-out and post-treatment BMI regain? • Could the help of a social nurse improve outpatient pediatric obesity treatment outcome and limit drop-out? BMI regain • How long do the cardiometabolic ameliorations of an initial BMI loss persist and what is the role of the amount of BMI relapse on the persistence of these benefits?

Lastly, it has to be said that although this thesis focuses on the treatment trajectory of children with obesity, it should be mentioned that primary prevention, e.g. preventing obesity from developing, will always be of prime importance relative to any aspect of obesity treatment.

Chapter 10: Summary

In 2018, 5.8% of Belgian children were diagnosed with obesity. Even in childhood, obesity is associated with several comorbidities, including dyslipidemia, hypertension and endothelial dysfunction. The current obesity pandemic with its comorbidities is estimated to account for 6-8% of Belgium's annual health expenditure. This dissertation examined various aspects ranging from clinical evaluation to management and treatment outcome of children with obesity.

Regarding clinical evaluation a first question arose as to how to evaluate the treatment effect in children with obesity. BMI SDS – although widely used - correlates only weakly with fat mass and metabolic comorbidities. Body composition measurement could offer a solution, but current techniques are unfeasible for repeated measurements. In **chapter 4**, body composition measurements were compared between the Body Composition Monitor (BCM), a device based on bioimpedance spectroscopy suitable for bedside evaluation, and Dual Energy X-ray Absorptiometry, the current clinical golden standard. Our results showed that the BCM could not be used to monitor individual children with obesity, but could be useful in large clinical studies to measure changes in body composition at a group level.

Current obesity treatment in children has a rather moderate outcome. Previous research discovered a relation between more self-control and improved treatment success. In the WELCOME trial **(chapter 5)**, we examined whether adding an online self-control training improved BMI outcome of current pediatric obesity programs. Children aged 8-18 years with obesity were included from one in- and two outpatient centers. Our results showed a potential favorable treatment effect only for 8- to 12 year old children in inpatient care, potentially due to external control on training execution and prepubertal brains being more prone to the training effect. As this was one of the first large-scale trials translating in-lab findings to a real-world application of an online self-control training, we made recommendations to improve participation and adherence to online (self-control) training for future research within this target population.

As illustrated by the WELCOME trial, pediatric obesity treatment is not a 'one-size-fits-all'-phenomenon. In Belgium, in- and outpatient obesity treatments are available, but long-term results are modest. Despite 2 in 3 children with obesity having at least 1 cardiometabolic risk factor, little is known on how this affects treatment outcome. **Chapter 6** zoomed in on the pretreatment patient characteristics and metabolic derangements predicting treatment outcome. Residentially, BMI declined less during treatment when more pretreatment metabolic comorbidities and a higher baseline BMI were present, indicating these potentially preclude optimal treatment participation. As a solution, pretreatment preparation programs aimed at already changing family habits and losing some weight beforehand could be implemented. This could also help counteract the BMI regain seen after returning home as this favorably affects those at older age already having a higher BMI before treatment started. Furthermore, treatment seemed least feasible for children with a higher weight or older age, as they dropped out more often during residential stay or aftercare, possibly due to the lack of success compared to their counterparts, similar to children in outpatient care. In turn, higher leptin and adiponectin levels before starting residential treatment were predictive of less BMI gain after the end of treatment, a finding requiring further research.

Outpatient drop-out during the first treatment year was predicted only by BMI loss during the first 6 months and was attributed mainly to motivational reasons, promoting rapid treatment redirection or intensification when treatment fails. In the second treatment year, patients with high BMI were more prone to drop-out and this was attributed to social motives in half of the patients underpinning a need for social support in pediatric obesity treatments. Cardiometabolic comorbidities could not predict treatment outcome after one or two years of outpatient treatment, suggesting possibly more impact of psychosocial or economic factors in this setting.

Interestingly, despite BMI regain being common, its cardiometabolic consequences were hardly studied in pediatric populations. Therefore, in **Chapter 7**, we reviewed the literature asking: "What is the effect of a new BMI increase after previous BMI loss on cardiometabolic health in children with obesity?" The nine included studies showed that the benefit of initial BMI reduction persisted on some cardiovascular risk factors, such as HDL-cholesterol, despite BMI regain. Furthermore, no arguments could be found that a new BMI increase (following an initial reduction) negatively affected cardiometabolic health compared to baseline. In **Chapter 8** our data confirmed that patients still benefited in terms of insulin resistance, pro-inflammatory status, and triglycerides after 6 months of achieving their BMI nadir – despite some regain. HDL-cholesterol and endothelial function even further improved. The changes in cardiometabolic risk factors, including lipids, pro-inflammatory status, insulin resistance, and endothelial function, were mainly related to the net BMI decrease over time and not to the variability.

In conclusion, achieving BMI reduction is prioritized over the variability of how it is achieved. An online self-control training was not effective in reducing BMI in a general population of children with obesity, but a subgroup potentially benefited. In the future, more research on how to implement online trainings and how to adapt them to a certain target population is therefore warranted. In inpatient treatment, more metabolic comorbidities and a higher BMI impact outcome, including drop-out and BMI reduction. In outpatient care, initial treatment success is important to retain children, but the long-term results are mainly determined by other factors than personal or physical pretreatment characteristics. Lastly, focusing on body composition measurements by bioimpedance techniques as an evaluation tool has potential, but currently the BCM device should only be used on a cohort level due to insufficient reliability in individual measurements.

This thesis reinforces current insights on the clinical evaluation, approach and outcome of children with obesity, but these findings need further validation in new cohorts.

Chapter 11: Samenvatting

In 2018 leed maar liefst 5.8% van de kinderen in België aan obesitas. Zelfs op kinderleeftijd is obesitas al geassocieerd met verschillende comorbiditeiten, waaronder dyslipidemie, hypertensie en endotheeldysfunctie. De huidige obesitas pandemie met zijn geassocieerde comorbiditeiten is naar schatting verantwoordelijk voor 6-8% van de jaarlijkse gezondheidsuitgaven in België. Dit proefschrift onderzoekt verschillende aspecten gaande van de evaluatie tot de aanpak en behandeluitkomst in kinderen met obesitas.

Allereerst stelt zich de vraag hoe het behandeleffect bij kinderen met obesitas moet worden geëvalueerd. BMI SDS correleert slechts zwak met de vetmassa en metabole comorbiditeiten. Het meten van lichaamssamenstelling kan een oplossing bieden, maar de huidige technieken zijn klinisch onbruikbaar voor het uitvoeren van herhaaldelijke metingen onder andere door stralingsbelasting of een lange meettijd. In **hoofdstuk 4** vergeleken we lichaamssamenstelling gemeten met de 'Body Composition Monitor' (BCM), een toestel gebaseerd op bio-impedantie spectroscopie, met de metingen van de 'Dual Energy X-ray Absorptiometry' (DEXA) scan. Onze resultaten toonden dat de BCM niet gebruikt kon worden om individuele kinderen met obesitas te meten en te volgen, maar wel bruikbaar kan zijn in grote studies om de verandering in lichaamssamenstelling op groepsniveau te evalueren.

De huidige behandeling van obesitas bij kinderen heeft eerder matige resultaten. Voorgaand onderzoek toonde dat meer zelfcontrole de behandeluitkomst kan verbeteren. Daarom gingen we in **hoofdstuk 5**, de 'WELCOME' trial, na of een online zelfcontrole training toegevoegd aan bestaande behandelprogramma's leidde tot meer afname in BMI SDS. Kinderen tussen 8 en 18 jaar oud met obesitas werden geïncludeerd in één residentieel en twee ambulante behandelcentra. Helaas, kon er geen effect in de totale populatie worden aangetoond. In een subgroep van 8- tot 12-jarige kinderen, die residentieel werden behandeld, werd echter wel een potentieel behandeleffect gemeten.

Dit gemeten effect zou verklaard kunnen worden door de aanwezigheid van externe controle op het uitvoeren van de training en een hogere vatbaarheid van het prepubertaire brein voor het trainingseffect. Omdat dit de eerste grootschalige studie was die een online zelfcontrole training uit het laboratorium naar een echte patiëntenpopulatie bracht, formuleerden we aanbevelingen voor toekomstig onderzoek om deelname en therapietrouw te bevorderen.

Zoals de WELCOME trial aantoont, is de behandeling van kinderobesitas geen "one-size-fits-all"-verschijnsel. In België zijn in- en extramurale behandelingen beschikbaar, maar de resultaten op lange termijn zijn suboptimaal. Hoewel 2 op de 3 kinderen met obesitas minstens 1 cardiometabole risicofactor hebben, is er weinig bekend over hoe dit de behandeluitkomst beïnvloedt. In **hoofdstuk 6** werd daarom onderzocht daarom welke patiëntenkenmerken en metabole risicofactoren voorspellend zijn voor de uitkomst van de behandeling. In een residentiële behandeling daalde de BMI minder bij aanwezigheid van meer metabole comorbiditeiten en een hogere BMI voorafgaand aan de behandeling, wat erop wijst dat deze mogelijk een optimale deelname aan de behandeling in de weg staan. Een oplossing zou kunnen zijn om voor de behandeling reeds voorbereidingsprogramma's te implementeren die erop gericht zijn al levensstijlveranderingen teweeg te brengen om zo vooraf reeds gewicht te verliezen. Dit zou ook kunnen helpen om de BMI toename na thuiskomst tegen te gaan, aangezien dit voornamelijk de oudere deelnemers treft die al een hogere BMI hadden voordat de behandeling begon. Bovendien vielen kinderen met een hoger gewicht of een oudere leeftijd vaker uit tijdens de residentiële behandeling of in de nazorg, mogelijk vanwege het gebrek aan succes in vergelijking met hun mede-deelnemers, vergelijkbaar met wat onze data toonden bij kinderen in ambulante zorg. Een hoger leptine- en adiponectinegehalte vóór aanvang van de residentiële behandeling waren dan weer beschermend voor een BMI toename na afloop van de behandeling, een bevinding die verder onderzoek vereist.

Ambulante uitval tijdens het eerste behandeljaar werd alleen voorspeld door de BMI reductie tijdens de eerste 6 maanden en werd voornamelijk toegeschreven aan motivationele redenen, waardoor een snelle heroriëntatie of intensivering van de behandeling moet overwogen worden bij onvoldoende initiële resultaten. In het tweede behandeljaar vielen vaker patiënten met een hogere BMI uit en werd dit bij de helft van de deelnemers aan sociale redenen toegeschreven, hetgeen de noodzaak van een sociaal verpleegkundige in de behandeling van kinderobesitas onderstreept. Cardiometabole comorbiditeiten konden het resultaat van de behandeling na één of twee jaar niet voorspellen, wat wijst op een mogelijk grotere invloed van psychosociale of economische factoren bij ambulante patiënten.

Opvallend is dat ondanks dat een nieuwe BMI toename veelvoorkomend is, er bijna geen pediatrische studies zijn die zich verdiepen in de cardiometabole gevolgen hiervan. Daarom hebben we in **hoofdstuk 7** een literatuurreview geschreven met als vraag: 'Wat is het effect van een nieuwe BMI toename na voorgaande BMI afname op de cardiometabole gezondheid in kinderen met obesitas?' De negen geïncludeerde studies toonden dat het voordeel van de initiële BMI reductie op sommige cardiovasculaire risicofactoren, zoals HDL-cholesterol, langer persisteerde, ondanks een nieuwe BMI toename. Verder waren er geen argumenten dat een nieuwe BMI toename (volgend op een initiële afname) de cardiometabole gezondheid negatief beïnvloedde vergeleken met de cardiometabole gezondheid voor de initiële BMI reductie. In **hoofdstuk 8** bevestigden we met onze eigen data dat patiënten - ondanks een nieuwe gewichtstoename - 6 maanden na het bereiken van hun maximaal gewichtsverlies nog steeds voordelen hadden op vlak van insulineresistentie, pro-inflammatoire status, en triglyceriden met zelfs nog een toename van de HDL-cholesterol en een verbetering van de endotheelfunctie. Verder zagen we dat de veranderingen in cardiometabole risicofactoren, waaronder lipiden, pro-inflammatoire status, insuline-resistentie en endotheelfunctie, voornamelijk gerelateerd waren aan de netto BMI afname.

We concludeerden dat het bereiken van BMI-reductie prioritair is ten opzichte van de variabiliteit waarmee die wordt bereikt. Een online zelfcontrole training was niet effectief in het verlagen van de BMI in een algemene populatie van kinderen met obesitas, maar een subgroep had er mogelijk baat bij. In de toekomst is daarom meer onderzoek nodig naar hoe online trainingen kunnen worden geïmplementeerd en hoe ze kunnen worden aangepast aan deze doelgroep. Bij intramurale behandeling hebben meer metabole comorbiditeiten en een hogere BMI een negatieve invloed op de uitkomst, waaronder drop-out en BMI reductie. Ambulant is voornamelijk het initiële behandelsucces belangrijk om kinderen in behandeling te houden, maar de resultaten op lange termijn worden vooral bepaald door andere factoren dan de persoonlijke of lichamelijke kenmerken voorafgaand aan de behandeling. Ten slotte heeft het meten van lichaamssamenstelling door bio-impedantietechnieken als evaluatie-instrument potentieel, maar momenteel mag het BCM toestel alleen op groepsniveau worden gebruikt vanwege onvoldoende betrouwbaarheid in individuele metingen.

Dit proefschrift versterkt de huidige inzichten over de klinische evaluatie, aanpak en uitkomst van kinderen met obesitas, maar deze bevindingen moeten nog verder worden gevalideerd in nieuwe cohorten.

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Curriculum vitae

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Publications related to the dissertation

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Grants and scientific awards

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Educational activities

- Supervisor of master thesis of master in Biomedical Sciences of Makhout S in period 2020-2021

The role of brain-derived neurotrophic factor in obstructive sleep apnea and endothelial function in an obese pediatric population

- Supervisor of master thesis of master in Medicine of Basstanie R, Vandenbroucke SA and Viskens AS in period 2018-2021

The relation between OSAS and NAFLD in an obese pediatric population: a prospective cohort study

- Supervisor of master thesis of master in Medicine of Willaert L and Mattheesen A in period 2020-2023

The use of the ApneaLink Air as a screening device for the diagnosis of obstructive lseep apnea in a pediatric population with obesity

Certificates

- Certificate 'Advanced pediatric life support' provided by the Advanced Life Support Group in 2022

- Course 'ICH-GCP certificate E6R2' + certificate provided by the Antwerp University Hospital, Edegem, Belgium in 2018 with renewal in 2020

- Certificate 'Statistics in Medicine'. Online course provided by Stanford University, California, USA in 2018

- Course 'linear mixed models' provided by StatUA, University of Antwerp, Antwerp, Belgium 2019.

- Course 'Writing Academic Papers' provided by the Antwerp Doctoral School, University of Antwerp, Antwerp, Belgium in 2019

- Course 'Snellezen' provided by the Antwerp Doctoral School, University of Antwerp, Antwerp, Belgium in 2019

- Certificate 'Neonatal life support' provided by the European Reanimation Council (ERC) in 2018

Memberships

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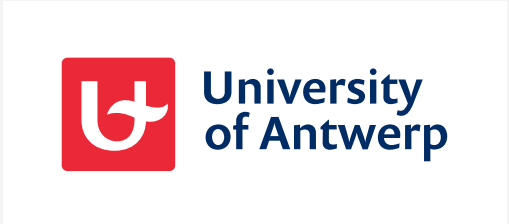
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