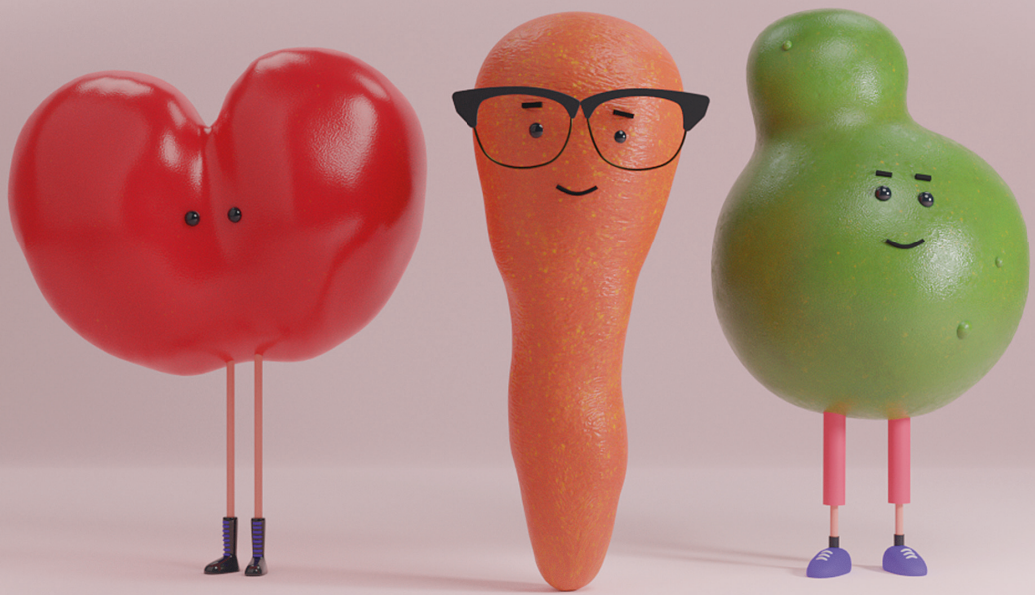
Childhood obesity

Behind the doors of the epidemic



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Thesis

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CHAPTER 1

General Introduction

Childhood obesity is reaching alarming proportions and is currently one of the most important public health problems. It is associated with significant physical and psychosocial health consequences, both in the short and long term.[1] In addition to the negative health outcomes and reduced quality of life, obesity poses a substantial economic burden on global health-care systems. Black et al. calculated the additional annual medical costs due to overweight and obesity among 6 to 13 year olds to be about $43 million (in 2015 AUD). This is driven by a higher utilisation of general practitioner and specialist doctors.[2] In a recently published study in The Netherlands, Wijga et al. found that mean 1-year healthcare expenditure was €837 per overweight child, and for non-overweight children €616.[3] This difference was mainly due to significant differences in utilisation of hospital care and mental healthcare. In view of the prevalence, health consequences, and costs of childhood obesity, there has been substantial interest in identifying effective interventions to prevent and treat excess weight gain in young people.

ECHO recommendations:

1. Implement comprehensive programmes that promote the intake of healthy foods and reduce the intake of unhealthy foods and sugar-sweetened beverages by children and adolescents.
2. Implement comprehensive programmes that promote physical activity and reduce sedentary behaviours in children and adolescents.
3. Integrate and strengthen guidance for noncummunicable disease prevention with current guidance for preconception and antenatal care, to reduce the risk of childhood obesity.
4. Provide guidance on, and support for, healthy diet, sleep and physical activity in early childhood to ensure children grow appropriately and develop healthy habits.
5. Implement comprehensive programmes that promote healthy school environments, health and nutrition literacy and physical activity among school-age children and adolescents.

In 2014 the Commission on Ending Childhood Obesity (ECHO) was established, to review, build upon and address gaps in existing mandates and strategies. In 2016 this commission produced its final report to the World Health Organization (WHO). The report presents a comprehensive, integrated package of recommendations to address childhood obesity (see text box), and proposes actions and responsibilities of key stakeholders. In this thesis, the focus is on the sixth recommendation of the Commission: weight management. But in addition to questions regarding the development of more effective and targeted treatments for children and adolescents with overweight and obesity, many other obesity-related problems and questions are faced in daily practice. Therefore, in this thesis obesity will be approached from different points of view; the research presented here is based on clinically encountered research questions and problems. The next paragraphs of this General Introduction will provide some general background information about the childhood obesity epidemic, supplemented with more specific information about the subjects brought forward in the chapters. The General Introduction ends with the Scope and outline of this thesis.

LOOKING BEYOND PREVALENCE – THE OBESITY EPIDEMIC

Definition and diagnosis of childhood obesity

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.[4] Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity. BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. For adults, WHO defines overweight and obesity as follows: overweight is a BMI greater than or equal to 25 kg/m^2, and obesity is a BMI greater than or equal to 30 kg/m^2. For children, however, age needs to be considered when defining overweight and obesity, due to the changing body proportions during growth. Cole et al. proposed a standard definition for child overweight and obesity, based on and linked to the corresponding adult BMI cut-offs.[5] However, the disadvantage of these cut-offs is that they are not expressible as BMI centiles. Therefore, in 2012 the international cut-offs were reformulated in terms of underlying LMS (normality [L], median [M], and dispersion [S]) curves, which allowed BMI to be expressed as a centile or Z-score[6], making it possible to compare with international and WHO cut-offs. In this thesis, we have used these widely accepted international cut-offs, which are often referred to as the International Obesity Task Force (IOTF) criteria. Important to remark, is the fact that recent analyses suggest that BMI Z-scores poorly reflect adiposity among children and adolescents with severe obesity.[7,8] Therefore, the Centers for Disease Control and Prevention (CDC) recommended using a relative BMI measure to describe youth with severe obesity.[9] Nowadays, this new classification system is frequently used[10], while others still use the IOTF criteria, as in this thesis.

Prevalence of childhood obesity

Although some studies showed a stabilisation and (temporarily) reversal of child obesity, especially in the young age group[11–14], in the past few years the prevalence of childhood obesity has not leveled off. In contrast, an increase has been shown. In 2015-2016, in US children and adolescents aged 2 to 19 years the prevalence of overweight and obesity class 1, 2, and 3, defined using the CDC recommendation using a relative BMI measure[9], were 35.1%, 18.5%, 6.0%, and 1.9%, respectively.[10] Non-Hispanic African American and Hispanic children had higher prevalence rates of overweight and all classes of obesity compared with other races. The prevalence of overweight and obesity increased with age. When compared to 2013-2014, most notably were the increase in prevalence of class 1 obesity among young boys (2-5 years), and an increase of overweight among older adolescent girls. No other significant changes were observed for any of the race and/or sex subgroups in any of the

obesity categories. In the Netherlands, using the IOTF criteria[6], in 2017 the prevalence of overweight (excluding obesity) was 11.1% in boys and 9.9% in girls; the prevalence of obesity was 2.5% and 3.1%, respectively.[15] Earlier studies in the Netherlands showed considerable differences between ethnic groups: Turkish children had the highest mean BMI Z-score, followed by Moroccan and Dutch children.[12] Also educational level influences the prevalence of overweight and obesity: the mean BMI Z-score of children whose parents had a low education was clearly higher than in those of higher educated parents.[12,16]

Etiology of childhood obesity: targets for treatment

The pathophysiology of excess weight gain is complex with interactions between genetic factors, environment and biological factors. In 2001, Davison et al. proposed a contextual model for predictors of childhood overweight and recommendations for future research, the ecological model. They highlighted the importance of considering the context, or ecological niche, in which a person is located.[17] The ecological model is primarily directed at evaluating and integrating research assessing risk factors for childhood overweight, but in our opinion it can also be applied to the treatment setting. We will discuss the influence of family and environment on obesity treatment here, using the ecological model as outline.

First of all, central in the ecological model are the child characteristics and child risk factors. Behaviour change is not one size fits all. Burgermaster et al. suggested the presence of specific subgroups of participants who respond differently to behaviour change interventions.[18]

Second, parenting styles and family characteristics are mentioned in the ecological model. A healthy lifestyle evolves within the context of the family. The widely applied family systems theory (FST) views the family as a complex, interacting system, and provides a framework for understanding family functioning as an open, ongoing, goal-seeking, self-regulating social system.[19] FST-specific variables are rarely assessed in childhood obesity treatment studies, but they likely exert great influence on health behaviours of the family.[19] According to FST, change happens at the family level to influence overall family functioning and long-term individual behavioural change.[20] As summarised by Pratt et al., significant associations between impaired family functioning, risk of developing overweight/obesity and current overweight/obesity in youth has been found before.[19] Of note, family functioning is distinctively different from parenting, which has also shown to influence obesity prevalence and treatment.[21]

Family-based lifestyle interventions are recognised as the mainstay of treatment for paediatric overweight and obesity. Parents play a key role in influencing healthy weight management in children through role modelling and encouraging appropriate lifestyle behaviour patterns. A recently published systematic review showed that parents provide the impetus for programme initiation, which was driven largely by a concern for their child's psychological health and wellbeing.[22] During adolescence, family dynamics have been shown to be an important issue in weight-loss treatment. Including both parents and adolescents in therapy

is crucial for tackling obesity and addressing health needs related to this age group.[23] The importance of involving parents or the family in paediatric overweight and obesity treatment has been widely emphasised.[24] However, it remains largely unknown how to optimise the involvement of parents and family members in treatment, especially when it comes to long-term weight maintenance.

Parental control over their children's behaviours typically diminishes as the child develops and becomes increasingly subject to the influences of people and environments outside of the family unit.[24] Summarised as 'community, demographic, and societal characteristics' in the ecological model, these are clearly associated with the development of weight excess and the potential result of obesity treatment. In children, school constitutes an important part of the daily life. Specific school food environment policies have shown to improve targeted dietary behaviours.[25] Furthermore, leisure time activity and accessibility of recreational facilities play an important role in childhood obesity. Best friends' BMI Z-score was the best predictor of participants' BMI Z-score in a study examining the variability in weight and health behaviours among weight-discordant siblings. In addition, being active and spending time with friends was associated with overall physical activity.[26] Place-based policies, shaping the environment in which children spend most of their time (i.e. neighborhoods and schools) have the potential to meaningfully reduce child obesity.[27] A healthy community environment is critical to promote a healthy lifestyle.[28]

In conclusion, a complex set of factors from multiple contexts, summarised in the ecological model, interact with each other to place a child at risk of overweight, and at least partly determine the effect of obesity treatment. Note that the three treatment programmes in Hospital Gelderse Vallei, elaborated on in the final section of this General Introduction, all apply the theoretical framework of Davison by differently directing the programme at the children themselves and their family. The influence of the environment, including challenging moments within the direct context of the child (i.e. breaks at school, influence of peers, holidays, etc.), is extensively discussed with the groups during the treatment programs.

CHILDHOOD OBESITY AND BEYOND – CONSEQUENCES OF CHILDHOOD OBESITY

The impact of childhood obesity goes beyond health: as previously illustrated, the economic consequences of childhood obesity are much larger than previously estimated. But even more important, persistence of overweight leads to serious physical and psychosocial health problems, affecting the child's and parent's everyday quality of life. Before we will elaborate on cardiometabolic risks associated with obesity in childhood and adolescents, we will therefore first comment on Health Related Quality of Life (HRQoL).

Health-related quality of life

HRQoL refers to the subset of quality of life directly related to an individual's health. Health, as defined by the World Health Organization (WHO), includes physical, mental and social wellbeing.[29] There are several feasible, reliable and validated pediatric quality of life questionnaires that can be used for research purposes.[30] These include generic and disease-specific questionnaires. Generic questionnaires intend to measure all dimensions of HRQoL, and can therefore be applied in healthy populations as well as in any clinical population regardless of the type of medical condition.[31] Disease-specific questionnaires focus on those dimensions that are likely to be affected by a specific condition or treatment. They are generally considered to be more sensitive to change in clinical applications for which they were developed compared with generic questionnaires.[32] A combination of generic and disease-specific questionnaires would be the most appropriate approach. For childhood obesity, the disease-specific questionnaire IWQOL-Kids is available for children aged 11 and older. Next, parent and self-reports are available, and provide different outlooks on childhood QoL.[30] Both views are useful in providing a complete picture of the impact of obesity on childhood HRQoL. HRQoL assessments can help patients and providers differentiate between treatments that have similar weight-loss patterns but different side-effect profiles or different impacts on HRQoL.[33]

Obesity has been argued to be a chronic relapsing progressive disease process, in the same sense that hypertension or hypercholesterolemia is a disease.[34] A large population-based study showed that prevalent childhood chronic conditions, such as asthma, eczema, ADHD, dyslexia and migraine/severe headache, have an important impact on HRQoL.[35] In view of obesity as a chronic disease, decrements in HRQoL can also be expected in the obese population. Indeed, there is growing recognition of the relationship between HRQoL and childhood obesity, although the literature is not entirely in agreement.[36–45] Most studies point to a decreased HRQoL in children with overweight or obesity, as well as to an improvement of HRQoL during obesity treatment which is not exclusively attributable to reductions in BMI Z-score. As chronic conditions in childhood are common and dynamic, the

importance of comprehensive treatment programmes is confirmed, preferably connecting to the principle of chronic disease by applying a chronic care model with providers and health systems working together to improve the management of these conditions and the related consequences.[46]

Cardiometabolic risk

In children, cardiovascular risk has been measured using various approaches. Traditionally, the term metabolic syndrome (MetS) has been used to identify adults with at least three of five cardiometabolic risk factors (hyperglycemia, increased central adiposity, elevated triglycerides, decreased high-density lipoprotein cholesterol, and elevated blood pressure) who are at increased risk of diabetes and cardiovascular disease (CVD). However, in children MetS is difficult to define[47,48] and has unclear implications for clinical care. Therefore, over time, the attention has been diverged to focusing on screening for and treating of individual risk factor components of MetS.[49] Hereby, cardiometabolic risk factor clustering is emphasised over the need to define a pediatric MetS. In literature, continuous cardiometabolic risk scores are used that incorporate components such as adiposity, lipids, metabolic factors and blood pressure. As summarised by Kamel et al. in a recently published review, the most commonly included score components are waist circumference, triglycerides, high-density lipoprotein cholesterol, glucose, and systolic blood pressure.[50] Although scores can be used as an organising frame, the focus for clinical screening and treatment should be on the individual cardiometabolic risk factors (i.e. hypertension, glucose abnormalities, dyslipidemia), for early identification before more serious complications result.[49,51]

One of the obesity-associated cardiometabolic risks is hypertension. Over the last few decades, the prevalence of primary hypertension in children and adolescents has increased, in parallel with the growing prevalence of childhood overweight and obesity.[52] Fowokan et al. recently evaluated and summarised the evidence for potential correlates of BP and hypertension in children aged 18 years and younger.[53] All correlates fell within one of three domains: physiological, social and behavioural. A broad variation in BP and in statistical methodology was identified in the studies, making it difficult to summarise the existing literature.

Many studies have demonstrated that elevated BP in children and adolescents is associated with hypertensive target-organ damage (TOD), including changes in left ventricular mass index and function, carotid intimal-medial thickness (cIMT), and pulse wave velocity (PWV).[54–60] Considering these detrimental short-term and long-term effects of high BP in childhood, measurement of BP and detection of HTN in the young have important implications for future cardiovascular health.[59] The diagnosis of elevated BP and HTN depends on an accurate blood pressure measurement, which can present a challenge to the clinician due to

potential problems including improper technique, observer bias, and accomodation effect. In order to overcome these limitations, ambulatory 24-hour BP measurement (ABPM) is now increasingly recognised as indispensable for the diagnosis and management of HTN.[61–66] Although scientific and practical shortcomings in the pediatic use of ABPM exist, it may be very valuable in longitudinal care of many children and adolescents with chronic conditions including obesity.[56,67]

Children with high BP and obesity frequently have other cardiometabolic risk factors. These risk factors are known to track into adulthood[68], and together they are linked to the development of cardiovascular disease. On the molecular level, low-grade inflammation has been addressed to play an important role in this relationship between obesity and increased cardiovascular risk, through a cascade of effects. The cascade starts with development of excessive adipose tissue. Adipose tissue consists of adipocytes, the mature fat cells, and a stromal-vascular fraction. The stromal-vascular fraction contains a mixture of cell types, including fibroblasts, pre-adipocytes, endothelial cells and an array of immune cells. With excessive fat accumulation, a substantial change in the amount and function of immune cells in the adipose tissue occurs, i.e. with regard to the number and activity of macrophages, mast cells, neutrophils, T- and B lymphocytes, and the activity of eosinophils and several subsets of T-lymphocytes. Additionally, as obesity develops, adipocytes undergo hypertrophy owing to increased triglyceride storage.[69] With limited obesity, it is likely that the tissue retains relatively normal metabolic function and has low levels of immune cell activation and sufficient vascular function. However, qualitative changes in the expanding adipose tissue can promote the transition to a metabolically dysfunctional phenotype. Immune cells, including macrophages and lymphocytes, infiltrate the adipose tissue where they alter adipocyte responses to metabolic signals, including insulin, as well as adipokine secretion, favouring adipose tissue expansion and activation. In states of obesity, adipose tissue generates large amounts of pro-inflammatory factors, including leptin, tumor necrosis factor (TNF), interleukin-6 (IL-6), chemerin, and IL-18. These pro-inflammatory factors are released in the circulation from adipose tissue, which causes low-grade inflammation.[70] Chronic low-grade inflammation is defined by a modest increase in circulating pro-inflammatory markers, whilst clinical signs of inflammation remain absent: subclinical inflammation. Visceral adipose tissue, located around the organs, is the major fat-sourced contributor to low-grade inflammation. Factors that are secreted by adipose tissue are collectively referred to as adipokines.[69,71,72] In addition to the numerous pro-inflammatory adipokines, adipose tissues also secrete a smaller number of anti-inflammatory factors, such as adiponectin.[69] Overall, adiponectin is a protective adipokine against the development of obesity-linked heart diseases.[69] The plethora of bioactive molecules secreted by adipose tissue plays a critical role on glucose and lipid metabolism as well as on cardiovascular pathophysiology. Adipocyte dysregulation induces an altered expression pattern of both pro- and anti-inflammatory adipokines. Dysregulation

of adipokine production can have local or systemic effects on inflammatory responses, thereby contributing to the initiation and progression of obesity-induced metabolic and cardiovascular complications.
The impact of circulating adipokines is not merely determined by plasma levels of the adipokines, but also orchestrated by differential adipokine receptor expression on target organs. Next to differences in tissue distribution, up/downregulation of adipokine receptor expression under specific conditions can also modulate adipokine effects. Taken together, both tissue distribution and disease-specific up/downregulation of adipokine receptors can modulate adipokine effects. Until now, the differential impact of circulating adipokine levels and adipokine receptor expression on adipokine signalling in childhood obesity remains largely unknown. Enhanced knowledge on this may help us to further unravel the process of low-grade inflammation in childhood obesity, which in the end becomes clinically relevant to our patients because of the abovementioned known linkage between low-grade inflammation and cardiovascular disease. Furthermore, it may provide us with new starting points for future 'bench' studies, including studies directed at novel therapeutic strategies i.e. by influencing the signalling pathways in low-grade inflammation.

WAY BEYOND WEIGHT – TREATMENT OF CHILDHOOD OBESITY

The rapid increase in prevalence and disease burden of elevated BMI highlights the need for continued focus on surveillance of BMI and identification, implementation, and evaluation of evidence-based interventions to address this problem. Many studies have been performed on identifying characteristics or factors that influence treatment outcome in childhood obesity.[73–76] Over the past decade, a range of interventions have been proposed in order to reduce obesity. Three recently published Cochrane reviews summarised the existing evidence about diet, physical activity and behavioural interventions for the treatment of overweight or obese children of different age groups (<6 years, 6 to 11 years, 12 to 17 years).[77–79] Generally taken, multi-component behaviour-changing interventions that incorporate diet, physical activity and behaviour change may be beneficial in the treatment of childhood obesity. However, the evidence is limited, very low to moderate in quality with a high risk of bias, and results are inconsistent.[77–79] High methodological and clinical heterogeneity exists. This means that the evidence should be interpreted with caution.

In Hospital Gelderse Vallei Ede, multidisciplinary and multicomponent childhood obesity treatment programmes for different age groups have been developed using the best available evidence combined with local knowledge and expertise.
Children and adolescents who fullfilled the criteria for participation in a treatment

programme (mentioned in the text box) commenced on one of the programmes according to their age. *AanTafel!* for children aged 3 to 7 years, *Basta* for children aged 8 years till the end of primary school, and *Toppers* for the adolescents. The development process, outline and content, and pilot results of the treatment programme *AanTafel!* have been reported earlier.[80] Shortly summarised, all programmes are multidisciplinary group interventions (6-12 children per group) that follow a cognitive-behavioural approach, guided by a paediatrician, psychologist, physiotherapist, and a dietician. They have a total duration of respectively nine months (*Toppers*) and one year (*AanTafel!* and *Basta*) and consist of three individual meetings: t=0 (start of treatment), t=1 (after intensive phase of treatment, see below), t=2 (end of treatment). Next to the individual meetings *AanTafel!* facilitates twelve other meetings of 1.5 hours: seven meetings for parents, four physical activity meetings for parents and children together, and one cooking and tasting workshop for parents and children. Thus, *AanTafel!* is primarily directed at the parents. Eight of the twelve meetings take place in the first four months (intensive phase), the other four meetings in the next eight months (less intensive phase). Face-to-face contacts are supported by a personal and secured digital workbook on the internet. Additional information (texts, videos) is provided here in accordance with the multicomponent structure of the programme (comprising information about behaviour change, physical activity, and diet), and assignments can be fulfilled to prepare the group sessions. After every meeting the digital workbook provides a new module. The digital workspace is connected with the electronic patient record system. Therapists can directly evaluate the completed assignments in the learning module and discuss the outcomes with the participants during the next meeting. A secure message system allows the interchange of individually tailored information between participants and health care professionals, and encourages adherence to the programme.

Obesity treatment Hospital Gelderse Vallei Ede

Inclusion criteria:

- Overweight or obesity according to the IOTF criteria[6]
- Age 3-18 years old
- Sufficient understanding of the Dutch language

Exclusion criteria:

- Endocrine, chromosomal or syndrome disorders
- Psychological or social problems interfering with treatment

Basta was developed in line with *AanTafel!* and also provides twelve meetings next to the three individual meetings: six in the first three months (intensive phase), the other six meetings during the remaining nine months (less intensive phase). The meetings have a duration of two hours: one hour psychology/dietetics and one hour physical activity with the children. There is one cooking and tasting workshop for parents and children. Meetings are directed either

at children or at parents and children together. Participants of *Basta* also use a personal and secured digital workbook on the internet.

Toppers is mainly directed at the adolescents themselves. *Toppers* starts with three meetings of four hours in one week for the adolescents and one meeting of two hours for the parents. The content of these meetings comprises information and interactive discussions about motivation, lifestyle, behaviour change, physical activity, and diet. The first three months of the programme comprises of nine physical activity meetings, and two meetings about 'me' where the focus is on individual challenges and behavioural change. In the remaining six months there are three physical activity meetings and one meeting about dietetics. During the programme there are two meetings for parents. The final meeting of the programme is a meeting for both adolescents and parents. Participants of *Toppers* also use a personal and secured digital workbook on the internet.

The programmes are based on self-monitoring and self-evaluation. Participants are encouraged to set personal and family goals, and to design a personal plan for managing their difficulties in daily life concerning a healthy lifestyle. Self-regulating skills are taught in order to achieve permanent lifestyle changes. In each programme, the three components of the intervention (behaviour, physical activity, diet) are adjusted to the specific age group, taking into account the challenges that are encountered.

Although several intervention programmes for children result in a decrease in BMI Z-score in the short term, from literature and experience we know that preventing relapse remains an important challenge. Many obese patients regain weight after treatment, probably because they abandon weight-loss techniques and relapse to inappropriate behaviours. Therefore, we performed a systematic review and meta-analysis on maintenance programmes in childhood obesity, which is presented in this thesis. By using the knowledge obtained from this review and meta-analysis, supplemented with the expert opinion of healthcare workers involved in the childhood obesity treatment at our hospital, we developed maintenance programmes following each treatment programme in Hospital Gelderse Vallei. These maintenance programmes have a duration of two years and focus on the motivation and capacity to continu weight maintenance behaviour over time. The programmes consist of a group conversation four times a year about challenging moments in establishing and sustaining new eating and activity behaviours, and include extended education of behavioural change and planning techniques. Local caregivers and initiatives are involved to garantee a seamless transfer to the home environment.

SCOPE AND OUTLINE OF THESIS

Childhood obesity has reached epidemic levels in many countries and poses an urgent and serious challenge. Although a few doors have been opened the last decades, important research questions remain to be answered and topics elucidated and clarified. The aim of this thesis is to look below the tip of the childhood obesity iceberg, and to dive into a few important issues encountered in daily clinical practice.

PART I of this thesis focuses on consequences of childhood obesity: ***Childhood obesity and beyond.***
Chapter 2 describes the results of a cross-sectional study investigating the health-related quality of life (HRQoL) in children and adolescents at the start of hospital-based obesity treatment. Next, in this chapter we further contemplate on the differences in HRQoL perception between adolescents and their parents, by analyzing both self-reports and parent-proxy reports.
In the next two chapters the focus is on cardiometabolic risk associated with childhood obesity, incorporating a 'bench' (Chapter 3) and a 'bedside' study (Chapter 4). **Chapter 3** covers the results of studying the expression of adiponectin and leptin receptors on circulating immune cells in obese children pre- and post-lifestyle intervention compared to normal weight control children. In **Chapter 4**, we describe the results of a study conducted to evaluate ambulatory blood pressure measurement (ABPM) patterns in a population of overweight and obese children and adolescents, in order to estimate the prevalence of (hidden) abnormal blood pressure (BP) patterns. Next, ABPM patterns were compared with regular office blood pressure measurements.

Moving to **PART II** of this thesis, we elaborate on the treatment of childhood obesity: ***Way beyond weight.***
In **Chapter 5** we describe the effects of a multidisciplinary multicomponent weight loss intervention, specifically comparing overweight/obese children with overweight/obese adolescents. Next, **Chapter 6** provides the overview and design of a systematic review summarising the existing knowledge on programmes and initiatives aimed at long-term maintenance of a healthy or reduces weight in children and adolescents following initial treatment of overweight. Subsequently, we present the findings of this systematic review and meta-analysis on maintenance interventions.
Finally, in **Chapter 7** (General Discussion) we describe the main findings of this thesis and critically discuss theoretical, practical, and methodological issues derived from this thesis. Furthermore, implications for clinical practice and directions for future research are highlighted, ending with an overall conclusion.

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PART I

Childhood obesity and beyond

CHAPTER 2

Quality of life of children and adolescents with clinical obesity

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ABSTRACT

Background

Childhood obesity can have important psychological impacts. The objective of this study was to evaluate the Health Related Quality of Life (HRQoL) of overweight and obese children and adolescents with clinical obesity. The participants were referred to an outpatient hospital-based obesity treatment. Additionally, we investigated the differences between parent- and self-reported HRQoL.

Methods

In a population of children aged 3-18 years at the start of obesity treatment, parent-proxy reported HRQoL (n=119) was assessed using the Child Health Questionnaire Parental Form 50 (CHQ-PF50) and the Infant Toddler Quality of Life Questionnaire 97 (ITQOL-97). Adolescents completed CHQ Child Form 87 (CHQ-CF87, n=45) and Impact of Weight on Quality of Life-Kids (IWQOL-Kids, n=38) to assess self-reported HRQoL.

Results

The mean age of the children was 9.6 years (SD 4.3), one third were boys. Mean BMI Z-score of the children in the study sample was 3.3 (SD 0.8); fifteen percent had overweight, the others obesity grade 1 (39%), 2 (30%) or 3 (16%). Both parent-proxy reports and child self-reports showed lower HRQoL in children with a higher degree of obesity, especially in the physical domains of HRQoL ($P<0.05$). Child self-reported scores were significantly lower than parent-proxy scores on the subscales 'Bodily Pain/Discomfort' and 'General Health Perceptions', and significantly higher on 'Behaviour' and 'Family Cohesion' ($P<0.05$).

Conclusion

Childhood obesity has a negative effect on HRQoL, especially on the physical aspects. The discordance between parent and child reports underscores the importance of using a combination of parent-proxy and child self-reports to assess HRQoL.

INTRODUCTION

Being overweight or obese can have important psychological impacts in childhood and adolescence leading to a significant reduction in health-related functioning.[1] This is reflected in compromised scores on Health Related Quality of Life (HRQoL). Overweight and obese children have low scores for several HRQoL domains, i.e. physical and social functioning, even when compared to other chronic diseases.[2–10]

In mid-adolescent girls, the influence of overweight and obesity on the development of self-image is substantial.[11] Body image dissatisfaction has shown to be an important mechanism linking obesity and decreased HRQoL among adolescents.[12] In addition, bullying and social stigma are serious problems associated with childhood overweight and obesity.[13] These problems are again associated with low self-esteem, body dissatisfaction, poor psychosocial adjustment, depression, eating disorders, and low HRQoL.[14–18]

Measurement of HRQoL provides an indicator of health and disease burden, which is useful for tailoring treatments and assessing outcomes. HRQoL increasingly becomes a separate outcome measure of obesity treatment and is essential for improving care as well as the development of public health policy.[19]

Because HRQoL is a subjective concept, it should be assessed whenever possible from the patients' own perspective.[16] Generally, parents of obese children perceive their child's HRQoL lower than the children themselves.[5,7] Additionally, it has been known that the child's physical and/or psychosocial health has direct influence on the parental subscales of HRQoL.[20]

We evaluated the HRQoL of children and adolescents at the start of hospital-based obesity treatment, and investigated the differences between parent-reported HRQoL and children's self-reported HRQoL from the age of 10 years onwards.

METHODS

Participants

Children and adolescents aged 3-18 years with overweight or obesity according to the IOTF criteria[21], referred by their general practitioner or youth health care physician to the paediatric outpatient clinic of Hospital Gelderse Vallei (Ede, the Netherlands) for multidisciplinary obesity treatment, were enrolled in this study between March 2010 and July 2017. Children with an endocrine disease, chromosomal disorder or syndrome were excluded from treatment. The used baseline data were obtained as part of a longitudinal observational study evaluating the effect of the obesity treatment. This longitudinal study was approved by the ethical committee of Wageningen UR (NL41253.081, METC number

12/26) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants and/or their parents.

Health Related Quality of Life

Parent-proxy reported HRQoL was assessed by the Child Health Questionnaire Parental Form 50 (CHQ-PF50, n=101) in children aged 5-18 years. The Infant Toddler Quality of Life Questionnaire 97 (ITQOL-97) was used in children aged 3 or 4 years (n=18). Children aged 10-18 years filled out the CHQ Child Form 87 (CHQ-CF87, n=45). Additionally, children aged 11-18 years completed the weight specific Impact of Weight on Quality of Life-Kids (IWQOL-Kids) (n=38).

The CHQ-PF50 is a 50-item parent-report survey commonly used for assessment of the physical and psychosocial well-being of children.[22] The CHQ-PF50 assesses fifteen physical and psychosocial scales. Per scale, the belonging items were summed up with equal weight per item (some recoded and/or recalibrated) and transformed into a 0 (worst possible score) to 100 (best possible score) scale. The individual scale scores are aggregated to derive two summary component scores: the Physical Functioning and Psychosocial Health summary scores.[23]

The CHQ-CF87 is a questionnaire with 87 items regarding physical and psychosocial concepts developed for completion by children from ages 10 and older. The CHQ-CF87 consists of ten multi-items scales and four single-items scales. The CHQ-CF87 and the CHQ-PF50 have roughly comparable scales: the CHQ-PF50 contains two additional scales ('Parental Impact - Emotional' and 'Parental Impact - Time') and the CHQ-PF50 scale 'Role Functioning - Emotional/Behaviour' is a combination of the CHQ-CF87 'Role Functioning - Emotional' and 'Role Functioning - Behaviour'.[24]

The ITQOL was developed for use in infants and toddlers from 2 months to 5 years of age, to be completed by one of their parents. In our study we used the 97-item full-length version of the ITQOL, the ITQOL-97, comprising ten multi-item scales and two single-item scales.[25,26]

The IWQOL-Kids is a 27-item questionnaire modelled after the IWQOL-Lite, assessing weight-specific HRQoL. It is designed for adolescents aged 11 to 19 and provides scores on Physical Comfort, Body Esteem, Social Life, Family Relations, and a Total Score. Higher scores indicate better HRQoL.[27]

Anthropometrics

Height (measured to the nearest 0.1 cm with a calibrated wall-mounted stadiometer (Holtain Ltd., Crymych, Cryfed, UK)), and weight (measured in underwear on an electronic calibrated scale (Seca 761) to the nearest 0.1 kilogram) were used to calculate the age and sex-specific BMI Z-scores according to the Dutch growth curves of 2010 based on the LMS-methods.[28] The condition of overweight and obesity (weight status) was determined according to the

internationally used BMI cut-off points as proposed by Cole et al..[21] Cut-off values for obesity grade 2 and 3 were based on the study of Van Buuren et al..[29] In the remaining sections of this paper, the term overweight will be used to indicate both overweight and obesity.
Waist circumference (WC) was measured in centimetres with a flexible tape to the nearest 0.1 cm at umbilicus height.
Blood pressure (BP) was measured in supine position with an automated blood pressure monitor (Welch Allyn VSM 300, Skaneateles Falles, NY, USA) after 5 minutes of rest.

Obesity-related comorbid conditions

The prevalence of common obesity-related comorbid conditions was assessed at enrolment, including abnormal blood pressure (defined according to the Clinical Practice Guideline of Flynn et al.[30]), abnormal glucose metabolism (defined by the criteria of the American Diabetes Association (ADA) 2018[31]), abnormal lipid profile (defined as elevated total cholesterol and/or elevated low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol below cut-off, and/or elevated triglycerides, according to the Dutch guideline for childhood obesity and cardiovascular risk management as published by the Dutch Paediatric Association[32,33]). Diagnosing MetS required the presence of central obesity plus any of the other four factors: elevated triglycerides, HDL-cholesterol below cut-off, abnormal glucose metabolism, and/or abnormal blood pressure.

Statistics

Data analyses were performed using SPSS 24.0 (IBM SPSS Statistics Inc., Chicago, IL) statistical package. Normalcy of the data was determined with Skewness and Kurtosis tests. Children with overweight and obesity (grade 1, 2, or 3) were compared on mean age, BMI, BMI Z-score, WC, and WC Z-score by means of one-way analysis of variance (ANOVA). Differences between boys and girls with regard to these variables were calculated using unpaired t-tests. Pearson Chi-Square tests were performed to compare categorical variables among the weight and gender categories.
With regard to HRQoL, differences between boys and girls were determined using Mann-Whitney U Tests. To analyse the effect of age on the parent-proxy CHQ-PF50 scores, participants were subdivided in 'children' (3-12 years) and 'adolescents' (13-18 years), and differences in HRQoL scores between these groups were evaluated using Mann-Whitney U Tests. Differences in child-reported and parent-proxy reported HRQoL data were tested using the Related-Samples Wilcoxon Signed Rank Test.
Linear regression modelling was performed to evaluate the association of subsequent predictor variables with the CHQ-PF50 Physical and Psychosocial Summary Score: age, demographic variables (gender, ethnicity, family status, siblings in household, highest parental education level, presence/absence of 1 parent with overweight/obesity), anthropometric

variables (BMI Z-score, WC Z-score, weight status), and variables regarding obesity-related comorbid conditions (presence/absence of abnormal blood pressure, abnormal glucose metabolism, abnormal lipid profile, and MetS).

Associations between degree of obesity and reported QoL scores were determined using linear regression models. Adjustments were made for age, gender, ethnicity, siblings in household, and highest parental education level. These covariates were selected based on the literature and associations found in the bivariate linear regression models. The regression coefficients represent the change in outcome (i.e. scores on parent-proxy scales) per degree of obesity as compared with the reference population (children with overweight).

A P value <0.05 was considered to be statistically significant. Significant results were checked for clinically relevance by using a minimally important difference in HRQoL between subgroups defined as half a standard deviation of the total group score.[34]

RESULTS

Patient sample

The mean age of the children in the sample was 9.6 years (SD 4.3) (Table 1). One-third were boys, and they presented with a significant higher BMI Z-score (3.6 versus 3.1, P<0.01) than girls. Fifteen percent of the participants presented with overweight, the others with obesity grade 1, 2 or 3. Children with a higher degree of obesity presented significantly more often with hypertension (P=0.01) and a non-Dutch ethnicity (P=0.01). Two adolescents were diagnosed with diabetes. MetS was present in 13.4% of the participants, and more prevalent in children with higher degrees of obesity (P=0.06). Fifty-five percent of all children in the sample presented with at least one obesity-related comorbid condition.

Parent-proxy reported HRQoL

In the CHQ-PF50 age group (5-18 years old, n=101), girls presented with a significant lower 'Physical Summary Score' than boys (Figure 1A, P=0.04). Furthermore, girls scored significantly lower on the 'Bodily Pain/Discomfort' scale (P<0.01). Children showed significantly higher scores than adolescents on the CHQ-PF50 scales 'Global Health', 'Self-Esteem', 'General Health Perceptions', and 'Family Cohesion'. Bivariate regression analysis revealed that gender (β -3.64, P=0.04) and having 1 brother or sister (β 5.65, P=0.04) were significantly associated with the CHQ-PF50 Physical Summary Score. For the CHQ-PF50 Psychosocial Summary Score there were no significant predictors. In children aged 5-18 years, the higher the degree of obesity, the lower the parent-reported scores on the CHQ-PF50 scales 'Physical Functioning', 'Role/Social Limitations - Physical', and the lower the 'Physical Summary Score' (Table 2A). After adjustment for age, gender, ethnicity, siblings

in household, and highest parental education level the scores on 'Role/Social Limitations - Physical' remained significantly lower for children with obesity grade 3 (P<0.05). A lower score on the 'General Health Perceptions' scale was observed in more obese children, and this was significant for children with obesity grade 3 (P<0.05). In addition, parents of children with obesity showed lower scores on the 'Change in Health' scale, significant for obesity grade 1 (P<0.05). All statistically significant results were also clinically relevant according to the abovementioned definition.

In the younger age group (3-4 years old, n=18), there were no significant differences in HRQoL between boys and girls (Figure 1B, P>0.05). At this age, low HRQoL scores were detected in particular on the 'Overall Health', 'General Health Perceptions', and 'Change in Health' scales (Table 2B). Due to the small sample size regression analyses were not performed in this age group.

Child-reported HRQoL

Figure 1C shows that there are no statistically significant differences between boys and girls with regard to child-reported HRQoL as measured with the CHQ-CF87 questionnaire (P>0.05). However, a clinically relevant difference between boys and girls was detected on the CHQ-CF87 scale 'Bodily Pain/Discomfort'. Moreover, girls presented with a clinically relevant lower IWQOL-Kids score on 'Body Esteem' (Figure 1D).

Participants with obesity grade 3 reported a significantly lower score on the CHQ-CF87 'Physical Functioning' scale when compared to the reference category overweight, but this significance disappeared in the adjusted model (Table 3A). Furthermore, participants with obesity grade 3 presented with clinically relevant lower scores on the 'Family Cohesion' scale. In contrast, participants in the obesity grade 1 and 2 groups presented with clinically relevant higher scores on the 'Family Cohesion' scale. Finally, obese adolescents had lower scores on the 'Change in Health' scale than their overweight peers, clinically relevant for all degrees of obesity and statistically significant for obesity grade 1 (P<0.05).

The weight-specific IWQOL-Kids showed a lower score on 'Physical Comfort' in obese adolescents when compared to overweight adolescents, significantly in the obesity grade 3 group after adjustment for the covariates (Table 3B, P<0.05). The IWQOL-Kids 'Total Score' decreased with increasing degree of obesity, significant for obesity grade 3 in the crude but not in the adjusted model. For participants with obesity grade 2 and 3, compared to the reference category the difference in scores on 'Physical Comfort', 'Social Life' and 'Total Score' were clinically relevant, as was the difference in score on 'Body Esteem' in participants with obesity grade 3.

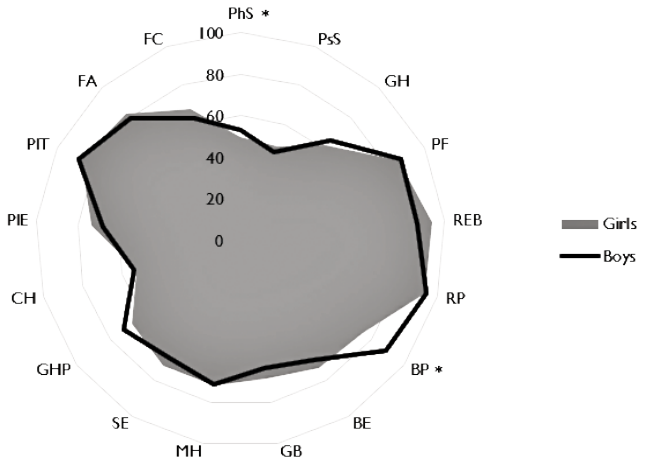

Figure 1A. CHQ-PF50 scores of boys and girls (children aged 5-18 years).
* P<0.05 using Mann-Whitney U tests to compare boys with girls.
FC, Family Cohesion; GB, Global Behaviour; GH, Global Health; GHP, General Health Perceptions; MH, Mental Health; PF, Physical Functioning; PhS, Physical Summary Score; PIE, Parental Impact - Emotional; PIT, Parental Impact - Time; PsS, Psychosocial Summary Score; REB, Role/Social Limitations - Emotional/ Behavioural; RP, Role/Social Limitations - Physical; SE, Self Esteem

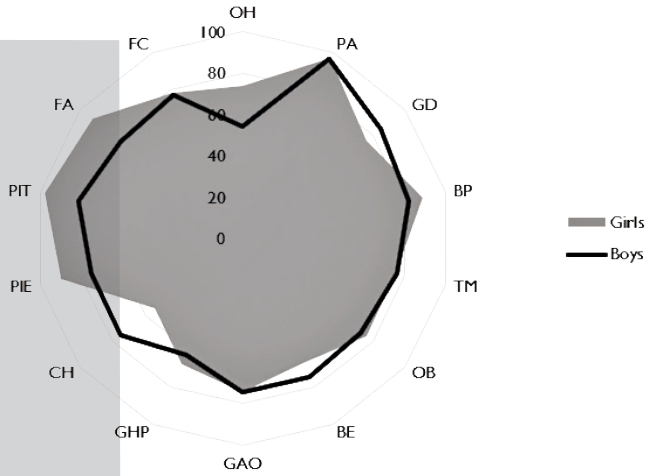

Figure 1B. ITQOL-97 scores (children <5 years old).
* P<0.05 using Mann-Whitney U tests to compare boys and girls.
BE, Global Behaviour; BP, Bodily Pain/Discomfort; CH, Change in Health; FA, Family Activities; FC, Family Cohesion; GAO, Getting Along with Others; GD, Satisfaction with Overall Growth and Development; GHP, General Health Perceptions; OB, Overall Behavior; OH, Overall Health; PA, Physical Ability; PIE, Parental Impact - Emotional; PIT, Parental Impact - Time; TM, Temperament and Moods

Table 1. Characteristics of participants.

	Total group (n=119)	Overweight (n=18)	Obesity grade 1 (n=46)	Obesity grade 2 (n=36)	Obesity grade 3 (n=19)	P value[$]	Boys (n=38)	Girls (n=81)	P value[#]
Male	38 (31.9)	3 (16.7)	15 (32.6)	10 (27.8)	10 (52.6)	0.11	NA	NA	NA
Age	9.6 (4.3)	9.5 (4.3)	9.7 (4.3)	10.0 (4.4)	8.2 (4.3)	0.50	10.1 (4.1)	9.3 (4.4)	0.33
BMI	26.4 (5.9)	22.0 (3.5)	25.1 (4.3)	28.5 (5.8)	29.7 (7.8)	**<0.001**	26.7 (5.0)	26.3 (6.3)	0.70
BMI Z-score	3.3 (0.8)	2.2 (0.3)	3.0 (0.2)	3.6 (0.2)	4.5 (0.5)	**<0.001**	3.6 (0.8)	3.1 (0.7)	**<0.01**
WC*	88.2 (19.6)	77.3 (15.6)	87.6 (17.2)	93.8 (20.4)	89.5 (23.4)	**0.03**	91.0 (20.3)	86.9 (19.2)	0.298
WC Z-score (n=116*)	3.1 (0.6)	2.3 (0.7)	3.0 (0.4)	3.3 (0.4)	3.6 (0.4)	**<0.001**	3.1 (0.6)	3.1 (0.6)	0.84
Casual blood pressure									
Normal BP	63 (52.9)	11 (61.1)	28 (60.9)	17 (47.2)	7 (36.8)	0.25	24 (63.2)	39 (48.1)	0.13
Elevated BP	25 (21.0)	4 (22.2)	12 (26.1)	7 (19.4)	2 (10.5)	0.56	8 (21.1)	17 (21.0)	0.99
Hypertension	31 (26.1)	3 (16.7)	6 (13.0)	12 (33.3)	10 (52.6)	**0.01**	6 (15.8)	25 (30.9)	0.08
Glucose metabolism (n=112**)									
Prediabetes	12 (10.7)	1 (6.3)	5 (11.9)	5 (13.9)	1 (5.6)	0.74	6 (17.1)	6 (7.8)	0.14
Provisional diagnosis of diabetes	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	**0.01**	0 (0.0)	2 (2.6)	0.34
Lipid profile (n=112**)									
Elevated total cholesterol	6 (5.4)	1 (6.3)	1 (2.4)	2 (5.6)	2 (11.1)	0.59	2 (5.7)	4 (5.2)	0.91
Elevated LDL-cholesterol	5 (4.5)	1 (6.3)	1 (2.4)	1 (2.8)	2 (11.1)	0.45	2 (5.7)	3 (3.9)	0.67
HDL-cholesterol below cut-off	12 (10.7)	0 (0.0)	4 (9.5)	7 (19.4)	1 (5.6)	0.15	5 (14.3)	7 (9.1)	0.41
Elevated triglycerides	9 (8.0)	1 (6.3)	3 (7.1)	5 (13.9)	0 (0.0)	0.34	3 (8.6)	6 (7.8)	0.89
MetS (n=112***)	15 (13.4)	0 (0.0)	4 (9.5)	9 (25.0)	2 (11.8)	0.06	3 (8.3)	12 (15.8)	0.28
Ethnicity						**0.01**			0.49
Dutch/Western immigrant	101 (84.9)	17 (94.4)	38 (82.6)	34 (94.4)	12 (63.2)		31 (81.6)	70 (86.4)	
Non-Western immigrant	18 (15.1)	1 (5.6)	8 (17.4)	2 (5.6)	7 (36.8)		7 (18.4)	11 (13.6)	
Family status (n=118[†])						0.22			0.36
Two-parent family	104 (88.1)	18 (100.0)	41 (89.1)	31 (86.1)	14 (77.8)		35 (92.1)	69 (86.3)	
Single-parent family	14 (11.9)	0 (0.0)	5 (10.9)	5 (13.9)	4 (22.2)		3 (7.9)	11 (13.8)	
Siblings in household						0.60			0.44
Only child	16 (13.4)	2 (11.1)	5 (10.9)	5 (13.9)	4 (21.1)		5 (13.2)	11 (13.6)	
1 brother or sister	50 (42.0)	7 (38.9)	24 (52.2)	14 (38.9)	5 (26.3)		13 (34.2)	37 (45.7)	
>1 brother or sister	53 (44.5)	9 (50.0)	17 (37.0)	17 (47.2)	10 (52.6)		20 (52.6)	33 (40.7)	
Highest parental education level (n=101[‡])						0.80			0.68
No or low	54 (53.5)	7 (46.7)	21 (51.2)	17 (58.6)	9 (56.3)		16 (50.0)	38 (55.1)	
Medium	38 (37.6)	5 (33.3)	17 (41.5)	10 (34.5)	6 (37.5)		12 (37.5)	26 (37.7)	
High	9 (8.9)	3 (20.0)	3 (7.3)	2 (6.9)	1 (6.3)		4 (12.5)	5 (7.2)	
At least 1 parent with overweight/obesity	116 (97.5)	18 (100.0)	43 (93.5)	36 (100.0)	19 (100.0)	0.18	38 (100.0)	78 (96.3)	0.23

Number (%), except for age, BMI, BMI Z-score, WC, WC Z-score (mean, SD)
* Obesity grade 1: n=44; Obesity grade 3: n=18; Girls: n=78
** Overweight: n=16; Obesity grade 1: n=42; Obesity grade 3: n=18; Boys: n=35; Girls: n=77
*** Overweight: n=17; Obesity grade 1: n=42; Obesity grade 3: n=17; Boys: n=36; Girls: n=76
† Obesity grade 3: n=18; Girls: n=80
‡ Overweight: n=15; Obesity grade 1: n=41; Obesity grade 2: n=29; Obesity grade 3: n=16; Boys: n=32; Girls: n=69
$ Continuous variables: one-way analysis of variance. Categorical variables: Pearson Chi-Square.
# Continuous variables: unpaired t-test. Categorical variables: Pearson Chi-Square.
BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL: low-density lipoprotein; MetS, metabolic syndrome; WC, waist circumference
Child ethnicity was determined based on the parent's country of birth. If both parents were born in the Netherlands, the child was classified as native Dutch. Ethnicity was classified as 'Western immigrant' when one or two parents originated from Europe (excluding Turkey), North America, Oceania, Indonesia or Japan, and as 'Non-western immigrant' when one or two parents originated from Africa, South America, Asia (excluding Indonesia and Japan) or Turkey. One child was adopted at the age of 10 months. In this case, the country of origin was chosen as ethnicity. Family status was classified as either two-parent family (both parents or parent and step-parent) or one-parent family (mother only or father only). Level of education of parents was categorized into low (no education, primary school, or ≤3 years of general secondary school), mid-low (>3 years of general secondary school), mid-high (higher vocational training, undergraduate programs, or bachelor's degree), and high (higher academic education).

Table 2A. Crude and adjusted associations between categories of obesity and (parent-proxy reported) CHQ-PF50 scores (0-100).

	Model	Overweight (ref.; n=14)	Obesity grade 1 (n=39)			Obesity grade 2 (n=33)			Obesity grade 3 (n=15)		
		Mean (SD)	B	95% CI		B	95% CI		B	95% CI	
Physical Summary Score	Crude	52.2 (7.5)	-0.507	-5.620	4.606	-1.162	-6.397	4.072	-5.597	-11.696	0.501
Psychosocial Summary Score	Crude	47.3 (9.2)	0.170	-5.801	6.142	0.590	-5.523	6.703	1.469	-5.653	8.592
Global Health	Crude	60.7 (13.8)	4.680*	-7.204	16.565	-0.558**	-12.739	11.623	3.619	-10.507	17.745
Physical Functioning	Crude	89.3 (17.5)	-0.397	-10.163	9.370	-2.249	-12.247	7.750	**-12.249**	**-23.898**	**-0.600**
RSL - Emotional/Behavioural	Crude	94.4 (17.8)	-2.991	-15.757	9.774	-3.199	-16.268	9.870	-6.296	-21.523	8.930
RSL - Physical	Crude	98.8 (4.5)	-2.228	-12.064	7.608	-4.365	-14.434	5.704	**-17.698**	**-29.430**	**-5.967**
	Adjusted		-2.349	-12.566	7.868	-3.983	-14.267	6.300	**-14.487**	**-27.310**	**-1.664**
Bodily Pain/Discomfort	Crude	69.3 (25.0)	10.971	-2.847	24.788	11.926	-2.219	26.072	13.381	-3.100	29.862
Behaviour	Crude	68.3 (16.4)	2.280	-7.434	11.993	6.323	-3.621	16.267	1.991	-9.595	13.577
Global Behaviour	Crude	65.0 (15.3)	2.632*	-9.937	15.200	1.970	-10.853	14.792	0.667	-14.273	15.606
Mental Health	Crude	70.7 (11.1)	2.555	-6.199	11.309	0.839	-8.123	9.801	-3.381	-13.823	7.061
Self Esteem	Crude	67.0 (17.8)	5.450	-4.793	15.693	0.536	-9.951	11.022	5.813	-6.404	18.031
General Health Perceptions	Crude	72.9 (10.9)	-3.690	-13.096	5.716	-5.937	-15.566	3.692	-8.583	-19.802	2.635
	Adjusted		-6.247	-15.694	3.200	-8.357	-17.866	1.151	**-12.516**	**-24.372**	**-0.659**
Change in Health	Crude	62.5 (25.5)	-11.859	-24.853	1.135	-12.500**	-25.864	0.864	-4.167	-19.665	11.332
	Adjusted		**-13.566**	**-26.873**	**-0.259**	-10.383**	-23.843	3.078	-3.858	-20.540	12.825
Parental Impact - Emotional	Crude	78.0 (15.5)	-10.348	-23.177	2.481	-10.299	-23.433	2.834	4.246	-11.055	19.547
Parental Impact - Time	Crude	85.7 (23.2)	-0.814	-13.387	11.759	5.868	-7.003	18.740	0.212	-14.785	15.208
Family Activities	Crude	78.3 (20.4)	1.374	-8.640	11.387	8.241	-2.010	18.493	3.115	-8.829	15.059
Family Cohesion	Crude	54.6 (24.5)	**14.041***	**0.319**	**27.763**	13.482**	-0.582	27.546	12.357	-3.953	28.668

* n=38; ** n=32

Ref. indicates a category used as a standard reference. Data are presented as unstandardized regression coefficients (B) and 95% confidence intervals estimated by linear regression models. The crude model shows the association between degree of obesity and the QoL score, unadjusted for covariates. Results of the adjusted model, adjusted for age, gender, ethnicity, siblings in household, and highest education level of parents, are only presented when significant. Bold numbers indicate a significant difference (P<0.05) in HRQoL score relative to the reference group.

RSL, Role/Social Limitations

Table 2B. Mean ITQOL-97 scores (0-100).

	Total group (n=18)
	Mean (SD)
Overall Health	67.2 (19.1)
Physical Ability	96.7 (5.6)
Satisfaction with Overall Growth and Development	78.7 (12.0)*
Bodily Pain/Discomfort	86.8 (13.2)*
Temperament and Moods	75.9 (9.7)
Overall Behaviour	75.2 (15.7)
Global Behaviour	69.4 (17.2)*
Getting Along with Others	74.5 (10.3)
General Health Perceptions	66.0 (11.7)
Change in Health	61.1 (19.6)
Parental Impact - Emotional	84.7 (16.5)
Parental Impact - Time	92.3 (19.5)
Family Activities	89.2 (14.9)**
Family Cohesion	77.8 (15.6)

* n=17; ** n=5

Due to the small sample size regression analyses were not performed in this age group.

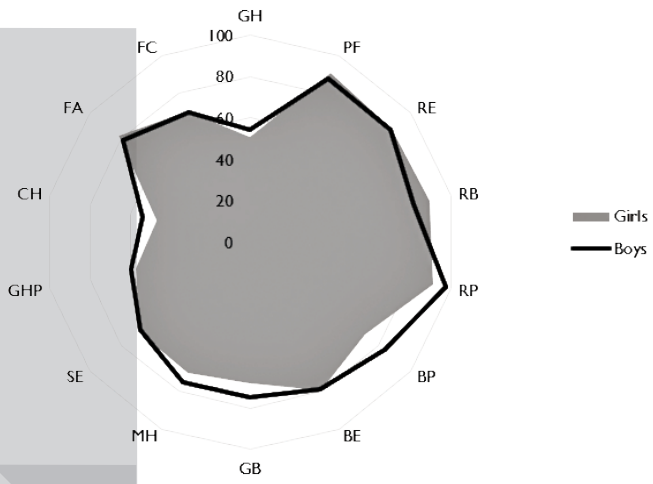

Figure 1C. CHQ-CF87 scores of boys and girls.

* P<0.05 using Mann-Whitney U tests to compare boys with girls.

BE, Behaviour; BP, Bodily Pain/Discomfort; CH, Change in Health; FA, Family Activities; FC, Family Cohesion; GB, Global Behaviour; GH, Global Health; GHP, General Health Perceptions; MH, Mental Health; PF, Physical Functioning; RE, Role/Social Limitations - Emotional; RB, Role/Social Limitations - Behavioural; RP, Role/Social Limitations - Physical; SE, Self Esteem

Table 3A. Crude and adjusted associations between categories of obesity and (self-reported) CHQ-CF87 scores (0-100).

	Model	Overweight (ref.; n=8)	Obesity grade 1 (n=21)			Obesity grade 2 (n=12)			Obesity grade 3 (n=4)		
		Mean (SD)	B	95% CI		B	95% CI		B	95% CI	
Global Health	Crude	53.8 (23.9)	3.618*	-16.878	24.115	-14.750***	-37.818	8.318	-2.500	-32.281	27.281
Physical Functioning	Crude	94.0 (7.1)	-4.916	-13.370	3.537	-3.704	-12.991	5.583	**-12.500**	**-24.960**	**-0.040**
RSL - Emotional	Crude	93.1 (5.8)	-7.341	-26.246	11.563	-60.190	-26.787	14.750	-1.389	-29.252	26.474
RSL - Behavioural	Crude	88.9 (15.7)	-6.349	-25.687	12.988	2.778	-18.466	24.022	5.556	-22.946	34.057
RSL - Physical	Crude	91.7 (15.4)	1.455	-11.925	14.835	2.778	-11.922	17.477	2.778	-16.944	22.499
Bodily Pain/Discomfort	Crude	83.8 (23.9)	-8.988	-27.076	9.100	-10.417	-30.288	9.454	-16.250	-42.910	10.410
Behaviour	Crude	76.5 (10.4)	3.662	-5.814	13.138	1.863	-8.548	12.273	5.662	-8.305	19.629
Global Behaviour	Crude	63.1 (8.8)	9.625**	-6.414	25.664	10.625	-6.875	28.125	-4.375	-27.854	19.104
Mental Health	Crude	66.7 (14.6)	8.214	-3.701	20.128	3.521	-9.568	16.611	0.456	-17.106	18.017
Self Esteem	Crude	63.8 (13.5)	7.419	-5.909	20.748	7.177	-7.465	21.820	-1.786	-21.431	17.859
General Health Perceptions	Crude	62.3 (22.2)	-2.283	-16.860	12.295	-10.294	-26.308	5.721	-9.583	-31.069	11.902
Change in Health	Crude	68.8 (34.7)	**-25.000****	**-48.865**	**-1.135**	-23.295****	-49.803	3.212	-25.000	-59.934	9.934
	Adjusted		**-30.390****	**-57.251**	**-3.528**	-26.764****	-56.576	3.049	-17.298	-57.387	22.792
Family Activities	Crude	82.3 (17.1)	-0.417**	12.553	11.719	1.736	-11.505	14.978	-13.542	-31.307	4.224
Family Cohesion	Crude	60.6 (24.0)	**16.625****	**0.740**	**32.510**	11.875	-5.457	29.207	-15.625	-38.879	7.629

* n=19; ** n=20; *** n=10; **** n=11

RSL, Role/Social Limitations

Table 3B. Crude and adjusted associations between categories of obesity and (self-reported) IWQOL-Kids scores (0-100).

	Model	Overweight (ref.; n=6)	Obesity grade 1 (n=16)			Obesity grade 2 (n=12)			Obesity grade 3 (n=4)		
		Mean (SD)	B	95% CI		B	95% CI		B	95% CI	
Physical Comfort	Crude	92.8 (5.7)	-7.986	-19.106	3.134	**-12.778**	**-24.392**	**-1.164**	**-31.111**	**-46.105**	**-16.117**
	Adjusted		-6.009	-20.407	8.389	-9.262	-24.035	5.510	**-27.284**	**-47.194**	**-7.373**
Body Esteem	Crude	73.0 (11.4)	4.884	-12.225	21.994	-5.926	-23.796	11.944	-22.407	-45.478	0.663
Social Life	Crude	91.1 (7.2)	-2.861	-15.811	10.088	-10.505#	-24.234	3.224	-7.778##	-26.905	11.350
Family Relations	Crude	90.0 (14.8)	1.875	-8.036	11.786	6.970#	-3.537	17.477	-1.111##	-15.750	13.528
Total Score	Crude	85.3 (6.8)	-0.436	-9.824	8.953	-5.782#	-15.735	4.172	**-14.397##**	**-28.265**	**-0.529**

n=11; ## n=3

Ref. indicates a category used as a standard reference. Data are presented as unstandardized regression coefficients (B) and 95% confidence intervals estimated by linear regression models. The crude model shows the association between degree of obesity and the QoL score, unadjusted for covariates. Results of the adjusted model, adjusted for age, gender, ethnicity, siblings in household, and highest education level of parents, are only presented when significant. Bold numbers indicate a significant difference ($P<0.05$) in HRQoL score relative to the reference group.

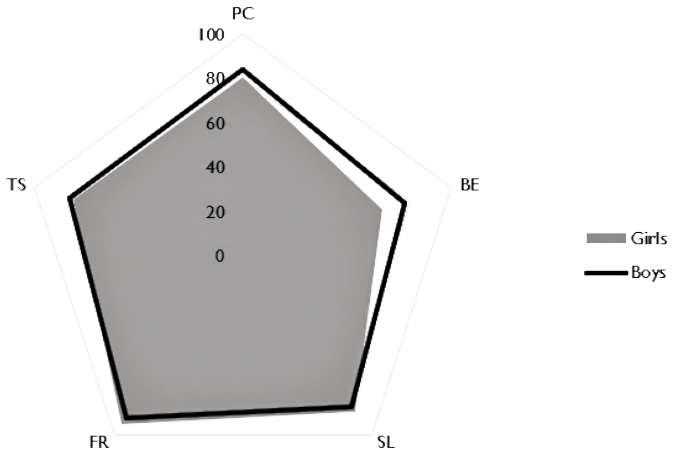

Figure 1D. IWQOL-Kids scores of boys and girls.
* P<0.05 using Mann-Whitney U tests to compare boys and girls.
BE, Body Esteem; FR, Family Relations; PC, Physical Comfort; SL, Social Life; TS, Total Score

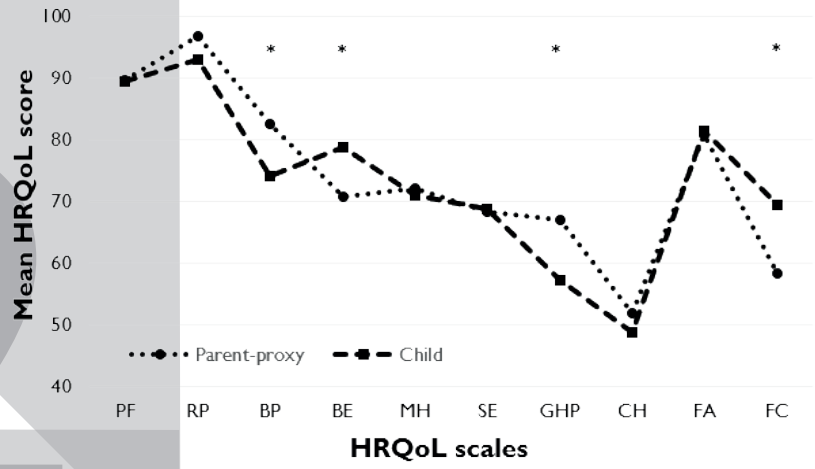

Figure 2. Child self-reported (CHQ-CF87) and parent-proxy (CHQ-PF50) reported HRQoL scores.
* P<0.05 using Related-Samples Wilcoxon Signed Rank Tests to compare CHQ-CF87 and CHQ-PF50 scores.
BE, Behaviour; BP, Bodily Pain/Discomfort; CH, Change in Health; FA, Family Activities; FC, Family Cohesion; GHP, General Health Perceptions; MH, Mental Health; PF, Physical Functioning; RP, Role/Social Limitations - Physical; SE, Self Esteem

Comparison of child-reported and parent-proxy reported HRQoL

For 43 children from ages ten and older (mean 14.4 years, SD 2.2), both child-reported and parent-proxy reported data were available. Children scored significantly lower than their parents on the scales 'Bodily Pain/Discomfort' and 'General Health Perceptions', and significantly higher on 'Behaviour' and 'Family Cohesion' (Figure 2, $P<0.05$). All other HRQoL scales were comparable.

DISCUSSION

In both parent-proxy reports and child self-reports we found a lower HRQoL in children aged 5-18 years with an increasing degree of obesity, especially in children with obesity grade 3. When comparing the parent-proxy CHQ-PF50 Summary Scores of our population of overweight and obese children with summary scores of healthy children described in other cohorts, our HRQoL scores were >0.5 SD lower, pointing to a clinically relevant difference in HRQoL between children with and without overweight or obesity.[20,24,35] Other chronic conditions during childhood (i.e. asthma, eczema, dyslexia, ADHD, or migraine/ severe headache) have also shown to reduce HRQoL. Our CHQ-PF50 Summary Scores were comparable with the HRQoL scores of children with these conditions, or even worse.[24,35]

In our study, the diminished HRQoL was most pronounced in the physical domains of HRQoL. Van Grieken et al showed similar parent-reported results in their large cross-sectional study.[20] They mentioned the possibility that parents suspect that their overweight children are not able to join their peers in the same level of physical activity, which thus may contribute to low scores for overweight children on the physical activity scales. In our study, also the scores on the self-reported 'Physical Functioning' scale were lower with increasing obesity, as were the weight-specific IWQOL-Kids 'Physical Comfort' scores, implicating that obese adolescents themselves perceive a worse physical ability too. It has been hypothesised that physical activity has a BMI-independent positive effect on HRQoL in adults.[36,37] In childhood, active children reported significantly higher HRQoL than participants with an inactive or moderate profile.[38–40] In the study of Rank et al, long-term changes in physical activity level were positively associated with HRQoL, with particular improvements in self-esteem, and these changes explained 30% of the variation in overall HRQoL.[41]

Scores on the CHQ-PF50 'General Health Perceptions' scale are lower in children with increasing obesity, indicating that parents believe their child's health is poor and likely to get worse. This is also reflected in the lower 'Change in Health' scale scores in obesity than in overweight, and in line with the child self-reports. On the other site, parent-reported psychosocial HRQoL scores were not consistently different across weight categories in the present study. This has been reported by others[14,20,42], and confirms the additional value

of child self-reports as parents might underestimate psychosocial problems of their child. Indeed, self-reported IWQOL-Kids scores on 'Body Esteem' and 'Social Life' were lower in adolescents with obesity grade 2 and 3.
In our <5 years age group, in general the reduced HRQoL in childhood obesity is less pronounced when compared to the older age group. Regression analysis could not be performed due to small sample sizes. It could be that obesity-related consequences on HRQoL become more prominent at later age, but also that parents overestimate their child's HRQoL, supposing that their child is not old enough to be unhappy due to his or her weight.[20] On the other side, low HRQoL scores were detected especially on scales concerning perception of health and health change, which indicates that parents are worried about their child's actual and future health even at this age. This emphasises the need of early commencement of obesity treatment and careful attention to the possibility of emerging obesity-related problems.

As reported in literature both parent-proxy and child self-reports have proven to be valid.[43–46] In our study, significant differences were observed between parent-proxy reports and child self-reports. This is in line with available evidence, and suggests that the informant's perspective (i.e. parent-proxy or self-report) influences the resultant HRQoL scores.[5,7,16,47–50] Participants in our study scored significantly lower than their parents on scales 'Bodily Pain/ Discomfort' and 'General Health Perceptions'. This could point to parental underestimation of these health consequences of overweight. Generally, however, parents report worse HRQoL scores than their children. Low parent reported scores could be in part related to the parents' own feelings at the time of the evaluation, or parents perhaps underestimate their children's capacity for adaptation.[47] In our study, a significantly lower parental score was observed for the 'Behaviour' and 'Family Cohesion' scales when compared to the self-reported score. A lower score on the 'Behaviour' scale suggests that parents, more than the participants themselves, experience aggressive, immature, or delinquent behaviour of their child. Probably this is at least partly caused by the changing roles and interaction during puberty. On the other hand, children may underestimate their own problems when responding to HRQoL questionnaires. Measures alone in children might be inadequate as a proxy for HRQoL as children may adapt to their current healthy state or may not have experienced a healthier state, which could result in high self-reported HRQoL scores despite obvious functional limitations. With regard to the 'Family Cohesion' scale, interestingly, parents of obese children reported a better family's ability to get along than parents of overweight children. However, children with obesity grade 3 themselves showed a lower score on the scale 'Family Cohesion' when compared to their peers. One could hypothesise that, with an increasing degree of obesity, adolescents feel more isolated and alone and experience less support of their family. Indeed, this matches with the low emotional impact that parents of children with obesity grade 3 experience.

Agreement between parent and child may be better on good observable, less abstract HRQoL domains[45], although the definition and content of 'good observable' may differ within individuals and families. Next, parent and child differences could result from different reasoning and different response styles between adults and children[51], and levels of agreement can differ with age.[46,52] Further information about variables contributing to parent-child agreement levels are largely unknown.[49]

Determinants of HRQoL

Gender differences in HRQoL have been described earlier in overweight and obese children, especially regarding psychosocial HRQoL parameters as body satisfaction and self-esteem. Low scores on these variables are more pronounced in girls than in boys[53], probably caused by more weight stigmatisation and discrimination and excess overweight concerns in girls, which has been strongly associated with depressive symptoms.[54] In our study, gender differences were more prominent in the physical HRQoL parameters: parent-proxy reports of girls aged 5-18 years noted a significant lower 'Physical Summary Score' compared to boys, and a significantly lower score on the 'Bodily Pain/Discomfort' scale. The lower score for girls compared to boys on 'Bodily Pain/Discomfort' was also present in the CHQ-CF87, indicating that adolescent girls more than boys experience severe, frequent, and limiting bodily pain. This could interfere with their ability to physically exercise. This in turn could affect their psychosocial health and self-esteem, which has been shown to be prominently influenced by physical activity.[38,41] Indeed, child self-reported scores on 'Body Esteem' are lower in girls than in boys, which is also described earlier[27], although other factors may play a role in this.

Another factor to account for is age. The effect of age on HRQoL has been reported in literature, although the age effect has not been systematically analyzed.[14,16,47] In line with previously published papers, in our study adolescents showed significantly lower scores than children on several CHQ-PF50 scales, i.e. on self-esteem and global perception of health. It has been hypothesised that adolescence may be a particularly vulnerable period for decrements in HRQoL, probably because of increased awareness for example on appearance, social interactions, and participation limitations.

With regard to other variables associated with HRQoL, ethnicity has been shown to be of influence.[20,55] In our study, no differences in CHQ-PF50 Summary Scores were detected between subgroups regarding ethnicity and highest parental education level. However, regression analysis revealed that having 1 brother or sister was significantly associated with the CHQ-PF50 Physical Summary Score. To the best of our knowledge, the presence of siblings in the household has not been associated with HRQoL before.

Finally, a recent study reported a lower HRQoL particularly in those overweight adolescents having additional cardiometabolic risk factors.[56] Also in other studies the presence of

obesity-related comorbidity has been related to impairments in QoL.[57] No association was found in our study.

Strengths and limitations

This study has the advantage of studying a clinical sample of children with obesity aged 3-18 years. We recommend to repeat this study in different countries and settings in order to increase the generalisability of the findings. We used cross-sectional data to investigate the relationship between weight status and HRQoL, and thus assumptions regarding the causality of associations cannot be made. Overweight could be a cause of low HRQoL, but in turn a low HRQoL probably contributes to becoming overweight. Second, low patient numbers prevented us from more extensive analyses in the age group <5 years, and in determining factors associated with HRQoL. Next, not all potential associated factors of HRQoL were included in our study. For example, a recent study investigating the determinants of HRQoL in a large population of school-aged children found that the best predictors of HRQoL are variables that describe the use of healthcare and the number of disorders and health complaints, and that child's HRQoL, as reported by the parent, is only to a smaller extent dependent on demographic, socio-economic and family/environmental determinants.[58] In our study parent-reported health conditions/disorders/complaints were not available. Third, our population consisted of overweight and obese children at the start of hospital-based treatment. However, HRQoL in this population may be lower than in non-treatment seeking children, and thus we need to be reserved with generalising our study results to all children with overweight.[55]

In conclusion

Continued overweight leads to serious physical and psychosocial health problems, affecting the child's and parent's everyday life. In this study, both parent-proxy reports and child self-reports showed a lower HRQoL in children aged 5-18 years with an increasing degree of obesity, especially in the physical domains of HRQoL. This points to the importance of physical fitness, both as a cause and as a consequence of childhood overweight. In the younger age group, low HRQoL scores were detected especially on scales concerning perception of health and health change, confirming the need of early commencement of obesity treatment and careful attention to the possibility of emerging obesity-related problems.

The discordance between parent and child reports indicate that children and parents may not necessarily share similar views about the impact of overweight. To gain a complete picture of functioning, it is preferable to obtain data from children's point of view supplemented with data from the parents' perspective.

Finally, routine assessment of HRQoL and psychological functioning should be performed in all overweight and obese children, followed by family-oriented treatment with the focus

on behaviour change including psychological determinants in both children and parents, considering the impact on parents' psychosocial situation as well.

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2

CHAPTER 3

Differential adipokine receptor expression on circulating leukocyte subsets in lean and obese children

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ABSTRACT

Background

Childhood obesity prevalence has increased worldwide and is an important risk factor for type 2 diabetes (T2D) and cardiovascular disease (CVD). The production of inflammatory adipokines by obese adipose tissue contributes to the development of T2D and CVD. While levels of circulating adipokines such as adiponectin and leptin have been established in obese children and adults, the expression of adiponectin and leptin receptors on circulating immune cells can modulate adipokine signalling, but has not been studied so far. Here, we aim to establish the expression of adiponectin and leptin receptors on circulating immune cells in obese children pre and post-lifestyle intervention compared to normal weight control children.

Methods

13 obese children before and after a 1-year lifestyle intervention were compared with an age and sex-matched normal weight control group of 15 children. Next to routine clinical and biochemical parameters, circulating adipokines were measured, and flow cytometric analysis of adiponectin receptor 1 and 2 (AdipoR1, AdipoR2) and leptin receptor expression on peripheral blood mononuclear cell subsets was performed.

Results

Obese children exhibited typical clinical and biochemical characteristics compared to controls, including a higher BMI Z-score, blood pressure and circulating leptin levels, combined with a lower insulin sensitivity index (QUICKI). The 1-year lifestyle intervention resulted in stabilisation of their BMI Z-score. Overall, circulating leukocyte subsets showed distinct adipokine receptor expression profiles. While monocytes expressed high levels of all adipokine receptors, NK and iNKT cells predominantly expressed AdipoR2, and B-lymphocytes and CD4+ and CD8+ T-lymphocyte subsets expressed AdipoR2 as well as leptin receptor. Strikingly though, leukocyte subset numbers and adipokine receptor expression profiles were largely similar in obese children and controls. Obese children showed higher naïve B-cell numbers, and pre-intervention also higher numbers of immature transition B-cells and intermediate CD14++CD16+ monocytes combined with lower total monocyte numbers, compared to controls. Furthermore, adiponectin receptor 1 expression on non-classical CD14+CD16++ monocytes was consistently upregulated in obese children pre-intervention, compared to controls. However, none of the differences in leukocyte subset numbers and adipokine receptor expression profiles between obese children and controls remained significant after multiple testing correction.

Conclusions

First, the distinct adipokine receptor profiles of circulating leukocyte subsets may partly explain the differential impact of adipokines on leukocyte subsets. Second, the similarities in adipokine receptor expression profiles between obese children and normal weight controls suggest that adipokine signalling in childhood obesity is primarily modulated by circulating adipokine levels, instead of adipokine receptor expression.

INTRODUCTION

Obese children often remain obese in adulthood, and are at risk for metabolic syndrome and cardiovascular disease later in life.[1–3] Over the last few decades, enhanced excretion of inflammatory adipose tissue derived proteins (adipokines) emerged as one of the mechanisms underlying the cardiometabolic sequelae in obesity.[4,5] The adipokine profile in childhood and adulthood obesity includes increased levels of the inflammatory adipokines chemerin and leptin, and decreased levels of the anti-inflammatory adiponectin, which together propagates systemic inflammation, insulin resistance and vascular dysfunction, as a precursor for cardiovascular disease.[4,6–11]

The impact of circulating adipokines is not merely determined by plasma levels, but also orchestrated by differential adipokine receptor expression on target organs. For example, adiponectin receptor 1 (AdipoR1) and receptor 2 (AdipoR2) are significantly homologous (67% amino acid identity), and both serve as a receptor for globular and full-length adiponectin.[12] However, AdipoR1 is predominantly expressed in liver, skeletal muscle, macrophages and hypothalamus, while AdipoR2 is most abundant in liver, white adipose tissue, and the vasculature. The differential tissue distribution and downstream signalling pathways of AdipoR1 and AdipoR2 importantly contribute to the plethora of adiponectin's biological actions.[10] Next to differences in tissue distribution, up/downregulation of adipokine receptor expression under specific conditions can also modulate adipokine effects. Natural Killer (NK) cells, for instance, critically depend on leptin receptor expression for their activation and function.[13] While leptin receptor-deficient mice showed impaired NK cell activity, leptin receptor expression was upregulated in rats with diet-induced obesity, apparently to compensate for decreased downstream signalling.[14] Taken together, both tissue distribution and disease-specific up/downregulation of adipokine receptors can modulate adipokine effects.

Whereas studying adipose tissue, liver and vascular distribution of adipokine receptors is precluded for medical ethical reasons, circulating leukocytes are readily available and play a pivotal role in systemic inflammation in obesity.[15–18] Here, we used recently available flow cytometry antibodies to study the expression of AdipoR1, AdipoR2 and leptin receptor on circulating leukocyte subsets, in addition to measuring circulating adipokine levels. Considering the pivotal role of adipokine signalling in obesity, we included obese children pre and post-lifestyle intervention, next to normal weight control children. This study thus aims to unravel the differential impact of circulating adipokine levels and adipokine receptor expression on adipokine signalling in childhood obesity.

MATERIALS AND METHODS

Patients

This observational cohort study included 15 lean control children and 13 obese children aged 4-18 years, all patients of the paediatric outpatient department of Meander Medical Centre in Amersfoort and Hospital Gelderse Vallei Hospital in Ede, The Netherlands. Body Mass Index standard deviation (BMI Z-score) values were calculated based on results of the Fifth Dutch Growth Study.[19] Obesity was defined using established international age and sex-specific BMI cut-off points.[20] The obese patients were enrolled in an established 1-year multidisciplinary, multicomponent, family-based treatment programme developed in Hospital Gelderse Vallei in Ede, The Netherlands.[21] Patients were included from 2010 to 2015. Anthropometric measurements, blood pressure (BP) measurements and laboratory samples were collected at baseline (lean controls, obese children), and at the end of the 1-year intervention programme (obese children). The study was approved by the ethical committee of Wageningen UR (METC 12/26) and the University Medical Centre Utrecht (METC 09/217K). Written informed consent was obtained from children older than 12 years and from the parents.

Clinical variables

Waist circumference was used as a marker of central adiposity and measured with a flexible tape to the nearest 0.1 cm at umbilicus height. Blood pressure (BP) was measured in supine position with an automated blood pressure monitor (Welch Allyn VSM 300, Skaneateles Falles, NY, USA) after 5 minutes of rest during a well visit in the outpatient clinic. A minimum of two BP measurements was performed, with an interval of at least one minute between the measurements. The mean of these two measurements was collected for data analysis. Blood pressure percentile scores were obtained according to the Fourth Report on BP in children.[22]

Routine laboratory measurements

Routine laboratory testing included fasting glucose, insulin levels and lipid profiles (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides), as well as samples for leukocyte differentiation, and alanine-aminotranspherase (ALT). The insulin sensitivity index (QUICKI) was calculated according to international standards.[23]

Flow cytometry

Whole blood samples collected in sodium heparin tubes (BD vacutainer 367876) where spun down at room temperature, 160g for 10 minutes. Plasma was subsequently removed and stored at -80°C awaiting further use. Peripheral Blood mononuclear cells (PBMC) were isolated using Ficoll-Paque density gradient centrifugation and samples were stored in foetal bovine serum (FBS) (Biowest) supplemented with 10% DMSO (Sigma-Aldrich) at -150°C. All children donated 6-12ml whole blood, with 6-10 million PBMC per 6ml whole blood sample. Upon preparation for flow cytometry, the stored PBMC samples where thawed and washed in medium comprising of RPMI1640 supplemented with L-glutamate and 25 mM HEPES (Gibco), containing 2% FBS (Biowest) and penicillin/streptomycin (100 U/mL) (Invitrogen). Cells were spun down for 10 minutes at 280g at room temperature. All samples were stained for 20 minutes in the dark at 4°C and subsequently analysed on the BD LSR Fortessa. For monocyte, NK cell, B-cell, T-helper, T-effector/memory and Treg phenotyping, 200.000 PBMCs were analysed per sample. For iNKT cell phenotyping, 750.000 PBMCs were analysed per sample. The following antibodies were used: CD3 AF700 (Biolegend, clone UCHT1), CD4 PerCP-Cy5.5 (BD, clone SK3), CD25 PE-Cy7 (BD, clone M-A251), CD45RO BV711 (Biolegend, clone UCHL1), CD127 BV421 (BD Horizon, clone HIL-7R-M21), CD8 V500 (BD, clone RPA-T8), Leptin receptor Alexaflour647 (BD,clone 52263), ADIPOR1 FITC (USBio, rabbit polyclonal antibody). ADIPOR2 PE (USBio, rabbit polyclonal antibody), CD27 APC-eFluor780 (eBioscience, clone O323), CD28 BV421 (BD Horizon, clone CD28.2), CCR6 PE-Cy7 (eBioscience, clone R6H1), CXCR3 BV510 (Biolegend, clone GO25H7), CD16 V500 (BD Horizon, clone 3G8), CD56 PE-Cy7 (BD, clone NCAM16.2), CD1d tetramer BV421 (NIH, hCD1d-PBS-57), CD10 PE-Cy7 (BD, clone HI10A), CD19 APC-efluor 780 (eBioscience, clone HIB19), CD21 BV711 (BD, clone B-ly4), CD27 BV510 (BD Horizon, clone L128), CD38 PerCP-Cy5.5 (BD Pharmigen, clone HIT2). Leukocyte subset numbers were calculated using the differential blood count (e.g. number of CD14++CD16+ monocytes = (fraction of CD14++CD16+ monocytes / total monocytes) x differential blood count monocyte number). Gating strategy of the leukocyte subsets is shown in the S1 Figure.

Multiplex immune assay (MIA)

Plasma levels of adiponectin, chemerin and leptin were measured by a MIA using Luminex xMAP technology (xMAP, Luminex Austin TX USA) validated by the Laboratory of Translational Immunology, University Medical Centre Utrecht.[24] Biorad FlexMAP3D (Biorad laboratories. Hercules USA) and xPONENT software version 4.2 (Luminex) were used for acquisition and data was analysed by 5-parametric curve fitting using Bio-Plex Manager software, version 6.1.1 (Biorad).

Statistical analysis

Differences between groups were studied with an independent-sample Student's t-test for normally distributed data, and with a Mann-Whitney U test for non-parametric comparisons. Multiple testing correction using the Benjamini and Hochberg False Discovery Rate (FDR) procedure was applied when assessing leukocyte subset numbers and comparing adipokine receptor expression of leukocyte subsets in lean versus obese children pre and post-intervention. Pearson's correlation coefficients were calculated to determine the correlation between levels of circulating adipokines and the expression of adiponectin and leptin receptors on circulating immune cells. Statistical analyses were performed with the SPSS 22 statistical package (IBM SPSS Statistics Inc, Chicago, IL, USA).

RESULTS

Circulating leukocyte subset numbers

Obese children exhibited typical clinical and biochemical characteristics compared to age and sex-matched normal weight controls, with a higher BMI Z-score, waist circumference and blood pressure, combined with a lower insulin sensitivity index (QUICKI) and higher plasma levels of alanine aminotransferase, chemerin and leptin (Table 1). The obese children participated in an established lifestyle intervention programme[21], which resulted in stabilisation of their BMI Z-score and other clinical and biochemical characteristics, and enabled sampling pre and post-lifestyle intervention (Table 1).
Circulating leukocytes were analysed with multi-parameter flow cytometry, and leukocyte subsets were gated according to international standards (Figure 1, S1 Figure).[25] Overall, leukocyte subset numbers were comparable between obese children and lean controls. However, obese children pre and post-intervention showed higher naïve B-cell numbers, and obese children pre-intervention showed higher numbers of immature transition B-cells and intermediate CD14++CD16+ monocytes than lean controls (Table 2). Obese children pre-intervention additionally showed lower total monocyte numbers than lean controls. Notably, differences in leukocyte subset numbers did not survive multiple testing correction.

Focussing on the innate immune cells, monocytes expressed high levels of adipokine receptors compared to other circulating leukocyte subsets (Figure 1). Whereas non-classical CD14+CD16++ monocytes particularly expressed high levels of AdipoR1, all monocyte subsets expressed AdipoR2, and classical CD14++CD16- and intermediate CD14++CD16+ monocytes particularly expressed high leptin receptor levels. In contrast, Natural Killer (NK) cells and invariant Natural Killer T-cells (iNKT) predominantly showed AdipoR2 expression,

next to discrete AdipoR1 expression by CD16+ NK cells (Figure 1, Tables 3, 4 and 5). Considering the adaptive immune cells, AdipoR1 expression appeared to be low, in general. Only part of the CD4+ CXCR3+ T-cells and CD8+ T-cells and a discrete subset of regulatory T-cells showed AdipoR1 expression. In contrast, AdipoR2 was particularly expressed by B-cells, next to a subset of CD4+ CXCR3+ T-cells and a subset of CD8+ CD45RO+ (memory) T-cells. Finally, leptin receptor was predominantly expressed by B-cells, and a subset of CD4+ CD45RO- (non-memory) CXCR3+ T-cells and of CD8+ CD45RO+ (memory) CCR7+ T-cells and regulatory T-cells (Figure 1, Tables 3, 4 and 5).

Taken together, circulating leukocyte subsets showed distinct adipokine receptor expression profiles. Monocytes generally expressed high levels of all adipokine receptors, while other leukocyte subsets showed a different pattern. NK and iNKT cells predominantly expressed AdipoR2, while B-lymphocytes and CD4+ and CD8+ T-lymphocyte subsets expressed AdipoR2 as well as leptin receptor. Notably, regulatory T-cells showed little adipokine receptor expression, but a discrete subset of regulatory T-cells expressed a combination of adipokine receptors (S2 Figure).

Table 1. Patient characteristics.

	Lean controls (n=15)	Obese - pre (n=13)	Obese - post (n=13)
Girls (number, %)	8 (53.3)	7 (53.8)	7 (53.8)
Age (years)	11.7 ± 2.9	10.7 ± 3.9	12.0 ± 3.9
BMI Z-score	0.5 ± 0.9*#	3.3 ± 0.7*	3.1 ± 0.7#
Waist (cm)	64.5 ± 7.5*#	94.4 ± 16.8*	98.4 ± 17.0#
Systolic blood pressure (SBP)	102.2 ± 12.7*#	113.2 ± 12.2*	114.8 ± 11.7#
SBP percentile	39.9 ± 23.6*#	65.7 ± 25.1*	65.5 ± 28.4#
Diastolic blood pressure (DBP)	57.7 ± 8.2*#	67.2 ± 9.5*	69.4 ± 10.5#
DBP percentile	35.9 ± 19.9*#	62.6 ± 23.9*	65.4 ± 27.1#
QUICKI	0.4 ± 0.0*#	0.3 ± 0.0*	0.3 ± 0.0#
Alanine aminotransferase (U/l)	18.0 (14.5-21.8)*#	29.5 (22.2-53.9)*	30.3 (22.9-41.2)#
Triacylglycerol (mmol/l)	0.6 ± 0.3*	1.0 ± 0.4*	1.0 ± 0.7
Total cholesterol (mmol/l)	4.0 ± 0.8	4.0 ± 0.8	3.9 ± 0.9
HDL-cholesterol (mmol/l)	1.7 ± 0.9	1.2 ± 0.3	1.3 ± 0.2
LDL-cholesterol (mmol/l)	2.2 ± 0.7	2.3 ± 0.7	2.2 ± 0.8
Adiponectin (ug/ml)	18.9 (15.6-26.5)	12.9 (9.5-21.3)	13.6 (10.4-19.8)
Chemerin (ug/ml)	1.2 (1.0-1.7)*#	1.9 (1.8-2.7)*	2.3 (1.8-2.5)#
Leptin (ng/ml)	125 (16-195)*#	399 (219-692)*	411 (308-600)#

Clinical characteristics and laboratory parameters for lean controls versus obese children pre-lifestyle intervention (pre) and post-lifestyle intervention (post). Normally distributed data are shown as mean ± SD, non-parametric data as median (interquartile range). * P<0.05 for lean controls compared to obese-pre. # P<0.05 for lean controls versus obese-post.

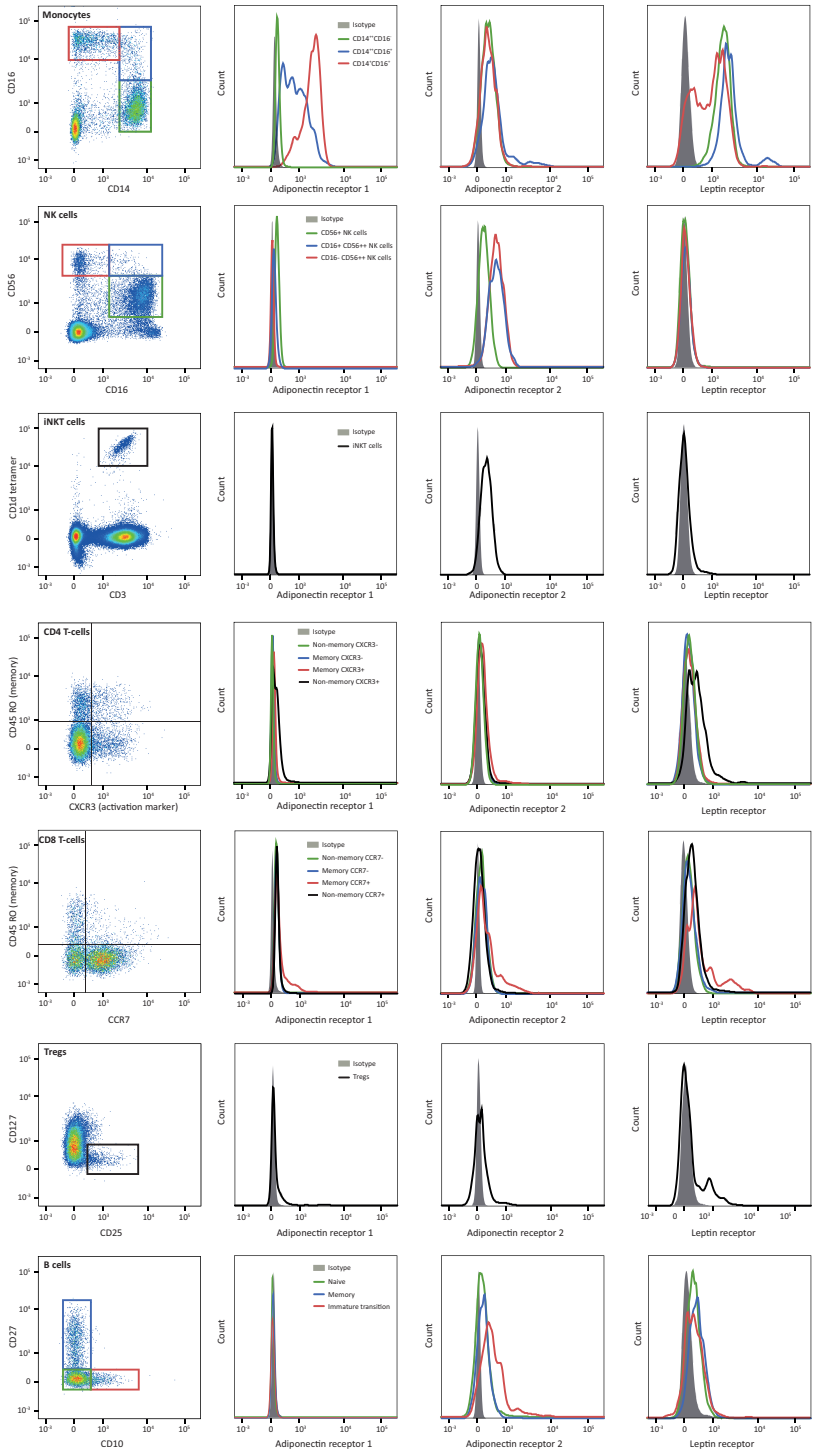

Figure 1. Adipokine receptor expression on leukocyte subsets.
The first column illustrates the gating strategy for the leukocyte subsets. The other columns show representative histograms of the AdipoR1, AdipoR2 and leptin receptor expression of the different leukocyte subsets.

Table 2. Leukocyte subset numbers.

	Lean controls	Obese-pre	Obese-post
Innate immunity			
Monocytes (total)	400 (300-600)*	300 (300-400)*	400 (300-500)
CD14++	352 (255-542)	244 (196-303)	330 (245-374)
CD14++CD16++	15 (11-19)*	16 (13-22)*	18 (13-39)
CD14+CD16++	37 (33-94)	39 (30-79)	40 (36-69)
Natural Killer cells (CD16+CD56+)	150 (80-211)	224 (116-321)	226 (134-287)
CD16+CD56++	8.7 (5.5-12)	8.0 (4.9-13)	9.3 (5.8-12)
CD16-CD56++	4.9 (2.8-8.0)	5.5 (3.4-8.1)	5.0 (4.4-8.9)
Bridging immunity			
Natural Killer T cells	1.2 (0.6-2.2)	1.4 (0.9-3.9)	1.2 (1.0-3.6)
Adaptive immunity			
B cells			
Naive (CD10-CD27-)	178 (132-270)*#	255 (189-454)*	316 (224-454)#
Memory (CD10-CD27+)	48 (41-73)	69 (45-113)	74 (56-117)
Immature transition (CD10+CD27+)	10 (5.4-17)*	23 (9.3-39)*	15 (10-31)
CD4+ T helper cells			
CD45RO- CXCR3-	511 (451-700)	639 (401-750)	624 (334-937)
CD45RO- CXCR3+	58 (40-176)	58 (32-110)$	85 (68-162)$
CD45RO+ CXCR3-	140 (115-196)	151 (125-227)	207 (103-251)
CD45RO+ CXCR3+	111 (84-134)	67 (43-115)	84 (57-117)
CD8+ cytotoxic T cells			
CD45RO- CCR7-	76 (37-138)	76 (43-178)	94 (29-161)
CD45RO- CCR7+	284 (275-358)	355 (272-434)	294 (238-477)
CD45RO+ CCR7-	82 (44-85)	56 (38-91)	52 (42-73)
CD45RO+ CCR7+	15 (12-19)	13 (8.6-30)	18 (13-22)
Regulatory T cells (CD25+CD127-)	26 (14-35)	21 (16-28)	22 (13-33)

Leukocyte subset numbers (x 10^6) of lean controls compared to obese children pre-lifestyle intervention (pre) and post-lifestyle intervention (post). Data are presented as median (interquartile range). * P<0.05 for lean controls compared to obese-pre. # P<0.05 for lean controls versus obese-post. $ P<0.05 for obese-pre compared to obese-post.

Table 3. Adiponectin receptor 1 expression.

	Lean controls	Obese-pre	Obese-post
Innate immunity			
Monocytes (total)	21 (18-31)	31 (18-36)	25 (20-29)
CD14++	10 (8.8-16)#	8.2 (4.6-27)	7.7 (3.7-11)#
CD14++CD16++	82 (68-88)	90 (81-94)	84 (73-93)
CD14+CD16++	84 (71-92)*	94 (77-98)*	91 (85-96)
Natural Killer cells (CD16+CD56+)	82 (56-92)	86 (76-95)	88 (78-95)
CD16+CD56++	41 (29- 63)	51 (39-58)	56 (44-64)
CD16-CD56++	1.6 (0.5 -3.1)	0.9 (0.1-4.6)	0.8 (0.4-1.8)
Bridging immunity			
Natural Killer T cells	7.6 (4.1-25)	12 (4.1-18)	6.9 (5.0-15)
Adaptive immunity			
B cells			
Naive (CD10-CD27-)	1.1 (0.6-2.2)#	0.8 (0.5-2.0)	0.5 (0.4-1.0)#
Memory (CD10-CD27+)	5.9 (3.8-6.6)	5.6 (3.8-8.8)	6.4 (3.5-9.6)
Immature transition (CD10+CD27+)	0.0 (0.0-0.2)*	0.7(0.3-1.0)*$	0.1 (0.0-0.5)$
CD4+ T helper cells			
CD45RO- CXCR3-	5.2 (1.6-21)	3.3 (1.0-22)	3.6 (1.6-19)
CD45RO- CXCR3+	64 (45-92)	47 (37-71)	63 (49-81)
CD45RO+ CXCR3-	6.1 (2.1-12)	4.7 (1.6-12)	6.6 (2.2-11)
CD45RO+ CXCR3+	24 (12-38)	21 (12-42)	41 (16-56)
CD8+ cytotoxic T cells			
CD45RO- CCR7-	46 (41-55)	51 (42-61)	50 (42-61)
CD45RO- CCR7+	60 (55-74)	54 (45-66)	53 (46-68)
CD45RO+ CCR7-	34(30-43)	36 (31-52)	38 (34-43)
CD45RO+ CCR7+	70 (66-77)	68 (52-90)	72 (67-87)
Regulatory T cells (CD25+CD127-)	3.9 (1.6-14)	4.0 (1.0-9.0)	4.8 (1.6-9.7)

Percentage expression of adiponectin receptor 1 on leukocyte subsets of lean controls compared to obese children pre-lifestyle intervention (pre) and post-lifestyle intervention (post). Data are presented as median (interquartile range). * P<0.05 for lean controls compared to obese-pre. # P<0.05 for lean controls versus obese-post. $ P<0.05 for obese-pre compared to obese-post.

Table 4. Adiponectin receptor 2 expression.

	Lean controls	Obese-pre	Obese-post
Innate immunity			
Monocytes (total)	60 (32-67)	68 (46-80)	57 (43-70)
CD14++	59 (29-66)	60 (45-80)	54 (41-67)
CD14++CD16++	79 (60-88)	80 (67-93)	75 (59-86)
CD14+CD16++	60 (44-70)	63 (46-80)	62 (44-68)
Natural Killer cells (CD16+CD56+)	67 (62-80)#	61 (53-72)	62 (53-66)#
CD16+CD56++	98 (97-100)	97 (95-99)	98 (93-99)
CD16-CD56++	99 (96-100)	97 (95-99)	98 (97-100)
Bridging immunity			
Natural Killer T cells	77 (70-89)	70 (61-74)	77 (62-82)
Adaptive immunity			
B cells			
Naive (CD10-CD27-)	38 (35-46)	36 (32-41)	35 (24-40)
Memory (CD10-CD27+)	45 (39-52)	43 (36-46)	41 (19-47)
Immature transition (CD10+CD27+)	74 (61-81)	72 (58-87)	77 (57-82)
CD4+ T helper cells			
CD45RO- CXCR3-	27 (25-32)#	25 (20-38)	25 (13-27)#
CD45RO- CXCR3+	54 (46-88)	49 (40-58)	50 (43-67)
CD45RO+ CXCR3-	34 (31-39)	32 (28-41)	33 (14-37)
CD45RO+ CXCR3+	43 (36-62)	40 (33-54)	47 (33-60)
CD8+ cytotoxic T cells			
CD45RO- CCR7-	29 (11-34)	31 (24-44)	29 (12-33)
CD45RO- CCR7+	26 (22-48)	24 (19-44)	25 (20-38)
CD45RO+ CCR7-	31 (13-41)	36 (30-44)	30 (7.6-35)
CD45RO+ CCR7+	58 (52-76)	55 (35-80)	58 (52-77)
Regulatory T cells (CD25+CD127-)	23 (21-27)	20 (15-27)	22 (19-28)

Percentage expression of adiponectin receptor 2 on leukocyte subsets of lean controls compared to obese children pre-lifestyle intervention (pre) and post-lifestyle intervention (post). Data are presented as median (interquartile range). * P<0.05 for lean controls compared to obese-pre. # P<0.05 for lean controls versus obese-post. $ P<0.05 for obese-pre compared to obese-post.

Table 5. Leptin receptor expression.

	Lean controls	Obese-pre	Obese-post
Innate immunity			
Monocytes (total)	96 (95-98)	97 (92-98)	97 (94-98)
CD14++	99 (99-100)	100 (99-100)	100 (99-100)
CD14++CD16++	100 (99-100)	100 (99-100)	100 (99-100)
CD14+CD16++	70 (61-81)	75 (65-84)	77 (77-81)
Natural Killer cells (CD16+CD56+)	8.0 (5.3-12)	8.8 (3.3-18)	6.1 (4.4-10)
CD16+CD56++	7.2 (5.3-9.6)	5.7 (3.0-14)	6.2 (3.0-9.7)
CD16-CD56++	6.6 (5.9-7.7)	5.3 (3.1-7.1)	6.4 (2.9-7.8)
Bridging immunity			
Natural Killer T cells	11 (5.8-19)	13 (5.2-32)	9.8 (8.7-18)
Adaptive immunity			
B cells			
Naive (CD10-CD27-)	51 (44-56)	51 (46-58)	47 (46-55)
Memory (CD10-CD27+)	60 (57-65)	63 (54-65)	57 (50-62)
Immature transition (CD10+CD27+)	46 (39-54)	50 (35-57)	46 (39-51)
CD4+ T helper cells			
CD45RO- CXCR3-	31 (28-40)	29 (24-41)	28 (24-36)
CD45RO- CXCR3+	69 (59-93)	62 (50-73)	71 (64-80)
CD45RO+ CXCR3-	26 (22-29)	25 (21-26)	24 (21-29)
CD45RO+ CXCR3+	42 (29-50)	41 (28-49)$	55 (44-66)$
CD8+ cytotoxic T cells			
CD45RO- CCR7-	22 (16-26)	22 (17-34)	25 (19-29)
CD45RO- CCR7+	41 (31-52)	39 (31-52)	38 (32-48)
CD45RO+ CCR7-	21 (19-32)	24 (19-32)	28 (24-31)
CD45RO+ CCR7+	65 (56-72)	67 (48-87)	69 (61-80)
Regulatory T cells (CD25+CD127-)	10 (7.8-17)	12 (5.9-15)	13 (11-17)

Percentage expression of leptin receptor on leukocyte subsets of lean controls compared to obese children pre-lifestyle intervention (pre) and post-lifestyle intervention (post). Data are presented as median (interquartile range). * P<0.05 for lean controls compared to obese-pre. # P<0.05 for lean controls versus obese-post. $ P<0.05 for obese-pre compared to obese-post.

Adipokine receptor expression in lean and obese children

In order to establish differences in adipokine receptor expression between obese children pre and post-intervention and normal weight controls, we studied differences in expression percentages (Tables 3, 4 and 5), as well as median fluorescence intensities (MFI) (S1-S3 Tables). In general, obese children pre and post-intervention and normal weight controls showed similar adipokine receptor expression on leukocyte subsets. In fact, none of the observed differences in adipokine receptor expression between obese children and lean controls remained significant after multiple testing correction.

As an alternative strategy to discriminate between random deviations and potentially relevant differences, we focused on differences in adipokine receptor expression that were consistent in percentages as well as fluorescence intensities. AdipoR1 expression on non-classical CD14+CD16++ monocytes was consistently upregulated in percentages and MFI in obese children pre-intervention, compared to lean controls (Table 3 and S1 Table). The other leukocyte subsets did not show consistent differences in AdipoR1, AdipoR2 or leptin receptor expression between obese children and lean controls.

Circulating adipokines and adipokine receptor expression

Finally, we wondered whether high circulating adipokine levels were associated with alterations in adipokine receptor expression, which could modulate adipokine signalling. First, we studied the relationship between circulating adipokine levels and adipokine receptor expression on monocytes. Neither did we observe a correlation between circulating adiponectin levels and AdipoR1/AdipoR2 expression (Figure 2A and 2B), nor a correlation between circulating leptin levels and leptin receptor expression (Figure 2C, Figure B in S3 Figure). Second, screening other leukocyte subsets did not yield a correlation between circulating adipokine levels and adipokine receptor expression either (Figure A in S3 Figure).

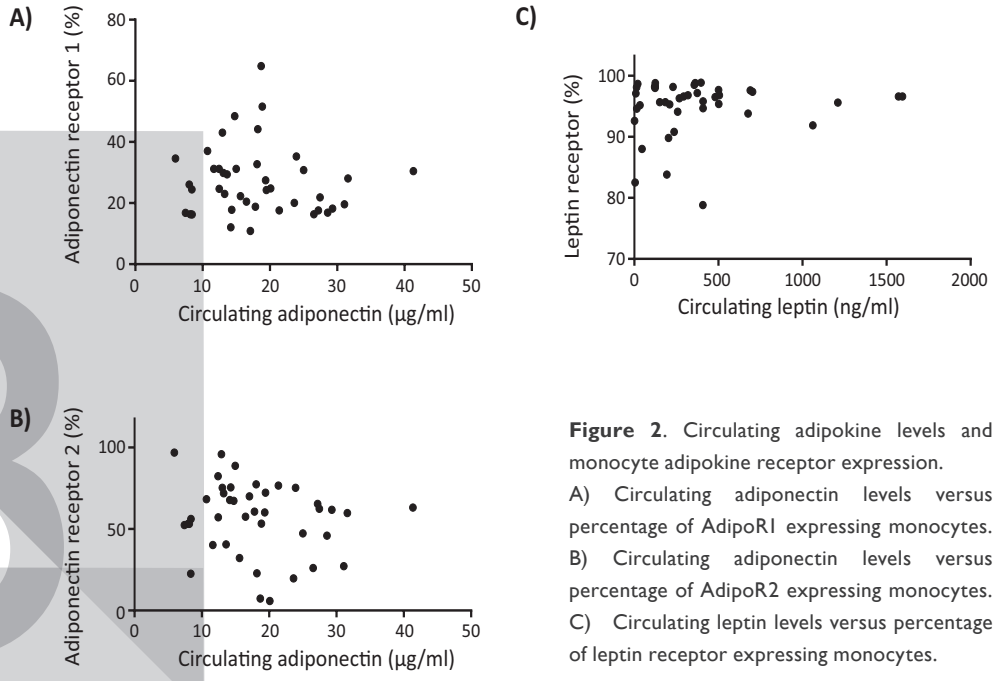

Figure 2. Circulating adipokine levels and monocyte adipokine receptor expression.
A) Circulating adiponectin levels versus percentage of AdipoR1 expressing monocytes. B) Circulating adiponectin levels versus percentage of AdipoR2 expressing monocytes. C) Circulating leptin levels versus percentage of leptin receptor expressing monocytes.

DISCUSSION

Over the last decades, enhanced circulating leptin levels and decreased adiponectin levels emerged as one of the mechanisms underlying the cardiometabolic sequelae in obesity.[4,5,11] This study aimed to establish the expression of adiponectin and leptin receptors on circulating immune cell subsets in obese children and normal weight controls, since adipokine receptor expression on circulating leukocytes can modulate adipokine signalling and obesity-induced systemic inflammation.[15,16] Here, we will discuss our two main findings.

First, circulating leukocyte subsets showed distinct adipokine receptor expression profiles, which may partly explain the differential impact of adipokines on leukocyte subsets. Whereas enhanced AdipoR1/R2 expression on the myeloid cell lineage has for example been associated with anti-inflammatory (M2) macrophage polarisation and suppression of foam cell formation[26,27], the decreased AdipoR1 expression on classical CD14++CD16- monocytes may be involved in their inflammatory fate and pivotal role in the development of cardiovascular disease.[28,29] Another example is the discrete subpopulation of Tregs expressing a combination of leptin receptor and adiponectin receptors (S2 Figure). Considering the role of peroxisome-proliferator-activated receptor γ (PPARγ) induced adiponectin signalling in adipose tissue differentiation of Tregs[30,31], and the pivotal role of leptin in T-cell differentiation[32–34], it is tempting to speculate that circulating leptin and adiponectin receptor positive Tregs represent recirculating adipose tissue Tregs. Taken together, our data provide an exciting starting point for future studies to the role of adipokine receptors in leukocyte differentiation and function.

Second, we observed largely similar leukocyte subset numbers and adipokine receptor expression profiles in obese children and controls. The high naive CD10-CD27- B-cell numbers in obese children pre and post-lifestyle intervention appear to be an exception to that. Interestingly, our findings correspond with recent studies observing high naive B-cell numbers in obese adults.[35,36] The high naïve B-cell numbers may be explained by leptin-induced B-cell hyperstimulation, which can impair B-cell function.[35,36] Indeed, B-cell responses to vaccination can be impaired in obesity.[35,37] With respect to the similar adipokine receptor expression profiles of obese children and lean controls, our findings suggest that in childhood obesity, adipokine signalling in circulating leukocytes is primarily modulated by circulating adipokine levels, instead of adipokine receptor expression.

Our study has a few limitations that have to be taken into account. Storage or freeze-thawing of the peripheral blood mononuclear cells may have neutralised differences in adipokine receptor expression between obese children and controls. Notably, differences in adipokine receptor expression between leukocyte subsets were preserved, which argues against significant storage or freeze-thawing effects. Next, while adipokine receptor expression in liver, skeletal muscle, adipose tissue and other tissues plays in important role in adipokine signalling as well, medical ethical reasons precluded tissue collection. Importantly, our observations in circulating leukocyte subsets do not extend to other tissues. Finally, our study may have been underpowered to identify

subtle differences in adipokine receptor expression due to relatively small patient numbers. In obese adults, lymphocyte AdipoR1 and AdipoR2 mRNA expression was reduced compared to anorexic adults.[38] Likewise, reduced monocyte AdipoR1 and AdipoR2 protein expression was observed in obese adults with coronary artery disease, compared to obese adults without cardiovascular disease.[39] However, the results in these studies may have been distorted due to the fact that multiple testing corrections were not applied and nor differentiation was made between functionally distinct leukocyte subsets.

In conclusion, our results cannot exclude subtle differences in adipokine receptor expression, but suggest that adipokine signalling in circulating leukocytes in childhood obesity is primarily modulated by altered adipokine levels.

ADDITIONAL INFORMATION (APPENDIX A)

S1 Figure, S2 Figure, S3 Figure, S1 Table, S2 Table, S3 Table

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CHAPTER 4

Office blood pressure versus ambulatory blood pressure measurement in childhood overweight and obesity

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4

Submitted for publication

ABSTRACT

Background

Parallel to the childhood obesity epidemic prevalence rates of obesity-related co-morbidities such as elevated blood pressure (BP) are increasing. The added value of ambulatory blood pressure measurement (ABPM) in relation to office blood pressure (OBP) measurements in obese children is unclear. Furthermore, it is unknown how many overweight and obese children present with abnormal ABPM patterns. The objective of this study was to evaluate ABPM patterns in a population of overweight and obese children and adolescents, and to compare these patterns with regular OBP measurements.

Methods

Cross-sectional study in overweight and obese children and adolescents aged 4-17 years, using ABPM to determine the frequency of white coat hypertension, elevated BP, masked hypertension, and ambulatory hypertension, and to correlate these findings with OBP measurements.

Results

We included 82 boys and girls aged 4-17 years, with mean BMI Z-score of 3.3 (standard deviation 0.6). Using ABPM, 54.9% of them were normotensive (95% confidence interval 44.1-65.2), 26.8% had elevated BP, 9.8% ambulatory hypertension, 3.7% masked hypertension, and 4.9% white coat hypertension. Twenty-four percent of the participants showed an isolated night-time BP load >25%, 40% of them lacked physiologic nocturnal systolic BP dipping. Twenty-two percent of those with normal OBP turned out to have either elevated BP or masked hypertension on ABPM.

Conclusion

This study shows a high prevalence of abnormal ABPM patterns in overweight or obese children and adolescents. OBP was often poorly correlated with a subject's actual ABPM pattern. This emphasises the usefulness of ABPM as a diagnostic tool in this population.

INTRODUCTION

As a consequence of the global obesity epidemic, prevalence rates of obesity-related co-morbidities such as elevated blood pressure (BP) in children are also increasing.[1] Hypertension prevalences up to almost 25% are found in overweight children and adolescents.[2–4] Although the cardiovascular sequelae of hypertension are clinically obvious in adulthood, the consequences of high BP in children and adolescents are usually less clear on first sight. Hypertension in children and adolescents is associated with the development of early, often subclinical, hypertensive targed-organ damage (TOD) including increased carotid intima-media thickness, left ventricular hypertrophy, insulin resistance, and renal damage.[5–8] In addition, numerous studies have shown that high BP in childhood increases the risk for adult hypertension and metabolic syndrome.[9–12]
The diagnosis of elevated BP and hypertension depends on an accurate BP measurement, which can present a challenge to the clinician. Ambulatory 24-hour blood pressure measurement (ABPM) is now increasingly recognised as indispensable for the diagnosis and management of hypertension.[13–16] ABPM allows a more representative observation of BP thoughout day and night compared to office blood pressure (OBP) measurements as well as assessment of the circadian and even ultradian BP variability. ABPM is useful to detect white coat hypertension, masked hypertension, and nocturnal hypertension.[17–19] White coat hypertension and masked hypertension are known to be more prevalent in obese compared to lean pediatric populations.[3] Furthermore, ABPM has been shown in children to be more predictive of end-organ damage.[20]
This study was conducted to evaluate ABPM patterns in a population of overweight and obese children and adolescents referred to our pediatric outpatient clinic, and to compare ABPM patterns with regular OBP measurements. Our hypothesis is that the prevalence of abnormal ABPM patterns, including white coat hypertension and masked hypertension, is substantial in childhood obesity. Furthermore, we expect a high prevalence of abnormal circadian variability in this population.

MATERIALS AND METHODS

Study design and participants

A retrospective study was performed using data of children and adolescent with overweight or obesity aged 4-17 years who were referred to the outpatient clinic of Hospital Gelderse Vallei Ede between April 2015 and July 2017. Inclusion criteria were 1) overweight or obesity[21] with no syndromal or endocrine underlying problem, 2) a height of ≥120 cm[20], and 3) no (past) treatment with medications influencing cardiovascular function, body composition, lipid, or glucose metabolism.
This study was approved by the institutional review board of Hospital Gelderse Vallei Ede.

Anthropometric measurements

Trained staff measured children's weight in underwear using an electronic calibrated scale (Seca 761), and height without shoes using a stadiometer (Holtain Ltd., UK). Age and sex-specific BMI Z-scores were calculated using Dutch growth curves of 2010 based on the LMS analysis method.[22] In the remaining sections of this paper, the term overweight will be used to indicate both overweight and obesity.

Waist circumference was used as a marker of central adiposity and measured with a flexible tape to the nearest 0.1 cm at umbilicus height.

BP measurements

Office blood pressure

Right arm OBP was measured in a supine position with an automated BP monitor (Welch Allyn VSM 300, USA) after 5 minutes of rest. A minimum of two OBP measurements was taken to obtain two values not differing >5 mmHg. The mean of these two measurements was used for data analysis. Reference values according to the recently updated Clinical Practice Guideline on BP in children were used.[23]

Ambulatory blood pressure measurement (ABPM)

All participants underwent a 24-hour ABPM on a regular week-day using a SpaceLabs Ultralite 90217-1Q monitor. Participants were instructed to record activity, sleep, and wake times in a diary, and to continue their normal activities but refrain from contact sports and vigorous exercise. Readings were automatically taken every 15 minutes (waking hours) and every 60 minutes (night-time). Measurements were repeated twice at 2-minute interval if systolic or diastolic BP was >95th percentile of reference population.

ABPM data were downloaded using the manufacturer's software Spacelabs Medical ABP Report Management System version 2.00.09, firmware version 03.02.15 and Sentinel Cardiology Information Management System. Only ABPM profiles with at least 10 valid recordings during daytime and five during night-time were accepted for analysis. Values that fall outside of the following range were discarded: systolic BP 60-220 mmHg, diastolic BP 35-120 mmHg, heart rate 40-180 bpm, pulse pressure 40-120 mmHg.[20]

Combining systolic and diastolic BP readings with the corresponding time of measurements, the variables were calculated as presented in Table 1. A combination of OBP[23], mean ambulatory BP, and BP load was used to categorise ABPM results as normal or abnormal, using the suggested scheme for staging of ambulatory BP levels in children as presented by Flynn et al. (Table 1).[20]

Laboratory measurements

After an overnight fast, serum glucose, glycated haemoglobin (HbA1c), insulin levels, and lipid profiles were determined. All participants underwent a 2-h oral glucose tolerance test with a 1.75 gram glucose dose per kilogram bodyweight (maximum of 75 gram). Glucose tolerance status was determined according to the American Diabetes Association 2018 criteria. Insulin resistance was analysed using the formula [fasting insulin (mIU/L) x fasting glucose (mmol/L)]/22.5. Homeostasis model assessment of insulin resistance (HOMA-IR) cut-off values were used as proposed by Kurtoglu et al.[29] Dyslipidemia was defined as elevated total cholesterol and/or elevated LDL cholesterol and/or HDL cholesterol below cut-off and/or elevated triglycerides, using the age-specific reference values obtained from the Dutch guideline for childhood obesity and cardiovascular risk management.[30,31] For the diagnosis of metabolic syndrome an adjusted definition was used; the presence of central obesity (waist circumference ≥90th percentile) plus any of the other four components of metabolic syndrome: elevated triglycerides, HDL cholesterol below cut-off, disordered glucose metabolism (prediabetes or diabetes)[31], or abnormal OBP[23].

Statistical analysis

SPSS 19.0 (IBM SPSS Statistics Inc., Chicago, IL) statistical package was used to analyze the data. Normalcy of the data was determined with Skewness and Kurtosis tests. Mann-Whitney U tests (for continuous variables) and Pearson Chi-Square tests (for categorical variables) were used to compare between dippers and non-dippers and between the different ABPM patterns with normal BP as the reference category. $P<0.05$ was considered statistically significant.

RESULTS

Our 82 participants were aged 4-17 years, and 39% of them were boys (Table 2). Ten participants were classified as having overweight, the remaining 72 (88%) were obese. Sixty percent of the participants presented with at least one obesity-related comorbidity. No participant was treated with antihypertensive medication at the time of the ABPM.

Based on OBP measurements 54.9% (95% confidence interval [CI] 44.1-65.2; n=45) of the participants were normotensive, 19.5% had elevated BP, 19.5% classified as stage 1 hypertension, and 6.1% were classified as stage 2 hypertension (Table 3). Twenty-two percent of the participants had an office systolic BP index ≥1.0, nine percent an office diastolic BP index ≥1.0.

Table 1. Overview of the ABPM variables calculated in this study, and the ABPM pattern definitions used.

	Background information	Definitions	Used cut-off values
OBP			[23]
ABPM variables			
Mean 24-hour, daytime and night-time ambulatory SBP and DBP			95th percentile mean ambulatory SBP and DBP cut-offs as specified in [20]
Indexation of BP	To control for differences in age and body size seen across a typical pediatric cohort.	Indexed blood pressure = average measured ambulatory blood pressure value / 95th percentile ambulatory blood pressure.[40]	
BP load during the 24-hour period, daytime and night-time period (both SBP and DBP)	The amount of time that a subject's SBP or DBP exceeds normal values. Mathematically it depends on both average BP levels and distribution of BP readings.[24,25]	Percentage of readings above the ambulatory 95th blood pressure percentiles as specified in [20].	Normal BP load: <25%.[27,28]
BP dipping		Percent decline in SBP and DBP during sleep ([mean daytime BP-mean night-time BP] / mean daytime BP x 100).	Normal dipping: ≥10% decline in mean systolic and diastolic ambulatory blood pressure levels from day to night.[26]

ABPM patterns (according to the suggested scheme for staging of ambulatory blood pressure levels in children as presented in [20])*

	OBP	Mean ambulatory SBP or DBP	SBP or DBP load
Normal blood pressure	<90th percentile	<95th percentile	<25%
White coat hypertension	≥95th percentile	<95th percentile	<25%
Elevated blood pressure	≥90th percentile or >120/80 mm Hg	<95th percentile	≥25%
Masked hypertension	<95th percentile	>95th percentile	≥25%
Ambulatory hypertension	>95th percentile	>95th percentile	25-50%, >50% severe ambulatory hypertension

For some participants (n=18) no specific ambulatory BP classification could be assigned based on the suggested scheme, i.e. 1) participants with normal OBP, normal mean ambulatory BP, but elevated load (n=9), or 2) participants with OBP 90-95h percentile, normal mean ambulatory BP, and normal load (n=6). These subjects were evaluated on a case-by-case basis, as suggested by Flynn et al.[20], taking into account the increased risk of cardiovascular disease (CVD) in subjects with overweight and the clinical relevance of elevated BP load. Those with unclassified AHA BP parameters in the first group were classified as 'elevated BP', subjects in the second group as 'normal BP'. Next, one participant with normal OBP, normal mean ambulatory BP, and elevated night-time BP load (>50%) with low systolic and diastolic BP dipping (respectively 4.9 and 0.4%) was classified as masked hypertension. Two participants with OBP in the 'elevated BP' range, normal mean ambulatory BP and elevated night-time BP load were classified as 'elevated BP'.

ABPM, ambulatory blood pressure measurement; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure
* In line with the recently published Clinical Practice Guideline[23] the term 'prehypertension' was replaced with 'elevated BP' in subjects with prehypertension according to this classification scheme.

Table 2. Participant characteristics of the total study population, and for the ABPM categories separately.

		ABPM				
	Total group (n=82)	**Normal BP (n=45)**	**WCH (n=4)**	**Elevated BP (n=22)**	**MH (n=3)**	**Ambulatory HTN (n=8)**
Male	32 (39.0)	20 (44.4)	3 (75.0)	6 (27.3)	1 (33.3)	2 (25.0)
Age	11.8 (8.8, 14.6)	11.5 (8.7, 14.6)	8.4 (5.9, 11.5)	12.9 (9.0, 14.9)	10.8 (6.8, NA)	9.9 (9.1, 16.3)
Ethnicity‡						
Dutch/Western immigrant	66 (81.5)	37 (82.2)	3 (75.0)	17 (77.2)	3 (100.0)	6 (75.0)
Non-western immigrant	16 (19.5)	8 (17.8)	1 (25.0)	5 (22.7)	0 (0.0)	2 (25.0)
BMI Z-score	3.3 (2.8, 3.6)	3.1 (2.8, 3.5)	3.1 (2.8, 3.6)	3.5 (2.9, 3.8)	2.7 (2.4, NA)	3.8 (3.1, 4.3)[b]
Glucose metabolism						
Prediabetes*	8 (10.4)	4 (9.5)	0 (0.0)	3 (14.3)	0 (0.0)	1 (12.5)
Elevated HOMA-IR†	33 (44.0)	16 (39.0)	0 (0.0)	9 (45.0)	0 (0.0)	8 (100.0)[a]
Lipid profile						
Elevated TC*	3 (3.9)	2 (4.8)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
Elevated LDL-C*	1 (1.2)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HDL-C below cut-off*	10 (13.0)	4 (9.5)	1 (25.0)	3 (14.3)	0 (0.0)	2 (25.0)
Elevated TG*	8 (10.4)	3 (7.1)	0 (0.0)	3 (14.3)	0 (0.0)	2 (25.0)
MetS**	11 (13.4)	2 (5.1)	1 (25.0)	6 (30.0)[a]	0 (0.0)	2 (28.6)[b]

Number (%), except for age and BMI Z-score (median, interquartile range)

* Total group: n=77; normal BP: n=42; elevated BP: n=21; MH: n=2

** Total group: n=79; normal BP: n=39; elevated BP: n=20; MH: n=2; (severe) ambulatory HTN: n=7.

† Total group: n= 75; normal BP: n=41; elevated BP: n=20; MH: n=2.

‡ Children whose parents were born outside the Netherlands were identified as immigrants (even if the child was of Dutch nationality). If both parents were born in the Netherlands, the child was classified as native Dutch. Western immigrants originated from Europe (excluding Turkey), North America, Oceania, Indonesia or Japan. Non-western immigrants originated from Africa, South America, Asia (excluding Indonesia and Japan) or Turkey.

a P<0.01 compared to normal BP, using Mann-Whitney U test for continuous variables and Pearson Chi-Square for categorical variables

b P<0.05 compared to normal BP, using Mann-Whitney U test for continuous variables and Pearson Chi-Square for categorical variables

ABPM, ambulatory blood pressure measurement; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; MH, masked hypertension; TC, total cholesterol; TC, triglycerides; WCH, white coat hypertension

The ABPM patterns also showed that 54.9% (95% CI 44.1-65.2) of participants had normal BP. However, this group differed from the OBP normotensive group (Table 3). Ten of the 45 participants (22.2%) with normal OBP turned out to have either elevated BP (n=9) or masked hypertension (n=1) on ABPM (Table 3). Of the 37 participants with abnormal OBP, ten had normal BP on APBM (27.0%). Eight of the 21 participants (38%) with OBP hypertension

were confirmed to have ambulatory hypertension. The others were diagnosed with elevated BP (n=8) or white coat hypertension (n=4). Of the 16 participants with elevated BP in the outpatient clinic, 56% had normal ABPM results, 13% had masked hypertension, and in 31% of the participants elevated BP was confirmed with ABPM. The correlation coefficient for the relationship between indexed office systolic BP (as a proxy of hypertensive status based on OBP) and indexed mean daytime systolic BP (hypertensive status based on ABPM) was 0.39.

Using ABPM, a BP load >25% was found in 24.4-26.8% of the participants during the whole 24-hour period. During night-time more often a BP load >25% was detected than during daytime. Twenty-four percent of all cases (n=20) showed an isolated night-time BP load >25% with normal daytime ABPM. Up to 40% of the participants lacked physiologic nocturnal systolic BP dipping.

No significant differences in terms of age and gender were observed between the different ABPM categories (Table 2). Participants with ambulatory hypertension had a significantly higher BMI Z-score (3.8, interquartile range [IQR] 3.1-4.3) compared to the normal BP group (BMI Z-score 3.1, IQR 2.8-3.5). Prediabetes was detected in 8 participants (11.1%); 50% of them had elevated BP or ambulatory hypertension.
Elevated HOMA-IR was present in all participants with ambulatory hypertension. The prevalence of metabolic syndrome was significantly higher in participants with elevated BP and ambulatory hypertension than in participants with normal ABPM. Of note, metabolic syndrome was significantly more prevalent in non-dippers when compared to dippers (29.6% versus 6.7%, respectively, P=0.009). Increasing severity of obesity was not associated with nocturnal non-dipping.

DISCUSSION

Our study confirms the high prevalence of abnormal BP in obese children and adolescents. It also underscores the unreliability of OBP measurement and the need for BP monitoring by APBM.
Using ABPM, 9.8% of our cohort was classified as ambulatory hypertension, of which 75% had severe ambulatory hypertension. Elevated BP was present in 26.8% of our participants. In literature, hypertension prevalence ranges from 3.8% to 24.8% in youth with overweight and obesity.[23] Prevalences of elevated BP up to around 15% are reported in unselected children, and to 20-30% in childhood obesity.[32–36] Elevated BP, or former 'prehypertension', has shown to be associated with cardiovascular TOD in adolescents and young adults and may be a risk factor of progressing to sustained hypertension.[36–42]

Table 3. Summary of blood pressure characteristics according to ABPM classification.

		ABPM				
	Total group (n=82)	**Normal BP (n=45)**	**WCH (n=4)**	**Elevated BP (n=22)**	**MH (n=3)**	**Ambulatory HTN (n=8)**
OBP						
Normal BP	45 (54.9)	35 (77.8)	0 (0.0)	9 (40.9)	1 (33.3)	0 (0.0)
Elevated BP	16 (19.5)	9 (20.0)	0 (0.0)	5 (22.7)	2 (66.7)	0 (0.0)
Stage 1 HTN	16 (19.5)	1 (2.2)	3 (75.0)	7 (31.8)	0 (0.0)	5 (62.5)
Stage 2 HTN	5 (6.1)	0 (0.0)	1 (25.0)	1 (4.5)	0 (0.0)	3 (37.5)
24-hour SBP						
Median (IQR)	109 (104, 116)	106 (101, 112)	106 (97, 113)	111 (107, 119)	123 (110, NA)	124 (114, 130)
BP index, median (IQR)	0.88 (0.84, 0.93)	0.86 (0.82, 0.88)	0.87 (0.83, 0.92)	0.92 (0.87, 0.95)	0.96 (0.94, NA)	1.02 (0.98, 1.05)
BP index ≥1.0, n (%)	7 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	6 (75.0)
BP load (%), median (IQR)	8.8 (3.6, 25.4)	6.1 (0.0, 14.2)	4.2 (1.0, 13.0)	16.2 (6.7, 27.9)	28.6 (17.2, NA)	58.1 (44.4, 72.9)
BP load >25%, n (%)	20 (24.4)	3 (6.7)	0 (0.0)	8 (36.4)	2 (66.7)	7 (87.5)
Dipping, median (IQR)	11 (7, 15)	12.8 (8.5, 17.1)	9.8 (7.5, 11.1)	10.4 (4.7, 13.4)	5.2 (4.9, NA)	6.8 (0.8, 12.1)
Dipping <10%, n (%)	33 (40.2)	14 (31.1)	2 (50.0)	11 (50.0)	2 (66.7)	4 (50.0)
24-hour DBP						
Median (IQR)	65 (61, 69)	63 (60, 66)	62 (56, 66)	67 (64, 71)	73 (64, NA)	76 (69, 81)
BP index, median (IQR)	0.86 (0.81, 0.91)	0.82 (0.79, 0.87)	0.83 (0.74, 0.85)	0.89 (0.84, 0.93)	0.96 (0.88, NA)	0.99 (0.91, 1.07)
BP index ≥1.0, n (%)	4 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	3 (37.5)
BP load (%), median (IQR)	15.5 (6.3, 25.7)	11.9 (4.1, 20.5)	8.8 (3.8, 21.3)	17.7 (13.1, 30.6)	37.9 (16.7, NA)	53.6 (22.3, 73.6)
BP load >25%, n (%)	22 (26.8)	6 (13.3)	0 (0.0)	9 (40.9)	2 (66.7)	5 (62.5)
Dipping, median (IQR)	19 (14, 22)	19.4 (14.3, 24.5)	16.2 (12.3, 23.0)	17.9 (14.7, 20.7)	19.4 (0.4, NA)	14.6 (7.0, 24.0)
Dipping <10%, n (%)	9 (11.0)	3 (6.7)	0 (0.0)	3 (13.6)	1 (33.3)	2 (25.0)
Non-dipper, n (%)	34 (41.5)	14 (31.1)	2 (50.0)	12 (54.5)	2 (66.7)	4 (50.0)

Number (%), except for age, BMI, BMI Z-score, WC, WC Z-score (median, IQR)

BP, blood pressure; HTN, hypertension; IQR, interquartile range; MH, masked hypertension; WCH, white coat hypertension

Three participants (3.7%) in our cohort were diagnosed with masked hypertension and four (4.9%) with white coat hypertension. In literature, masked hypertension prevalence ranges from 7.6% in unselected children[8], to 32.3% in obese children with a non-dipping pattern.[43] White coat hypertension prevalence ranges from 0.6% in 9-10 year old students[44], to 59% in a group of children referred for persistently elevated casual BP.[45] The divergence observed in the prevalence of masked hypertension and white coat hypertension is likely caused by measurements in different study populations using different diagnostic criteria[45], and by the choice of the upper limits of normalcy.[45,46] In our study 38.1% of the subjects with stage 1 or 2 hypertension based on OBP measurement demonstrated less severe elevation on ABPM and were classified as elevated BP, also suggesting a white coat phenomenon.
The clinical significance of masked hypertension in children lies in the potentially increased risk for target-organ damage (TOD) and future cardiovascular events.[8,47,48] The impact of white coat hypertension in children is far less clear.[48] Although white coat hypertension in adulthood has been associated with cardiovascular morbidity and mortality and progression to sustained hypertension[49,50], the published cardiovascular events incidences and all-cause mortality relative risks are only slightly higher compared to normotensive people and significantly below the risks associated with sustained hypertension.[51,52]
In our study, more than 20% of the participants with normal OBP turned out to have either elevated BP or masked hypertension on ABPM. These patients would have been missed if classified by OBP. Discrepancies between OBP and ABPM have been described before in different paediatric populations.[3,53,54] Considering (future) cardiovascular risks in patients with elevated BP or masked hypertension, this underscores the importance of performing ABPM in overweight children.

A high prevalence of abnormal circadian variation was present in our study. Nocturnal hypertension has shown to have significant prognostic implications.[20] In childhood and adolescence, literature on the association between nocturnal dipping and morbidity is scarce, although some studies show that non-dipping may be associated with insulin resistance.[55,56] In adults, a non-dipping status is associated with cardiac structural alterations and a higher risk of CVD events.[57] Although the suggested scheme for staging of ambulatory BP levels of Flynn et al. incorporates night-time mean BP and BP load, dipping status is not included. As such, dipping status represents an entity that needs separate attention. The high prevalence of abnormal circadian variation in this study, with the associated potential risk for TOD and CVD, confirms the importance of performing ABPM in overweight children in order to detect nocturnal hypertension or a decreased or absent dipping status.

No significant differences in terms of age, gender and ethnicity were observed between the different ABPM categories, perhaps due to small sample size. Previous studies noted that ambulatory BP is affected by sex and ethnicity.[58,59] A recently published systematic

review showed that when age was dichotomised according to puberty, elevated BP and hypertension were more prevalent in older children. This association was not consistent when using age as a continuous variable.[58]
A higher BMI is an independent risk factor of high BP in children.[58] In our study participants with ambulatory hypertension had a significantly higher BMI Z-score compared to the normal BP group.
Increased HOMA-IR was present in 39% of the subjects with normal BP in this study, pointing to the fact that overweight itself is a risk factor for hyperinsulinemia. All participants with ambulatory hypertension presented with an elevated HOMA-IR, and almost half of the participants with elevated BP. Moreover, a significantly higher prevalence of metabolic syndrome was detected in children with elevated BP and ambulatory hypertension, as well as in non-dippers, indicating the clustering of other CVD risk factors in overweight subjects with high BP when compared to overweight children with normal BP.

To our knowledge the present study is the first using the BP reference values as presented in the updated Clinical Practice Guideline[23] in an overweight childhood population, to compare with ABPM results. The main strength of our study is the large number of available ABPMs. Despite this, low patient numbers in the different ABPM classification groups made it difficult to study factors associated with the different ABPM diagnoses. A few other limitations need to be addressed. First, despite the widespread use of the 2014 AHA Scientific Statement values in the interpretation of ABPMs, several limitations has been recognised, i.e. with regard to generalisability.[20] Robust, universally applicable normative ABPM data in children and adolescents are lacking. Second, by using the current ABPM classification scheme some subjects remain unclassifiable, limiting the comparability between studies due to divergent solutions with regard to the individual classification of these patients. Third, normative data are based on auscultatory measurements, which may provide different values than measurement obtained by using oscillometric devices or ABPM, as obtaining BP by oscillometry could result in an overestimation of BP values.[60]

In conclusion, this study shows a poor correlation between OBP measurement and ABPM in diagnosing hypertension in our population of children and adolescents with overweight or obesity. ABPM allows us to detect white coat hypertension, masked hypertension and abnormal circadian variation in BP, such as isolated nocturnal hypertension and blunted dipping. The high prevalence of these abnormal ABPM patterns in our overweight pediatric population emphasises the usefulness of ABPM as a diagnostic tool. The advantage of ABPM to screen out children with 'hidden' abnormal ABPM patterns, keeping in mind the association of abnormal ABPM patterns with TOD and future cardiovascular risk, in our opinion outweighs the limitations of ABPM, i.e. the lack of robust, universally applicable normative ABPM data in children and adolescents.

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4

PART II

Way beyond weight

CHAPTER 5

The effects of a multidisciplinary, multicomponent, family-based childhood obesity treatment programme – comparing results in young children and adolescents

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ABSTRACT

Background

Pediatric obesity remains an ongoing serious health concern. Intensive, age-appropriate, culturally sensitive, and family-centred treatment programmes are essential in childhood obesity management.

Objectives

To study the effects of our outpatient multidisciplinary, multicomponent, family-based childhood obesity treatment, specifically comparing children with adolescents.

Methods

Anthropometric and metabolic measures were obtained at three time points from children (age 3-12) and adolescents (age 13-18) participating in our treatment programme: at the start of treatment, after the intensive phase of treatment (3-4 months), at the end of treatment (9-12 months). BMI Z-score was the primary outcome parameter.

Results

137 participants with overweight or obesity were enrolled, 95 children and 42 adolescents. BMI Z-score of the total group significantly decreased from baseline (3.3, SD 0.8) to both 3-4 months (3.1, SD 0.8; P<0.001) and 9-12 months (3.0, SD 0.8; P<0.001). Children showed significant larger BMI Z-score reductions than adolescents (-0.33 versus -0.09, P=0.03) and more often a clinically relevant BMI Z-score decrease of ≥0.25 (48% versus 26%, P=0.10). The prevalence of abnormal blood pressure, disturbances in glucose homeostasis, and metabolic syndrome decreased in the total group. The dropout rate was 30% in children and 41% in adolescents.

Conclusions

Our multidisciplinary intervention improved both anthropometric and metabolic measures. Children showed a more favourable effect than adolescents, confirming the importance of early start of treatment. The high dropout rate points to the need of a careful assessment of initial expectations including identification of barriers to follow-up, followed by individualised care.

INTRODUCTION

Pediatric obesity remains a serious international health concern.[1,2] It is associated with a range of short- and long-term health complications. Next to the well-known physical side effects and comorbidities[3,4], obesity-related psychosocial complications and reduction in health-related functioning constitutes a critical part of the consequences of childhood obesity.[5,6] Furthermore, childhood obesity tracks into adulthood and is associated with an increased risk for obesity-related comorbidities and cardiovascular disease.[7–10]

For pediatric patients, intensive, age-appropriate, culturally sensitive, and family-centred treatment programmes are an essential element of obesity management.[11] These lifestyle interventions may have beneficial effects on body composition and cardiometabolic health.[12–16] Multidisciplinary obesity interventions involving a combination of diet, physical activity and behavioural components appear to be the most effective treatment option for children of all age groups.[12–14,17] Additionally, in recent decades it has become clear that interventions involving parents are more effective than interventions solely focused on the child.[2] There also seems to be an influence of age on the success rate of intervention programmes, with younger children responding better than adolescents.[2,15,18] Using the best available evidence combined with local knowledge and expertise, we developed a multidisciplinary, multicomponent, family-based childhood obesity treatment for different age groups in our peripheral hospital.

In general, the efficacy of lifestyle intervention programmes is disappointing, with only a low or moderate rate of reduction in body mass index standard deviation score (BMI Z-) and high dropout rates.[15] Furthermore, long-term results from treatment are scarce, and many children experience a rise in BMI Z-score after the end of the treatment.[19]

Next, the optimal age of commencing a lifestyle intervention remains to be further elucidated. Therefore, the objective of this study is to describe the effects of our outpatient multidisciplinary multicomponent childhood obesity treatment, specifically comparing children with adolescents.

METHODS

Setting and participants

Children and adolescents with overweight or obesity were enrolled in the Pro- and Anti-Inflammatory Marker (PAIM)-study evaluating the effect of childhood obesity treatment at our regional hospital (Hospital Gelderse Vallei, Ede, The Netherlands), between March 2010 and June 2017. All participants were offered a multidisciplinary obesity treatment programme as described in the General Introduction of this thesis. Inclusion criteria were overweight or obesity according

to the IOTF criteria[20], age 3-18 years old, and sufficient understanding of the Dutch language. Children with endocrine, chromosomal or syndrome disorders and/or psychological or social problems interfering with treatment were excluded. For the analyses of this study, participants were subdivided in 'children' (3-12 years) and 'adolescents' (13-18 years).
The PAIM study was approved by the ethical committee of Wageningen UR and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from children >12 years and from the parents of all participants.

Measurements

Measurements were performed at t=0 (baseline, start of treatment), t=1 (after intensive phase of treatment; 3-4 months), and t=2 (end of treatment; 9-12 months).

Clinical parameters
Trained staff measured children's weight in underwear using an electronic calibrated scale (Seca 761), and height without shoes using a stadiometer (Holtain Ltd., Crymych, Cryfed, UK). Waist circumference (WC) was measured with a flexible tape to the nearest 0.1 cm at umbilicus height. Age and sex-specific BMI Z-score was calculated using Dutch growth charts 2010.[21] Cut-off values for obesity gradation were based on the study of Van Buuren et al.[22] WC Z-score was calculated using Growth Analyser Research Calculation Tools (Growth Analyser B.V. version 4.0).
Office blood pressure (BP) was measured in supine position with an automated BP monitor (Welch Allyn VSM 300, Skaneateles Falles, NY, USA) after 5 minutes of rest. BP percentile scores were obtained using the new normative pediatric BP tables.[23]

Biochemical parameters
Blood samples were taken after overnight fasting and analysed for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), glucose, glycated hemoglobin (HbA1c), and insulin. At t=0 participants underwent a 2-h oral glucose tolerance test (OGTT) with a 1.75 gram glucose dose per kilogram bodyweight (maximum of 75 gram).
The presence of impaired fasting glucose, impaired glucose tolerance, prediabetes, and diabetes mellitus was determined according to the American Diabetes Association (ADA) 2018 criteria.[24] Age-specific reference values for TC, HDL-C, LDL-C and TG were obtained from the Dutch guideline for childhood obesity and cardiovascular risk management.[25] For the diagnosis of metabolic syndrome (MetS) neither the definition presented in the IDF consensus report[26] nor the definition of Ahrens et al.[27] was applicable to all participants in our study. Therefore, an adjusted definition of MetS has been used, requiring the presence of central obesity plus any of the other four factors: elevated TG, HDL-C below cut-off, abnormal glucose metabolism (prediabetes or diabetes)[24], and/or abnormal BP (elevated BP or hypertension)[23].

Statistics

Statistical evaluation was performed using SPSS 19.0 (IBM SPSS Statistics Inc., Chicago, IL). Data are presented as mean (standard deviation, SD) or median (interquartile range, IQR), as indicated. Differences between independent groups were calculated using Mann-Whitney U test and Pearson Chi-Square test as appropriate. Wilcoxon Signed Rank Test and Related-Samples McNemar Test were used to compare between different time points. Complete case analyses were performed to determine the effect of treatment, using BMI Z-score as primary outcome parameter, and WC Z-score and the individual components of MetS as secondary outcome parameters. Pearson's Correlation Coefficient was used to investigate the relationship between two quantitative, continuous, normally distributed variables.
Univariate and multivariate linear regression modeling was performed with BMI Z-score difference between t=0 and t=2 as the dependent variable. Predictor variables included age, gender, BMI Z-score at baseline, highest educational level of parents, and ethnicity. Each predictor was considered by itself in a univariate linear regression model, and predictors found to be significantly associated ($P<0.05$) with change in BMI Z-score were then included in a multivariate linear regression model.
A P value <0.05 was considered statistically significant.

RESULTS

Anthropometrics and demographics

Baseline characteristics of the 137 participants are shown in Table 1. BMI Z-score (3.3, SD 0.8) and WC Z-score (3.1, SD 0.7) at baseline were not different between children (n=95) and adolescents (n=42), and neither were demographic parameters. BMI Z-score was significantly correlated with WC Z-score (Pearson Correlation 0.73, $P<0.001$). Boys had a significantly higher BMI Z-score at baseline than girls (S1 Table in Appendix B). No further differences between boys and girls existed.

Comorbidities

At baseline about 45% of all participants had elevated BP or hypertension, and almost 12% of the participants presented with prediabetes or diabetes (Table 1). Almost 22% of the participants showed at least one abnormal result in their lipid profile. Overall prevalence of MetS was 13.8%, and only 39.1% of the participants had zero components of MetS. An elevated TG-level was noted significantly more often in adolescents (17%) than in children (5%, P=0.02). Frequencies of other comorbidities were not significantly different between the age groups.

Table 1. Baseline characteristics of the total study population and separately for children and adolescents.

	Total group (n=137)	Children (n=95)	Adolescents (n=42)	P value
Male	46 (33.6)	32 (33.7)	14 (33.3)	0.97
Age	9.4 (4.3)	7.0 (2.4)	15.0 (1.6)	<0.001
BMI	26.3 (5.9)	23.5 (3.2)	32.8 (5.4)	<0.001
BMI Z-score	3.3 (0.8)	3.3 (0.9)	3.3 (0.7)	0.99
WC*	88.0 (19.7)	78.2 (13.1)	109.5 (13.8)	<0.001
WC Z-score	3.1 (0.7)	3.1 (0.7)	3.1 (0.4)	0.97
Overweight/obesity				0.58
Normal weight	1 (0.7)	1 (1.1)	0 (0.0)	
Overweight	20 (14.6)	13 (13.7)	7 (16.7)	
Obesity grade 1	52 (38.0)	35 (36.8)	17 (40.5)	
Obesity grade 2	41 (29.9)	27 (28.4)	14 (33.3)	
Obesity grade 3	23 (16.8)	19 (20.0)	4 (9.5)	
Excess adiposity*	129 (96.3)	87 (94.6)	42 (100.0)	0.12
Casual blood pressure				
Normal BP	74 (54.0)	51 (53.7)	23 (54.8)	0.91
Elevated BP	27 (19.7)	16 (16.8)	11 (26.2)	0.21
Hypertension	36 (26.3)	28 (29.5)	8 (19.0)	0.20
Glucose metabolism**				
Prediabetes	13 (10.0)	8 (9.0)	5 (12.2)	0.57
Provisional diagnosis of diabetes	2 (1.5)	2 (2.2)	0 (0.0)	0.33
Lipid profile**				
Elevated TC	6 (4.6)	4 (4.5)	2 (4.9)	0.92
Elevated LDL-C	5 (3.8)	5 (5.6)	0 (0.0)	0.12
HDL-C below cut-off	15 (11.5)	8 (9.0)	7 (17.1)	0.18
Elevated TG	11 (8.5)	4 (4.5)	7 (17.1)	0.02
MetS***	18 (13.8)	10 (11.4)	8 (19.0)	0.24
Components of MetS†				0.37
0	52 (39.1)	36 (39.6)	16 (38.1)	
1	63 (47.4)	45 (49.5)	18 (42.9)	
2	14 (10.5)	9 (9.9)	5 (11.9)	
3	3 (2.3)	1 (1.1)	2 (4.8)	
4	1 (0.8)	0 (0.0)	1 (2.4)	
Ethnicity‡				0.65
Dutch	106 (77.4)	73 (76.8)	33 (78.6)	
Western immigrant	7 (5.1)	4 (4.2)	3 (7.1)	
Non-western immigrant	24 (17.5)	18 (18.9)	6 (14.3)	
Family status				0.16
Two-parent family	119 (86.9)	81 (85.3)	38 (90.5)	
Single-parent family	17 (12.4)	14 (14.7)	3 (7.1)	
Other#	1 (0.7)	0 (0.0)	1 (2.4)	
Siblings in household				0.88
>1 brother or sister	62 (45.3)	42 (44.2)	20 (47.6)	
1 brother or sister	56 (40.9)	39 (41.1)	17 (40.5)	
Only child	19 (13.9)	14 (14.7)	5 (11.9)	
Highest education level parents$				0.39
No or low	58 (52.3)	36 (48.0)	22 (61.1)	
Medium	43 (38.7)	31 (41.3)	12 (33.3)	
High	10 (9.0)	8 (10.7)	2 (5.6)	
At least 1 parent with overweight/obesity	130 (94.9)	90 (94.7)	40 (95.2)	0.90
Drop-out	45 (32.8)	28 (29.5)	16 (40.5)	0.21

Number (%), except for age, BMI, BMI Z-score, WC, WC Z-score (mean, SD)

* Total group: n=134; Children: n=92. ** Total group: n=130; Children: n=89; Adolescents: n=41. *** Total group: n=130; Children: n=88.

† Total group: n=133; Children: n=91

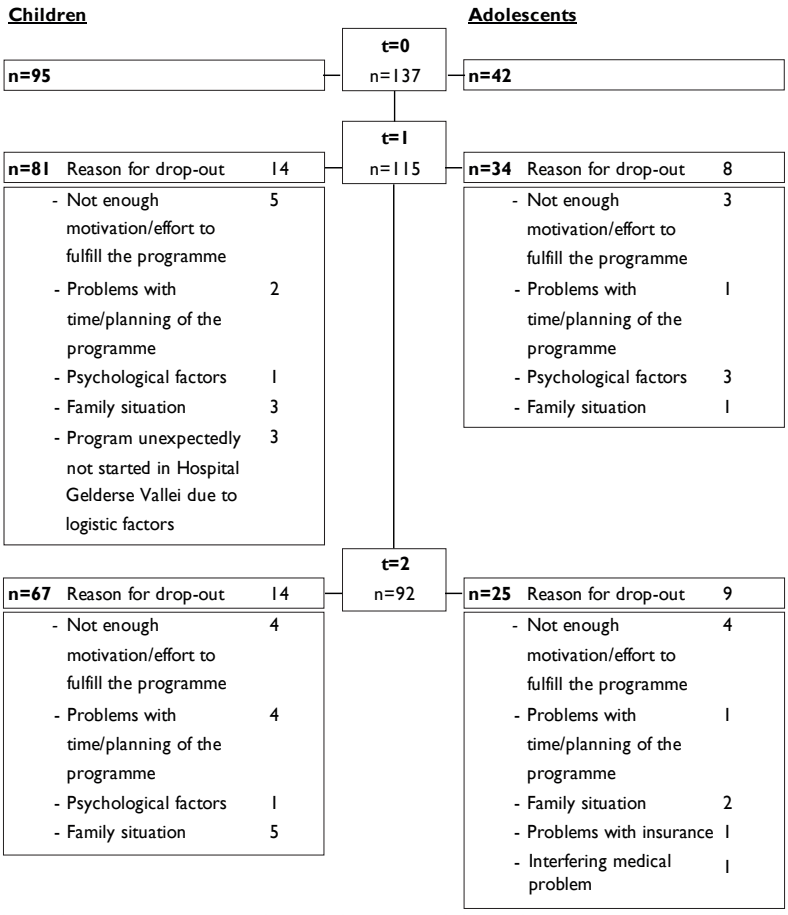
‡ One child was adopted at the age of 10 months. In this case, the country of origin was chosen as ethnicity.

Adolescent living on her own

$ Total group: n=111; Children: n=75; Adolescents: n=36

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TC, total cholesterol; TG, triglycerides; WC, waist circumference

Figure 1. Flowchart of participants in the study.



Dropouts

Although not statistically significant, the dropout rate during treatment in the adolescent group was higher (40.5%) than in the younger age group (29.5%, P=0.21). Reasons for dropout were mainly 'not enough motivation' and 'problems with planning of the programme' (Figure 1). Completers presented with a lower BMI Z-score and WC Z-score at baseline (Table 2), and significantly more often prediabetes (14.0% versus 2.3%; P=0.04) and parental overweight/obesity (97.8% versus 88.9%; P=0.03) were detected. Although not statistically significant (P<0.1), an HDL-cholesterol level below cut-off was detected more often in dropouts, and parents in the dropout group were lower educated.

Table 2. Characteristics of dropouts compared with children and adolescents who completed the obesity treatment programme.

	Completers (n=92)	Dropouts (n=45)	P value
Male	30 (32.6)	16 (35.6)	0.73
Age	9.0 (4.3)	10.3 (4.1)	0.08
BMI	25.5 (5.4)	28.1 (6.5)	0.02
BMI Z-score	3.2 (0.8)	3.5 (0.8)	0.06
WC*	84.9 (18.7)	94.4 (20.4)	0.02
WC Z-score*	3.0 (0.6)	3.3 (0.7)	0.04
Overweight/obesity			0.35
Normal weight	1 (1.1)	0 (0.0)	
Overweight	15 (16.3)	5 (11.1)	
Obesity grade 1	38 (41.3)	14 (31.1)	
Obesity grade 2	26 (28.3)	15 (33.3)	
Obesity grade 3	12 (13.0)	11 (24.4)	
Excess adiposity*	85 (94.4)	44 (100.0)	0.11
Casual blood pressure			
Normal BP	53 (57.6)	21 (46.7)	0.23
Elevated BP	17 (18.5)	10 (22.2)	0.61
Hypertension	22 (23.9)	14 (31.1)	0.37
Glucose metabolism**			
Prediabetes	12 (14.0)	1 (2.3)	0.04
Provisional diagnosis of diabetes	2 (2.3)	0 (0.0)	0.31
Lipid profile**			
Elevated TC	3 (3.5)	3 (6.8)	0.39
Elevated LDL-C	2 (2.3)	3 (6.8)	0.21
HDL-C below cut-off	7 (8.1)	8 (18.2)	0.09
Elevated TG	7 (8.1)	4 (9.1)	0.85
MetS***	13 (15.1)	5 (11.4)	0.56
Components of MetS†			0.35
0	37 (42.0)	15 (33.3)	
1	38 (43.2)	25 (55.6)	
2	11 (12.5)	3 (6.7)	
3	1 (1.1)	2 (4.4)	
4	1 (1.1)	0 (0.0)	
Ethnicity‡			0.33
Dutch	74 (80.4)	32 (71.1)	
Western immigrant	5 (5.4)	2 (4.4)	
Non-western immigrant	13 (14.1)	11 (24.4)	
Family status			0.74
Two-parent family	79 (85.9)	40 (88.9)	
Single-parent family	12 (13.0)	5 (11.1)	
Other#	1 (1.1)	0 (0.0)	
Siblings in household			0.97
>1 brother or sister	42 (45.7)	20 (44.4)	
1 brother or sister	37 (40.2)	19 (42.2)	
Only child	13 (14.1)	6 (13.3)	
Highest education level parents$			0.07
No or low	36 (45.6)	22 (68.8)	
Medium	34 (43.0)	9 (28.1)	
High	9 (11.4)	1 (3.1)	
At least 1 parent with overweight/obesity	90 (97.8)	40 (88.9)	0.03

Number (%), except for age, BMI, BMI Z-score, WC, WC Z-score (mean, SD)
* Completers: n=90; Dropouts: n=44. ** Completers: n=86; Dropouts: n=44.
† Completers: n=88
‡ One child was adopted at the age of 10 months. In this case, the country of origin was chosen as ethnicity.
# Adolescent living on her own
$ Completers: n=79; Dropouts: n=32
BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TC, total cholesterol; TG, triglycerides; WC, waist circumference

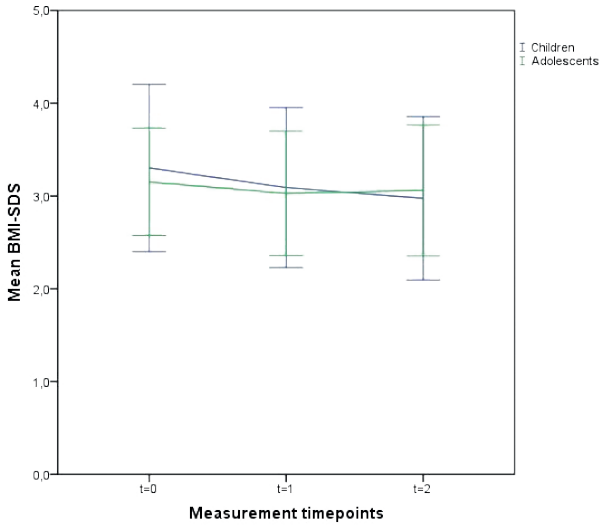


Figure 2A. Mean BMI Z-score at the different time points, children and adolescents compared.
Data represent the mean BMI Z-score (BMI-SDS) of cases with BMI Z-score available at all three time points (children n=54, adolescents n=19). Error bars indicate ±1 standard deviation. Children: t=0 to t=1 -0.21 (SD 0.32), P<0.001; t=0 to t=2 -0.33 (SD 0.48), P<0.001. Adolescents: t=0 to t=1 -0.13 (SD 0.23), P<0.05; t=0 to t=2 -0.09 (SD 0.28), not significant.

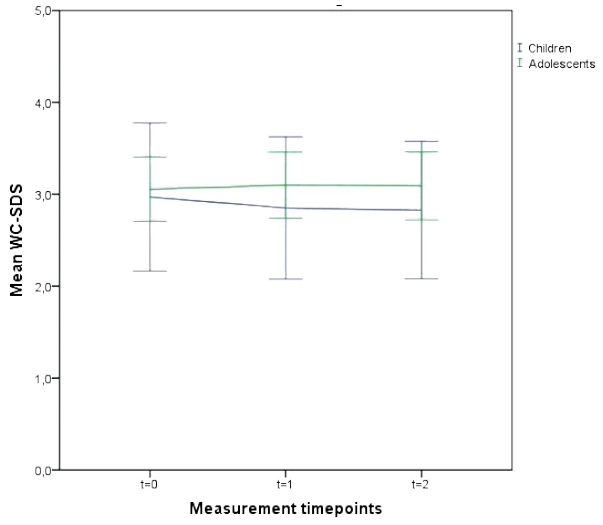


Figure 2B. Mean WC Z-score at the different time points, children and adolescents compared.
Data represent the mean WC Z-score (WC-SDS) of cases with WC Z-score available at all three time points (children n=54, adolescents n=19). Error bars indicate ±1 standard deviation. Children: t=0 to t=1 -0.15 (SD 0.43), P<0.01; t=0 to t=2 -0.14 (SD 0.40), P<0.01. Adolescents: t=0 to t=1 0.06 (SD 0.24), not significant; t=0 to t=2 0.05 (SD 0.30), not significant.

Effect of treatment

BMI Z-score of the total group of complete cases (n=73) significantly decreased from baseline (3.3, SD 0.8) to both 3-4 months (3.1, SD 0.8; P<0.001) and 9-12 months (3.0, SD 0.8; P<0.001). At baseline 82% of the participants was obese, this decreased to 74% at the end of treatment; 4% reached normal weight.

Children showed significant larger BMI Z-score reductions at both timepoints than adolescents (t=0 to t=2: BMI Z-score children -0.33, SD 0.48; adolescents -0.09, SD 0.28; P=0.03; Table 3). In children an ongoing decrease in BMI Z-score was observed between 3-4 months and 9-12 months (-0.12, SD 0.37), while in adolescents a rise in BMI Z-score was detected (0.03, SD 0.13; Figure 2A). WC Z-score in children significantly decreased (t=0 to t=2: WC Z-score -0.14, SD 0.40; P<0.01) (Figure 2B, Table 3).

Of the 73 participants, 17 (23%) did not show a decrease in BMI Z-score. Children reached a BMI Z-score decrease of ≥0.25 more often than adolescents (48% versus 26%, P=0.10). No significant differences were observed regarding gender, age, and demographic factors between participants with or without a BMI Z-score decrease of ≥0.25.

Although not significant, both in children and adolescents less participants were noted with abnormal BP at the end of treatment compared to baseline (Table 3). Furthermore, in children the prevalence of abnormal glucose metabolism decreased (14.9% to 2.1%, P=0.07). No significant changes in lipid profile were observed. The number of participants without any component of MetS increased during treatment. At baseline, 18% of the children was diagnosed with two or more components of MetS. The MetS prevalence halved in the child group to 7% at the end of treatment.

In univariate linear regression analysis the reduction in BMI Z-score from t=0 to t=2 was significantly larger for those with higher BMI Z-score at baseline (β -0.126, P=0.048), and for those who were younger (β 0.023, P=0.049). There was no significant difference between boys and girls (β 0.187, P=0.097) although boys showed slightly larger decrease. Highest educational level of parents and ethnicity showed no significant association with change in BMI Z-score. In the final multivariate model, BMI Z-score at baseline (β -0.381, P=0.006), age (β -0.09, P=0.095) and their interaction term (β 0.036, P=0.034) were significant and explained 16% of the variation. The interaction term BMI Z-score*age indicates that the decline in BMI Z-score over time was less steep in adolescents than in children.

Table 3. Effect of treatment as determined with complete case analysis, separately for children and adolescents.

	Children (n=54)			Adolescents (n=19)			P value†		
	Baseline (t=0)	After intensive phase (t=1)	End of treatment (t=2)	Baseline (t=0)	After intensive phase (t=1)	End of treatment (t=2)	t=0	t=1	t=2
BMI Z-score	3.3 (0.9)	3.1 (0.9)[a]	3.0 (0.9)[a]	3.2 (0.6)	3.0 (0.7)[c]	3.1 (0.7)	0.64	0.92	0.67
BMI Z-score difference versus t=0	NA	-0.21 (0.32)	-0.33 (0.48)	NA	-0.13 (0.23)	-0.09 (0.28)	NA	0.17	0.03
BMI Z-score difference versus t=1	NA	NA	-0.12 (0.37)	NA	NA	0.03 (0.13)	NA	NA	0.10
BMI Z-score reduction ≥0.25 versus t=0			26 (48.1)			5 (26.3)			0.10
WC Z-score*	3.0 (0.8)	2.8 (0.8)[b]	2.9 (0.7)[b]	3.0 (0.4)	3.1 (0.3)	3.1 (0.4)	0.55	0.42	0.58
WC Z-score difference versus t=0*	NA	-0.15 (0.43)	-0.14 (0.40)	NA	0.06 (0.24)	0.05 (0.30)	NA	0.03	0.03
WC Z-score difference versus t=1*	NA	NA	0.01 (0.38)	NA	NA	-0.00 (0.19)	NA	NA	0.88
Casual blood pressure**									
Normal BP	27 (52.9)	35 (68.6)	32 (62.7)	10 (58.8)	10 (58.8)	13 (76.5)	0.67	0.46	0.30
Elevated BP	9 (17.6)	10 (19.6)	12 (23.5)	5 (29.4)	3 (17.6)	3 (17.6)	0.30	0.86	0.61
Hypertension	15 (29.4)	6 (11.8)[d]	7 (13.7)	2 (11.8)	4 (23.5)	1 (5.9)	0.15	0.24	0.39
Glucose metabolism***									
Prediabetes	5 (10.6)	2 (4.3)	1 (2.1)	4 (19.0)	4 (19.0)	3 (14.3)	0.34	0.05	0.05
Provisional diagnosis of diabetes	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.34		
Lipid profile***									
Elevated TC	1 (2.1)	3 (6.4)	2 (4.3)	1 (4.8)	0 (0.0)	0 (0.0)	0.55	0.24	0.34
Elevated LDL-C	2 (4.3)	4 (8.5)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.34	0.17	0.50
HDL-C below cut-off	3 (6.4)	3 (6.4)	0 (0.0)	3 (14.3)	4 (19.0)	3 (14.3))	0.29	0.11	0.01
Elevated TG	2 (4.3)	2 (4.3)	4 (8.5)	3 (14.3)	4 (19.0)	5 (23.8)	0.14	0.05	0.09
MetS****	8 (18.2)	4 (9.1)	3 (6.8)	1 (7.7)	3 (23.1)	1 (7.7)	0.36	0.18	0.91
Components of MetS****							0.12	0.06	0.22
0	18 (40.9)	29 (65.9)	25 (56.8)	6 (46.2)	3 (23.1)	8 (61.5)			
1	18 (40.9)	11 (25.0)	16 (36.4)	6 (46.2)	7 (53.8)	4 (30.8)			
2	8 (18.2)	3 (6.8)	3 (6.8)	0 (0.0)	2 (15.4)	0 (0.0)			
3	0 (0.0)	1 (2.3)	0 (0.0)	1 (7.7)	1 (7.7)	1 (7.7)			
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			

Number (%), except for age, BMI, BMI Z-score, WC, WC Z-score (mean, SD)

* Children n=51, Adolescents n=16. ** Children n=51, Adolescents n=17. *** Children n=47, Adolescents n=21. **** Children n=44, Adolescents n=13

† Children versus Adolescents (Mann-Whitney U)

a P<0.001 Wilcoxon Signed Rank Test versus t=0

b P<0.01 Wilcoxon Signed Rank Test versus t=0

c P<0.05 Wilcoxon Signed Rank Test versus t=0

d P<0.05 Related-Samples McNemar Test versus t=0

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TC, total cholesterol; TG, triglycerides; WC, waist circumference

DISCUSSION

In this study the effect of our multidisciplinary weight loss intervention in an outpatient clinic setting was investigated, comparing children and adolescents. In general, a favourable effect of treatment was noted. BMI Z-score of the total group significantly decreased from baseline to both 3-4 months and 9-12 months. A BMI Z-score decrease of ≥0.25, a frequently used cutt-off for the definition of success in lifestyle intervention in children with obesity[2], was detected in 42% of the participants: in 48% of the children and in 26% of the adolescents. Children showed significant larger BMI Z-score reductions compared to adolescents. Thus, young children rather than adolescents profited from our lifestyle intervention. Comparable results were described by others.[2,15,18] Barriers to and enablers of healthy lifestyle behaviours are known to differ between children and adolescents. Kebbe et al. pointed to barriers and enablers specific to adolescents with obesity, suggesting the need for tailored and targeted treatment and attention to the individual and interpersonal factors that determine the success of behaviour change initiation and maintenance.[28] Furthermore, adolescents are probably less receptive to lifestyle interventions due to the (unaware) focus on other aspects of physical and psychological development in that age period. Next, it is known that lifestyle interventions are effective if parents are actively involved.[2] In adolescence the responsibility and involvement of parents change, which could affect treatment results. Hence, clinicians may consider the initiation of alternative treatment modalities in adolescents if a specific intervention does not result in weight loss.

During the last decade, characteristics of children and adolescents with obesity entering paediatric lifestyle intervention programmes have been changed.[29] Children and adolescents present with higher BMI Z-score at the onset of lifestyle interventions, and the proportion with obesity-related comorbidities increased.[29] Hence, prevention and early detection of overweight, including adequate referral and commencement of treatment seems to be an essential first step in the fight against childhood obesity.[2] In conclusion, our results suggest that it is critical to start treating overweight/obesity at early age.

There was a high dropout rate during treatment in our study: 33% of our participants dropped out (30% of the children and 41% of the adolescents). Before our treatment commenced, all referred candidates were screened by a child psychologist. Despite this screening a high dropout rate was detected. A comparable dropout rate was observed by others.[30,31] Several studies tried to identify factors that may predict participation and attrition.[32–34] Increasing the effort to engage patients and families at the first visit, to assess initial expectations, and to identify and address barriers to follow up may help to tailor the treatment to families' needs.[35,36] Furthermore, participants and their family should be intensively supported during and after treatment in order to increase adherence, reduce dropout, and guarantee maintenance of the treatment effect.

In our study differences regarding age and gender were observed. Boys were slightly older and had a significant higher BMI Z-score and degree of obesity at commencement of treatment than girls. Similar results were observed by others.[15,29] Evidence suggests that gender differences exist regarding exposure and vulnerability to obesogenic environments, and regarding the consequences of obesity and responses to interventions.[37] Greater concerns about body image and vulnerability to eating disorders may lead to an earlier seek for help in girls.

With respect to the metabolic consequences of childhood obesity, the prevalence of abnormal glucose metabolism was high in our study (12%). This is consistent with results presented in other studies.[38] Disturbed glucose and insulin homeostasis are early metabolic consequences of obesity, and impaired fasting glucose is strongly correlated with increased risk for future morbidity.[39] Next to a high prevalence of glucose disturbances, MetS was highly prevalent in our study (14%), and tended to be more frequently present in adolescents than in children (19% versus 11%). In line with literature[40], an evident decrease in the number of components of MetS was detected, and the MetS prevalence in the child group halved. In adults, presence of MetS is associated with increased risk for atherosclerosis and diabetes. However, the clinical value of MetS in children remains unclear. Furthermore, to use MetS as outcome parameter in paediatric research is difficult, as the existing definitions[26,27] are not applicable to all age groups. Rather a personalised diagnostic work-up should be performed in every child with obesity, at least evaluating the components of MetS and acting on that.[41] Finally, a high prevalence of abnormal BP was detected in our study population, pointing to the importance of accurate blood pressure measurement at every clinical encounter, as abnormal BP in childhood is associated with hypertensive target organ damage and adult cardiovascular disease.[42]

There are a few drawbacks of this study that need to be discussed. First, effect of treatment was determined by complete case analysis. The treatment effect could have been overestimated due to selection of (probably higher motivated) treatment completers, and therefore does not reflect real-life behaviour towards follow-up visits and duration of treatment which could affect treatment success. However, most likely this did not affect the primary objective of this study, namely the comparison of treatment effect between children and adolescents. Second, differences in treatment content provided to the child and adolescent groups (as described in the General Introduction of this thesis) could have influenced the observed treatment effect. However, the content of the treatment programmes is based on the same rationale (multidisciplinary multicomponent treatment programme with involvement of the whole family), Third, although puberty is an important developmental period for the establishment of adipose tissue mass and metabolic homeostasis[43], this factor has not been accounted for in this study.

CONCLUSION

In conclusion, this multidisciplinary weight loss intervention has shown to improve both anthropometric and metabolic outcomes. Children showed a more favourable effect of treatment than adolescents, confirming the idea that it is critical to start treating overweight/obesity at early age. The high dropout rate points to the need of a careful assessment of initial expectations including the identification of barriers to follow-up as a screening before treatment commences. Subsequent individualised care with attention to the participants and their families' needs, reacting to barriers and enablers specific to that individual or age group, remains the cornerstone of behaviour change inititiation and maintenance.

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ADDITIONAL INFORMATION (APPENDIX B)

S1 Table

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CHAPTER 6A

Maintenance interventions for overweight or obese children and adolescents who participated in a treatment programme: study protocol for a systematic review

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ABSTRACT

Background

Childhood overweight and obesity are associated with significant health consequences. Early and successful treatment of this public health issue is necessary. Although several intervention programmes for children result in weight loss or stabilisation in the short term, preventing relapse after weight loss remains an important challenge. Weight loss maintenance approaches in childhood are thought to be promising, but a structured overview of these maintenance interventions is lacking. The aim of the systematic review described in this protocol is to provide an overview of reports published about maintenance interventions in childhood overweight and obesity following initial treatment, in order to guide future directions in the development of maintenance programmes for childhood obesity.

Methods/design

The electronic databases PubMed, Embase, Cochrane Library, CINAHL, Web of Science, PsycINFO, Scopus, and SocINDEX will be searched for this review. Reference lists of eligible study reports will be scanned for relevant references. Article selection including risk of bias assessment will be performed independently in an unblinded standardised manner by three authors. All reports describing a maintenance intervention in overweight or obese children with a mean or median age of <18 years who have followed a treatment programme, regardless of the type of intervention, will be included. Data extraction will be performed using a predesigned pilot-tested data extraction sheet that covers participant characteristics, details about the treatment preceding the maintenance intervention, and the maintenance intervention itself. Body mass index standard deviation score (BMI-SDS or BMI Z-score) will be used to compare studies. If possible, a meta-analysis will be performed using the inverse variance random-effects method. Studies that are not included in the meta-analysis will be described in a narrative way in tables and/or in the text.

Discussion

This systematic review will give an overview of the existing knowledge on programmes and initiatives aimed at long-term maintenance of a healthy or reduced weight in children and adolescents following initial treatment of overweight. It will form a basis for future research and practice in this area, a topic on which studies are scarce but highly necessary.

BACKGROUND

Childhood overweight and obesity are associated with significant health consequences.[1,2] Besides cardiovascular morbidity and other medical conditions such as hepatic steatosis, cholelithiasis, orthopaedic complications, sleep apnoea, and polycystic ovary disease, obese children and adolescents and their families are at risk for psychological and social adjustment problems.[3] Early and successful treatment of this public health issue is necessary.[4] Although several intervention programmes for children result in weight loss or stabilisation in the short term, preventing relapse after finishing a lifestyle intervention remains an important challenge. Many obese children regain weight after treatment, probably because weight loss/stabilisation techniques are abandoned and relapse occurs into inappropriate behaviours.[5] Maintenance programmes that extend patient-therapist contacts beyond initial treatment have enhanced weight loss maintenance in adults.[6] Weight loss maintenance approaches in childhood are thought to be promising as well.[7–10] and are highly requested in the fight against increasing weight in children. However, a structured overview of these maintenance interventions is lacking, and the overall effect of maintenance programmes in childhood obesity has never been thoroughly evaluated. Furthermore, it is unknown which properties contribute to the success of a maintenance intervention. The aim of this systematic review is to fill in this gap of knowledge and to guide future directions in the development of maintenance programmes.

OBJECTIVES

The primary objective of this systematic review is to provide an overview of reports published about maintenance interventions in childhood overweight and obesity following initial treatment (review). In the remaining sections of this review protocol, the term overweight will be used to indicate both overweight and obesity.

The secondary objectives are the following:
– To consider the clinical effectiveness/efficacy of programmes and initiatives aimed at long-term maintenance of a healthy or reduced weight in children and adolescents following initial treatment of overweight, using meta-analysis.
– To identify determinants within a maintenance intervention that contribute to the success of that intervention, both at study level using meta-regression (determinants such as type, intensity, and duration of the maintenance intervention), and at the individual level using descriptive statistics (determinants such as age and sex of the patient, parental support).

METHODS/DESIGN

Criteria for considering studies for this review

Types of studies

Primarily, data from randomised controlled trials (RCTs) will be included in this systematic review. However, the value and appropriateness of these RCTs in assessing the efficacy of lifestyle interventions remains a contentious issue. Furthermore, a paucity of RCTs on maintenance interventions for childhood overweight is expected. Therefore, cohort studies (both prospective and retrospective, with and without control group) will also be included. Case reports will be excluded. Given the expected clinical and methodological heterogeneity, there will be no minimum length of follow-up.

Types of participants

Study groups comprising children and adolescents aged less than 18 years at the commencement of a maintenance intervention will be included in this review. If a range with a maximum value of >18 years old is noted, the report will be included if the mean or median age is less than 18 years at the start of the maintenance intervention. All participants should have followed a treatment programme for overweight, regardless of the type of intervention. In case the children are part of a family group receiving the intervention, the study will be included if data can be extracted separately for the children. Children with overweight due to a secondary cause or in the context of a syndrome will be excluded.

Non-responders are children with overweight or obesity who finished a treatment programme but did not participate in the maintenance intervention or initiative. Drop-outs are defined as participants ending the maintenance programme or initiative earlier than its normal termination. Both non-responders and drop-outs will be assessed in all studies included in the review.

Ideally (if this is published by the included reports), groups of patients undergoing a maintenance intervention will be compared with non-exposed control groups.

Types of interventions

All studies of maintenance or follow-up interventions or programmes with the aim to maintain weight loss or a healthy lifestyle after a treatment programme for overweight children will be included in this review. Components of the interventions can include diet and nutrition, exercise and physical activity, and lifestyle and social support. Studies are included if they teach skills specific to the maintenance of weight loss or if they otherwise try to stabilise or enhance adherence to a healthier lifestyle (e.g. with phone calls). There will be no restriction on the

discipline(s) involved in the maintenance intervention and whether the intervention concerns one discipline or is multidisciplinary in nature. Furthermore, studies to be included will not be selected on the setting of the maintenance intervention (community health, primary or secondary or tertiary care).

Types of outcome measures

To meet the aforementioned primary and secondary objectives, the following primary and secondary outcomes are defined.
Primary outcomes:
The primary outcome measure for this review will be the body mass index standard deviation score (BMI-SDS or BMI Z-score) based on measured height and weight. Studies with self-reported measurements of height and weight will not be included. BMI-SDS or BMI Z-scores are preferred because these scores account for sex- and age-related changes over time. Second best parameters such as BMI and percentage overweight will be used when BMI-SDS or BMI Z-scores cannot be extracted.
To be included, studies need to report a baseline and at least one post-intervention measurement.
Secondary outcomes: There are no secondary outcomes.

Search methods for identification of studies

Electronic searches

The following electronic databases will be searched: PubMed, Embase, Cochrane Library, CINAHL, Web of Science, PsycINFO, Scopus, and SocINDEX. Only studies published in English, Spanish, German, or Dutch will be included. There will be no publication date or publication status restrictions. Abstracts of conference presentations and posters will only be included if the results are not published otherwise. In that case, the investigators will be inquired about the study details.
The search strategy is added as Additional file 1. The search terms will be adapted for use in the different bibliographic databases.

Searching other resources

In addition to our electronic database search, reference lists of eligible study reports will be scanned for relevant references. Furthermore, subsequent trial registers will be checked: ClinicalTrials.gov, The European Union Clinical Trials Register, Current Controlled Trials, and the Netherlands Trial Register.

Data collection and analysis

Search results will be merged using EndNote, and duplicate records of the same report will be removed.

Selection of studies

The retrieved records will be screened independently on title and selected for possible inclusion by LvdH, EF, and AJ. Obvious irrelevant reports will be excluded. Subsequently, abstracts of the remaining records will be assessed against predetermined inclusion criteria by the same three researchers. In case of rejection, it will be recorded why the study failed to meet the inclusion criteria.
For studies that appear to meet the inclusion criteria, or in cases when a definite decision cannot be made based on title and/or abstract alone, the full paper will be obtained for detailed assessment. This will be performed independently in an unblinded standardised manner by LvdH, EF, and AJ using a checklist on characteristics of the study and inclusion criteria. Furthermore, the full paper will be checked on internal and external validity (see paragraph on 'Assessment of risk of bias in included studies'). The reason for exclusion of full-text articles will be provided and if any types of record are excluded, this will be stated. Disagreements will be discussed and, where possible, resolved by consensus after referring to the protocol. If necessary, a fourth person will be consulted. If needed, we will correspond with investigators to clarify study eligibility (it may be appropriate to request further information, such as missing results, at the same time). After final decisions on study inclusion, we will proceed to data collection.

Data extraction and management

A data extraction sheet will be developed and pilot-tested on ten randomly-selected included studies and refined accordingly. LvdH will extract the data from the included studies, and AJ will check the extracted data. Disagreements will be resolved by a discussion between LvdH and AJ. If no agreement is reached, it is planned that the third author (EF) decides. If information is not (or unclearly) reported, the authors will be contacted for further information, and the results of these contacts will be stated.

Information will be extracted from each included report on:
– Methods: study design, duration of study, length of follow-up.
– Characteristics of participants: total number of participants, setting, diagnostic criteria, age, sex, country, co-morbidity, socio-demographics, ethnicity, participant selection process (in- and exclusion criteria), non-responders.
– Type of treatment preceding the maintenance intervention.

– Type of maintenance intervention(s): total number of intervention/control groups. For each intervention/control group: number of participants, focus of intervention (parents, children, both), contents of intervention (components used), disciplines involved, length of intervention, number of sessions, duration/frequency/timing of delivery, participant responsiveness, drop-outs, concurrent interventions, unintended exposure.
– Outcome measures: abovementioned primary and secondary outcomes (if possible to extract), with definition, unit of measurement, time-point(s). For each outcome: sample size, missings, summary of data, estimate of effect, subgroup analysis (if applicable).

A preliminary literature survey showed substantial differences in 1) the treatment preceding the maintenance interventions, 2) the maintenance interventions themselves, and 3) the outcome measures (clinical heterogeneity). If the data extraction process will reveal descriptive factors or outcome parameters that are potentially useful but not yet included in the initial data extraction form, the data extraction form will be revised.

Assessment of risk of bias in included studies

Assessing the risk of bias in the included studies will be performed according to the Risk of Bias Assessment Tool form attached as Additional file 2. This form is based on the 'risk of bias' tool developed by The Cochrane Collaboration to assess risk of bias in randomised controlled trials[11], supplemented with items extracted from the Newcastle-Ottawa quality assessment tool[12] and from the Agency for Healthcare Research and Quality (AHRQ) publication of Viswanathan et al.[13] The tool added as Additional file 2 consists of items that cover five domains of bias (selection, performance, attrition, detection, and reporting), as well as an 'other bias' category to capture other potential threats to validity. Three review authors will assess the risk of bias for each study. Review authors will not be blinded with respect to study authors, institution, or journal as they are familiar with the literature. Any disagreements will be resolved by a discussion. Results of the risk of bias assessment will be presented in the final report. The findings will be taken into consideration when analysing the data and drawing conclusions, using sensitivity analysis where appropriate.
Assessment of the risk of selection bias in RCTs will include the criteria 'random sequence generation' and 'allocation concealment' ('low risk', 'high risk' or 'unclear risk' of bias). When the study investigators clearly describe a random component in the sequence generation process, a judgement of 'low risk' will be assigned to sequence generation. Allocation concealment will be assessed as 'low risk' if the method used to prevent the participants or investigators enrolling participants to foresee the group assignment is described. All nonrandomised studies will be assessed as 'high risk' for both sequence generation and allocation concealment. For non-randomised trials and observational studies, detailed criteria on selection bias (concerning comparability of groups, confounding, and adjustment)

are included. Furthermore, in cohort studies, the representativeness of the exposed cohort will be evaluated using the presented inclusion and exclusion criteria and selection procedure. Because of the expected clinical heterogeneity of the maintenance cohorts, the cohorts presented in the included reports will be accurately described in our paper.

The item 'blinding' will be used to assess the risk of performance and detection bias. A judgement of 'low risk' of bias will be assigned when the outcome assessors are blinded for the allocated intervention. With respect to performance and detection bias, in cohort studies, also the comparability of cohorts will be checked, as well as the impact from concurrent interventions or an unintended exposure that might bias the results.
With respect to attrition bias (completeness of sample, follow-up, and data), 'low risk' will be assigned to a study when the proportion of missing outcome data is well-described and relatively balanced between the intervention groups, and the reasons for incomplete outcome data across intervention groups are provided and unlikely to be related to the true outcome.
The risk of reporting bias will be considered low if a study protocol is available, and all of the study's pre-specified (primary and secondary) outcomes that are of interest have been reported in the pre-specified way.
If studies will be excluded from the review or any subsequent analyses on the basis of the risk of bias, this will be described and the reasons for the exclusions will be explained.
A preliminary literature survey on the topic of this review revealed a wide variety of study designs (methodological heterogeneity). In the Risk of Bias Assessment Tool added as Additional file 2, important criteria to take into account when encountering non-randomised trials or observational studies are enumerated, as well as items to consider in the assessment of RCTs. If other study designs will emerge during the study selection process, additional criteria will be added to the risk of bias assessment where appropriate to warrant an appropriate risk of bias assessment for each study type. At any time this will be described in the final paper.

Measures of treatment effect, data synthesis, and investigation of heterogeneity

BMI-SDS or BMI Z-scores will be collected to compare studies in the results section of this review. When BMISDS or BMI Z-scores are not reported, these will be calculated or extracted from the data given in the report. If calculation is not possible, the authors will be contacted. If BMI-SDS or BMI Z-scores are not available anyhow, the absolute change in BMI or percentage overweight will be used as second best outcome variable.
To decide as to whether a meta-analysis is appropriate, the amount of data available as well as the clinical (variability in terms of participants, interventions, and outcomes) and methodological (variability in study design and risk of bias) diversity will be taken into

account. The results of studies using the same type of intervention and comparator will be pooled using a meta-analysis on BMI-SDS or BMI Z-score. The means will be used to determine the difference between means of the BMI-SDS or BMI Z-score (change in BMI-SDS or BMI Z-score during the maintenance intervention). Corresponding measures of precision (standard deviations, standard errors, or 95% confidence intervals) of the means and the difference between means will be extracted. If not reported, the SD will be derived from the reported standard error (SE) of the mean or can be obtained from confidence intervals, t statistics, and P values. If SDs are given rather than SEs, the SE will be calculated by dividing the SD by the square root of n. If the SD or SE of the mean change is lacking, the following formula will be used: $\text{standard deviation}_{\text{difference}} = \text{square root } ([\text{variance}_{\text{baseline}} + \text{variance}_{\text{follow-up}}] - [2 \times \text{correlation}_{\text{baseline,follow-up}} \times \text{standard deviation}_{\text{baseline}} \times \text{standard deviation}_{\text{follow-up}}])$.[5,14] The median correlation between the baseline and postintervention BMI-SDS will be calculated from the selected studies, compared with other reports, and used in this formula.

The I^2 statistic will be used to assess whether the observed variability in study results is greater than expected to occur by chance (statistical heterogeneity). Thresholds for the interpretation of I^2 will be according to the guidance for Cochrane reviews[11]:

– 0%–40%: might not be important.
– 30%–60%: may represent moderate heterogeneity*.
– 50%–90%: may represent substantial heterogeneity*.
– 75%–100%: considerable heterogeneity*.

*The importance of the observed value of I^2 will depend on the magnitude and direction of the effects and the strength of evidence for heterogeneity.

If there is substantial or considerable heterogeneity in results, and particularly, if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect. The consistency of results across the studies will influence the decision whether or not to combine results in a meta-analysis.

Assuming that there is no common treatment effect for all included studies, the inverse-variance random effects meta-analysis method will be used. Where a study reports data immediately post-intervention and at a subsequent follow-up time point, only the data immediately post-intervention will be included in the meta-analysis. Analysis will be conducted using the statistical programme R version 2.15.1 with the metafor package. Data will be presented in forest plots.

Studies that are not included in the meta-analysis will be described in a narrative way in tables and/or in the text. If appropriate, these studies will be organised into groupings or clusters (e.g. by intervention type, population group, or setting).

Unit of analysis issues

If studies with multiple treatment groups are present, all intervention groups that meet the criteria for including studies in this review (if investigated alone) will be included and compared with the control arm (if applicable). If needed, groups will be combined to create a single pair-wise comparison.
If cluster-randomised trials are present, this will be noted in the final report and it will be explicitly stated how data were handled: either by conducting the analysis at the same level as the allocation, or by statistical methods that allow analysis at the level of the individual while accounting for the clustering in the data.

Dealing with missing data

Whenever possible, original investigators will be contacted to request missing data. Assumptions of any methods used to cope with the missing data will be made explicit. If appropriate, sensitivity analyses will be performed to assess how sensitive results are to reasonable changes in the assumptions that are made. Furthermore, the potential impact of the missing data on the findings of the review will be discussed in the Discussion section.

Assessment of reporting biases

If possible, for each trial, the effect by the inverse of its standard error will be plotted. The symmetry in the funnel plots will be assessed both visually[15], and formally with Egger's test. Asymmetry can result not only from non-publication of small studies with negative results but also from selective outcome reporting or poor methodological quality leading to inflated effects. The results and interpretation of the assessment of reporting biases will be discussed in the Discussion section.

Subgroup analysis

Subgroup analyses will be performed if enough data is available in order to explore possible heterogeneity (taking into account that investigations of heterogeneity when there are very few studies are of questionable value) and to investigate the effectiveness of maintenance interventions for particular patient groups or using different types of intervention. As the age of patients, the different components used in the maintenance programmes, and the intensity of the maintenance programmes are expected to mainly influence the effect of the maintenance programmes in overweight children, subgroup analyses will be performed with subgroups defined according to these determinants.
If more than ten studies are available in the meta-analysis, meta-regression will be considered to investigate how different characteristics (for example intensity and duration of maintenance contact) are associated with the intervention effect; in other words: to identify aspects within

a maintenance programme that contribute to the success of that programme.
All analyses will be performed using the statistical programme R version 2.15.1 with the metafor package.

Sensitivity analysis

If appropriate, sensitivity analyses will be performed to explore the degree to which the main findings of the review are affected by changes in the methods or in the data used from individual studies. Issues suitable for sensitivity analysis will be identified during the review process.

DISCUSSION

Early and successful treatment of childhood overweight is of the utmost importance as it is known to have significant impact on both physical and psychosocial health.[1,2] Currently, two great challenges of lifestyle interventions are the maintenance of achieved weight loss/stabilisation and the prevention of relapse into inappropriate health behaviours. This systematic review will give an overview of the existing knowledge on programmes and initiatives aimed at long-term maintenance of a healthy or reduced weight in children and adolescents following initial treatment of overweight. It will form a basis for future research and practice in this area, a topic on which studies are scarce but highly necessary.

ADDITIONAL INFORMATION (APPENDIX C)

Additional file 1, Additional file 2

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We would like to thank Dr. Ir. J.M.S. Renkema from the Wageningen UR Library for her assistance in the development of the search strategy.

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CHAPTER 6B

Maintenance interventions for overweight or obesity in children: a systematic review and meta-analysis

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ABSTRACT

Childhood obesity is associated with significant health consequences. Although several intervention programmes for children result in weight loss or stabilisation in the short-term, preventing relapse after treatment remains an important challenge. This systematic review summarises the evidence about maintenance interventions after treatment in childhood obesity. Studies were identified by searching PubMed, Embase, Cochrane Library, Scopus, Web of Science, PsycINFO, CINAHL and SocINDEX. The primary outcome measure for this review was body mass index standard deviation score (BMI Z-score). Data were pooled using quality effect models. Eleven studies (1,532 participants, age 2–18 years) were included, covering a wide range of maintenance approaches. Included studies varied widely in methodological quality. Pooled analysis showed that the BMI Z-score of maintenance intervention participants remained stable, whereas control participants experienced a slight increase. No differences were observed regarding intensity and duration of therapy. A slight preference for 'face-to-face' versus 'on distance' interventions was shown. In summary, this review shows that, although there is limited quality data to recommend one maintenance intervention over another, continued treatment does have a stabilising effect on BMI Z-score. Considering the magnitude of the problem of childhood obesity, this is an important finding that highlights the need for further research on weight loss maintenance.

INTRODUCTION

Childhood obesity brings forward an enormous health concern because it is associated with significant physical and mental health problems and comorbidities both at current age and later in life.[1–3] Numerous research studies have supported the effectiveness of multidisciplinary, family-based programmes for treating childhood overweight and obesity.[4–6] However, obesity is a chronic disease, and maintenance of a steady weight after an initial weight loss or stabilisation represents the main challenge.[7] A limited number of studies have measured long-term outcomes from paediatric weight management programmes. Finding effective interventions for weight loss maintenance is crucial for the long-term success of obesity interventions, emphasising the need for longer term follow-up and further research on the most appropriate forms of post-intervention maintenance in order to ensure sustainable intervention benefits.[5,8]

In adults, maintenance programmes that extend patient–therapist contacts beyond initial treatment have enhanced weight loss maintenance.[9,10] Approaches for weight loss maintenance in childhood are thought to be promising as well.[11–13] However, a structured overview of these interventions is lacking, and the effectiveness of maintenance programmes in childhood obesity has never been thoroughly evaluated. Furthermore, it is unknown which properties contribute to the success of a maintenance intervention. The aim of this systematic review is to fill in this gap of knowledge and to guide future directions in the development of maintenance programmes.

METHODS

The search strategy and details about study selection, quality assessment and data extraction have been previously published.[14] This review is registered in PROSPERO (registration number CRD42014008698), and reporting guidelines as indicated in the Preferred Reporting Items for Systematic reviews and Meta-Analyses Statement were used.[15]

Information sources and search

Studies were identified by searching PubMed, Embase, Cochrane Library, Scopus, Web of Science, PsycINFO, CINAHL and SocINDEX, using the search strategy as presented in our previously published protocol.[14] The date of the last search was April 2017 for all databases. The search was limited to articles published in English, Spanish, German or Dutch. No publication date or publication status restrictions were imposed. Abstracts of conference presentations and posters were only included if the results were not published otherwise. Letters to the editor, editorials and expert opinions were excluded. Reference lists of eligible study reports were scanned for relevant references not captured by our search. The trial

registers ClinicalTrials.gov, The European Union Clinical Trials Register, Current Controlled Trials and the Netherlands Trial Register were checked.

Study selection, data collection and synthesis of results

The study selection was directed at randomised controlled trials (RCTs) and cohort studies about maintenance interventions for children and adolescents with overweight or obesity. To be included in this review, a baseline and at least one post-intervention anthropometric measurement had to be reported. Study eligibility criteria are presented in Box 1. Three independent reviewers (LvdH, EF, AJ) performed the eligibility assessment and critically appraised the methodological quality using the Risk of Bias Assessment Tool presented in our protocol.[14] A risk of bias scoring system with a maximum score of 32 points was developed according to study design (RCT vs. cohort) and based on the risk of bias criteria described in our protocol.[14] Disagreements between reviewers were resolved by consensus. LvdH extracted the pre-specified data using a pilot-tested data extraction sheet. The primary outcome measure for this review was body mass index standard deviation score (BMI Z-score) based on measured height and weight. AJ checked the extracted data, and disagreements were resolved by discussion. When information was not or unclearly reported, authors were contacted at least twice for further information.
In the remaining sections of this systematic review, the term overweight will be used to indicate both overweight and obesity.

Data analysis

The MetaXL add-in for meta-analysis in Microsoft Excel (EpiGear International Pty Ltd; Sunrise Beach, Queensland, Australia) was used for the analyses. No common treatment effect was assumed for all included studies. The quality effects model provided by the MetaXL add-in leads to the maintenance of the correct coverage probability of the confidence interval (CI), regardless of the level of heterogeneity, as well as a lower observed variance compared with the random effects model.[16] Therefore, we used this model in our meta-analysis.
When mean differences and associated standard deviations for BMI Z-score were not published, they were estimated from the pre-values and post-values based on methods from the Cochrane Handbook for Systematic Reviews of Interventions.[17] When

Box 1. Study eligibility criteria.

Participants

- Children and adolescents <18 years at the commencement of a maintenance intervention.
- All participants should have followed a treatment program for overweight, regardless of the type of intervention.
- Exclusion: children with overweight due to a secondary cause or in the context of a syndrome.

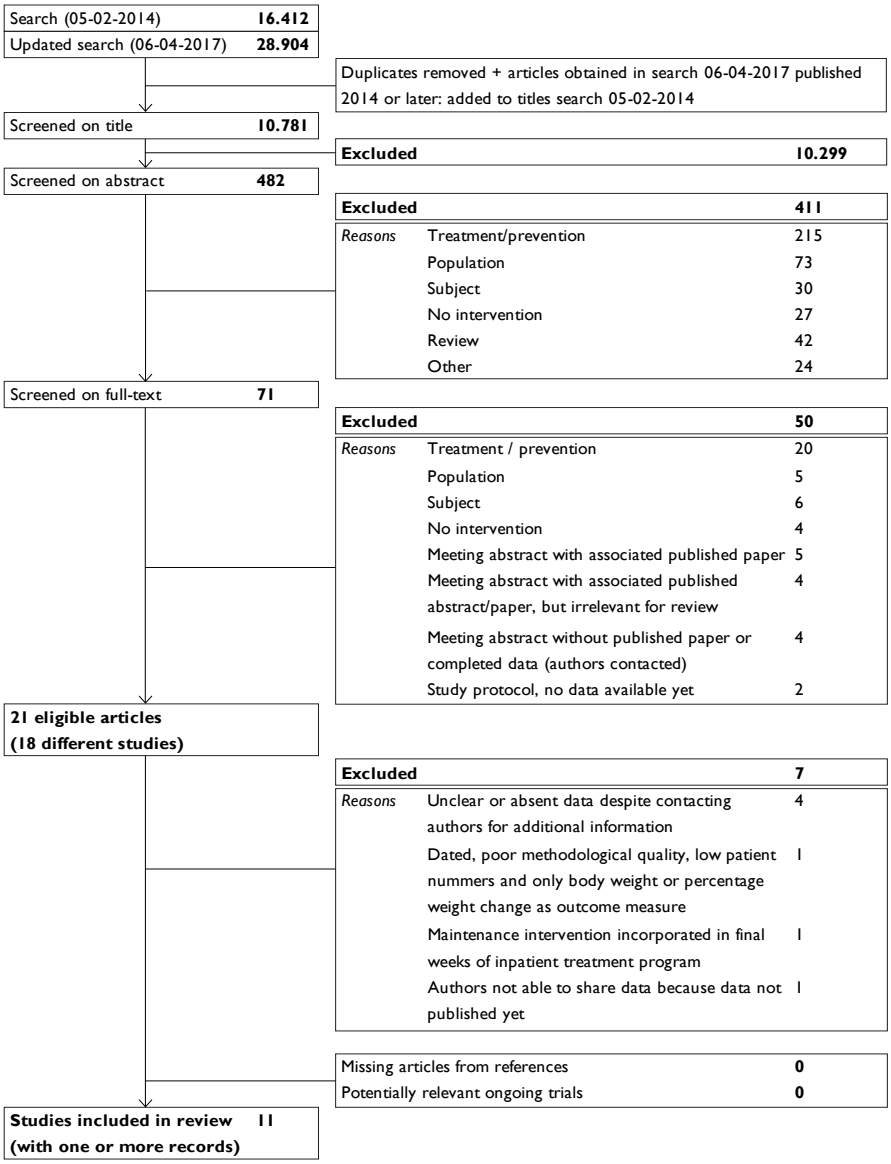
Interventions

- Maintenance or follow-up intervention or program with the aim to maintain weight loss or a healthy lifestyle.
- No restriction on the discipline(s) involved, no selection on the setting of the intervention.

Outcomes

- Primary outcome measure: BMI-SDS or BMI Z-score based on measured height and weight.
- Second best parameters: BMI and percentage overweight.

a study reported data immediately post-intervention and at a subsequent follow-up time point, only the data immediately post-intervention were included in the meta-analysis. Heterogeneity was assessed by I^2 statistics, as described in our review protocol.[14] Values less than 25%, 50% and 75% were considered as low, moderate, and high heterogeneity, respectively.[18] A weight was assigned to each study based on the results of the risk of bias assessment, dividing the study's absolute score by the maximum absolute score achieved by one of the studies. No sensitivity analyses were performed.



Using the MetaXL add-in, Doi plot symmetry and the quantitative measure of Doi plot asymmetry named the Luis Furuya-Kanamori (LFK) index were used for the assessment of reporting bias.[19] An LFK index within ±1 was interpreted as no asymmetry, an LFK index exceeding ±1 but within ±2 as minor asymmetry and an LFK index exceeding ±2 as major asymmetry.

RESULTS

The database searches identified 28,904 citations (Figure 1). Twenty-one citations (18 different studies) met all eligibility criteria.[12,13,20–38] Four studies were excluded because of unclear or absent data despite contacting the authors for additional information.[12,25,32,34] Another dated study was excluded because of poor methodological quality, low patient numbers and only body weight or percentage weight change as outcome measure.[30] In the study of Verbeken et al.[29], the maintenance intervention was incorporated in the final weeks of the in-patient treatment programme. Therefore, this study was also excluded. Finally, the authors of the study of Ek et al.[31] were not able to share their data because their data were not published yet. Eleven studies were included in this review[13,20,37,22–24,26–28,33,35], including a total of 1,532 participants. BMI Z-scores were available for all studies (either reported in the paper or provided by author upon request).

Characteristics of included studies

Six studies were conducted in the United States[13,23,24,26,28,35], two in Australia[22,37] and three originated in Europe.[20,27,33] The sample size of the maintenance interventions or control groups ranged from 14 to 271 participants. All studies enrolled both men and women. Studies were conducted only in children[13,20,28], in both children and adolescents[22,24,27,33], or in adolescents.[23,26,35,37] Table 1 summarises the study characteristics. More details of the studies including the content of the treatment and maintenance interventions are reported in S1 Table. The included studies varied tremendously in intervention design, outcome measurements and methodological quality. Only Van Egmond-Fröhlich et al.[33] and Wilfley et al.[13] included a control group. Both studies are well-designed RCTs with, respectively, an intermediate and low risk of bias (Table 2). Van Egmond-Fröhlich et al.[33] showed no effect of monthly outpatient aftercare with own physician compared to standard check-ups 6 and 12 months after in-patient rehabilitation. In contrast, the addition of maintenance-targeted treatment in the study of Wilfley et al.[13] improved short-term efficacy of weight loss treatment relative to no maintenance treatment, although the effects waned over 2 years of follow-up. Other researchers performed either a RCT with two different maintenance interventions[13,20,35,37] or a cohort study evaluating one intervention for weight maintenance.[22–24,26] Larsen et al.[27] and Rifas-Shiman et al.[28] facilitated a maintenance intervention after one or both arms of their treatment RCT. In our review, only the arm with both the treatment intervention and the maintenance intervention is included.

Table 1. Study characteristics of included studies, structured by year of publication.

Study; Country	Participants		Treatment prior to M		Maintenance intervention			
	Number	Age (years)	T	Duration	M1	M2	C	Duration
van Egmond-Fröhlich et al., 2006; Germany	M1 250, C 271	9-16	Inpatient medical rehabilitation	6 w	Check-up 6 m and 12 m after inpatient rehabilitation + once a month outpatient aftercare with own physician	NA	Check-up 6 m and 12 m after inpatient rehabilitation	12 m
Wilfley et al., 2007; US	M1 51, M2 50, C 49	7-12	Weekly multidisciplinary family treatment	5 m	Weekly group sessions with cognitive-behavioral approach	Weekly group sessions with focus on social facilitation	Discontinued contact; only FU assessments	4 m
Davis et al., 2012; US	M1 28, M2 33	14-18	Weekly dietary intervention (with or without strength training)	4 m	Monthly newsletters + 2 calls	Monthly class	NA	8 m
Nguyen et al., 2013; Nguyen et al., 2012; Australia	M1 69, M2 75	13-16	Weekly multidisciplinary group sessions	7 w	Quarterly booster group sessions + adjunctive telephone coaching	Quarterly booster group sessions only	NA	22 m
de Niet et al., 2012 (1+2); Bauer et al., 2010; NL	M1 73, M2 68	8-12	Eight multidisciplinary treatment sessions	3 m	Quarterly group session + weekly SMS	Quarterly booster group session only	NA	9 m
Straker et al., 2014; Australia	M1 44	11-16	Intensive multidisciplinary program with 2-hour group sessions twice per week	8 w	Structured telephone and text message contact at a decreasing frequency (starting with 3 messages per week)	NA	NA	12 m
Carraway et al., 2014; US	M1 33	12-18	Residential, immersion weight management summer camp	3 w	Monthly meetings with campers and their families	NA	NA	10 m
Hampl et al., 2016; US	M1 124	8-18	Multidisciplinary, behaviorally based program including group-format weekly meetings by health educators	24 w	Monthly follow-up visit and group session	NA	NA	24 m
Jensen et al., 2016; US	M1 16	13-17	Weekly group weight control program + electronic self-monitoring and text messaging	12 w	Electronic self-monitoring and text messaging (once per day) only	NA	NA	12 w
Larsen et al., 2016*; Denmark	M1 50	11-13	Day-camp intervention	6 w	Family-based intervention including four joint meetings	NA	NA	46 w
Rifas-Shiman et al., 2016*; US	M1 253	2-6	Two in-person visits and two phone calls with clinicians	1 y	Two in-person intervention visits	NA	NA	1 y

Abbreviations: C, control; FU, follow-up; m, months; M, maintenance; NL, the Netherlands; T, treatment; US, United States; w, weeks

* In this review, only participants randomised to T1 (intervention) were included.

Table 2. Risk of bias in individual studies.

	Risk of Bias						Total	
	Selection	Performance	Detection	Attrition	Reporting	Other	Absolute	Relative†
RCT maximum	10	6	8	6	2	0	32	NA
Cohort maximum	8	6	10	6	2	0	32	NA
van Egmond-Fröhlich et al., 2006; RCT	8	3	5	6	2	0	24	0.80
Wilfley et al., 2007; RCT	9	5	8	6	2	0	30	1.00
Davis et al., 2012; RCT	8	4	8	3	0	-1	22	0.73
de Niet et al., 2012; RCT	8	2	6	4	2	-2	20	0.67
Nguyen et al., 2013; RCT	10	5	8	6	1	-2	28	0.93
Straker et al., 2014; Waitlist CT --> Cohort	8	5	9	6	2	0	30	1.00
Carraway et al., 2014; Cohort	5	3	6	6	2	-2	20	0.67
Hampl et al., 2016; Cohort	7	3	7	4	1	0	22	0.73
Jensen et al., 2016; Cohort	7	4	7	3	2	0	23	0.77
Larsen et al., 2016; RCT*	8	3	8	4	2	0	25	0.83
Rifas-Shiman et al., 2016; RCT*	7	3	5	5	2	0	22	0.73

Abbreviations: CT, clinical trial; NA, not applicable; RCT, randomised controlled trial

* Risk of Bias Assessment in these studies was based on the overall study design (RCT), but only 1 treatment arm (the intervention arm) was included in this review.

† The relative risk of bias score was calculated by dividing the study's absolute score by the maximum absolute score achieved by one of the studies. A risk of bias score >0.80 was considered as 'low risk', 0.65-0.80 as 'intermediate risk', and <0.65 as 'high risk'.

Due to the considerable clinical and methodological diversity and the limited number of RCTs with a control group, it was decided to present the effects of all maintenance interventions in the meta-analyses. In general, the methodological quality of the included studies was suboptimal. Relative risk of bias scores ranged from 0.67 to 1.00 (Table 2).

Treatment programmes

In every instance, participants entered a treatment programme (T) and where subsequently assigned to a follow-up intervention aimed at maintaining their weight loss (M) or to a control group (C). The duration of the treatment prior to the maintenance intervention ranged from 4 weeks to 1 year. The treatment was in-patient in five studies.[23,27,33] Overall, one treatment primarily focused on diet (with or without physical activity component)[35], the others were multidisciplinary treatment programmes with an important place for teaching of strategies for managing behavioural change. The intervention content varied widely between the studies. Regarding the outpatient treatment programmes, sessions were organised at least once every 2 weeks. In all but one study, the target of intervention was the child with

his/her parent(s) or the family. Parents and/or families were either involved in the whole programme or invited for at least two or three separate days/classes, depending on the age of the participant and the structure and content of the programme.

Maintenance programmes

A wide range of approaches was examined as maintenance intervention after treatment. These include outpatient aftercare with the own physician, ongoing face-to-face family therapy, problem-solving approaches, cognitive-behavioural treatment and social facilitation therapy. Furthermore, adjunctive therapeutic contact via newsletters, short message service (SMS) and email was studied, as well as telephone coaching and a newly developed telemedicine support programme. The duration of the interventions ranged from 12 to 46 weeks. Most interventions were based on the concept of self-determined or autonomous motivation, focusing on the development of autonomous problem-solving and behavioural choice skills that are expected to promote maintenance of healthier behaviours and improved weight status.[13,22,23] Self-monitoring and personalised feedback, goal setting and contingency management were selected as important goals of the interventions.[20,24,26] Furthermore, in the view of obesity as a chronic and often a lifelong disease, treatment was considered within the broad framework of the Chronic Care Model[39], requiring system changes to achieve productive interactions between practice teams and patients.[28,37] All interventions were included in the meta-analysis assessing weight maintenance. Mean BMI Z-scores before and after the treatment and maintenance interventions are presented in Table 3. Pooled analysis showed that the BMI Z-score of maintenance intervention participants (n=1,213) remained stable (weighted mean difference [WMD] -0.02, 95% CI -0.09 to 0.05, I^2=55%), whereas control participants experienced a slight increase in BMI Z-score during the weight maintenance period (n=319; WMD 0.09, 95% CI 0.00 to 0.18, I^2=0%; Figure 2).
According to the protocol subgroup, analyses were performed to test the effects of different duration of the maintenance intervention, different intensity and the mode of delivery ('face-to-face' versus 'on distance').

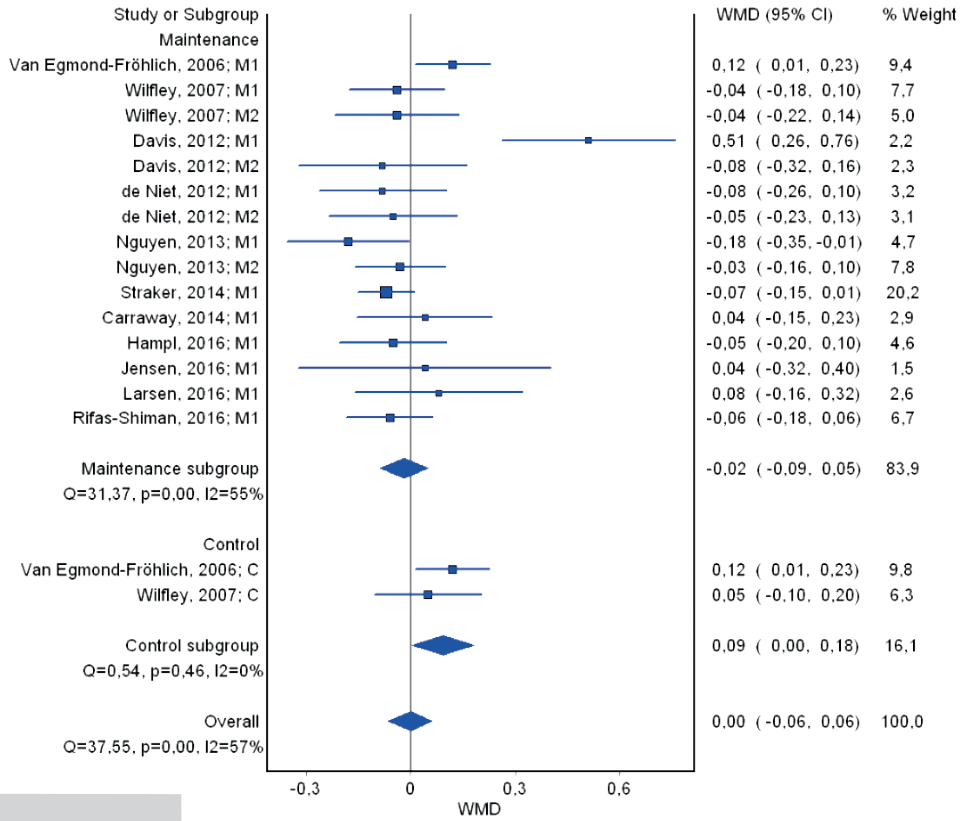


Figure 2. Forest plot detailing weighted mean difference (WMD) in body mass index standard deviation score and 95% confidence intervals (CIs) for the impact of maintenance and control interventions on body mass index standard deviation score in overweight and obese children.

Maintenance treatment intensity and duration

The maintenance intervention intensity varied greatly, from structured telephone and text message contact[22] to quarterly booster group sessions.[20,37] Meta-analysis of intensive maintenance interventions, defined here as interventions with follow-up contact at least once a month, versus less intensive interventions showed no difference in BMI Z-score weighted mean difference (WMD 0.01, 95% CI -0.08 to 0.09, I^2=66%; and WMD -0.03, 95% CI -0.11 to 0.05, I^2=0%, respectively). Furthermore, the effect on BMI Z-score of maintenance interventions with a relatively short duration (in this review defined as <1 year) was comparable to the effect of interventions of longer duration (WMD 0.01, 95% CI -0.10 to 0.12, I^2=57%; and WMD -0.01, 95% CI -0.08 to 0.07, I^2=62%, respectively).

Two studies included follow-up after finishing the maintenance intervention.[13,26] Wilfley et al.[13] observed their participants for 20 months after the end of the maintenance intervention. Although mean BMI Z-scores of the maintenance and control groups at the end of the follow-up period were still below the scores at baseline (before treatment), there was a general decline in effects during follow-up after the maintenance intervention (pooled maintenance treatment conditions: baseline BMI Z-score 2.22, post-weight maintenance 1.95 and end follow-up 2.00). In the study of Jensen et al.[26], the participants' BMI Z-score remained stable during the 9-month follow-up after the maintenance intervention.

'Face-to-face' versus 'on distance'

Five studies incorporated maintenance interventions 'on distance', i.e. using a telemedicine support programme, monthly newsletters and calls[35], adjunctive telephone coaching[37] and structured text message contact (with or without additional calls).[20,22,26] In contrast to interventions that consisted of ongoing group sessions or aftercare by the own physician ('face-to-face interventions'), the 'on distance' interventions were targeted at the child only. Pooled analysis showed a slight preference for 'face-to-face' therapy (WMD -0.03, 95% CI -0.09 to 0.02, I^2=0%) when compared with 'on distance' interventions (WMD 0.02, 95% CI -0.11 to 0.15, I^2=79%). In two studies, the 'on distance' intervention was added to booster group sessions.[20,37] In these studies, the adjunctive 'on distance' intervention provided no additional therapeutic benefit.

Table 3. Results (mean BMI Z-scores with standard deviation) of included studies, structured by year of publication.

Source (Country); Design		Results					
		M1		M2		Control	
		Mean	SD	Mean	SD	Mean	SD
van Egmond-Fröhlich et al., 2006 (Germany); RCT	Start T	2.64	0.39	NA	NA	2.67	0.46
	End T (6 w), start M	2.31	0.44	NA	NA	2.35	0.50
	Halfway M (6 m after end T)	NR	NR	NA	NA	NR	NR
	End M (12 m after end T)	2.43	0.66	NA	NA	2.47	0.67
Wilfley et al., 2007 (USA); RCT	Start T (baseline)	2.17	0.28	2.26	0.27	2.17	0.34
	End T (5 m), start M	1.94	0.34	2.03	0.42	1.99	0.39
	End M (9 m)	1.90	0.35	1.99	0.48	2.04	0.37
	After 1-y FU (12 m after end T)	1.99	0.39	2.03	0.51	2.07	0.38
	After 2-y FU (24 m after end T)	1.98	0.48	2.02	0.50	2.11	0.36
Davis et al., 2012 (USA); RCT	Start T	2.20	0.47	2.17	0.46	NA	NA
	End T (4 m), start M	2.16	0.46	2.18	0.47	NA	NA
	End M (8 m after end T)	2.67	0.44	2.10	0.50	NA	NA
de Niet et al., 2012 (the Netherlands); RCT	Start T	2.63	0.45	2.54	0.44	NA	NA
	End intensive part T (3 m), randomization M	2.46	0.54	2.39	0.52	NA	NA
	Halfway T (6 m)	2.40	0.59	2.30	0.56	NA	NA
	3/4 T (9 m)	2.36	0.62	2.42	0.59	NA	NA
	End T + M (12 m)	2.38	0.59	2.34	0.57	NA	NA
Nguyen et al., 2013 (Australia); RCT	Start T	2.03	0.37	2.02	0.29	NA	NA
	End T (2 m), start M	2.01	0.36	1.96	0.32	NA	NA
	Half-way M (12 m after start T)	1.97	0.42	1.94	0.32	NA	NA
	End M (24 m after start T)	1.83	0.51	1.93	0.39	NA	NA
Straker et al., 2014 (Australia); Waitlist CT	Baseline	2.14	0.07	NA	NA	NA	NA
	End waitlist (3 m), start T	2.12	0.07	NA	NA	NA	NA
	End T (8 m), start M	2.11	0.07	NA	NA	NA	NA
	1/4 M (3 m after end T)	2.09	0.15	NA	NA	NA	NA
	Halfway M (6 m after end T)	2.07	0.15	NA	NA	NA	NA
	End M (12 m after end T)	2.04	0.30	NA	NA	NA	NA
Carraway et al., 2014 (US); Cohort	Start T	2.48	0.35	NA	NA	NA	NA
	End T (3 w)	2.40	0.40	NA	NA	NA	NA
	End M (10 m after end T)	2.44	0.40	NA	NA	NA	NA
Hampl et al., 2016 (US); Cohort	Start T	2.38	0.28	NA	NA	NA	NA
	Halfway T (12 w)	2.33	0.30	NA	NA	NA	NA
	End T (24 w), start M	2.32	0.32	NA	NA	NA	NA
	Halfway M (12 m after end T)	2.31	0.33	NA	NA	NA	NA
	3/4 M (18 m after end T)	2.29	0.36	NA	NA	NA	NA
	End M (24 m after end T)	2.27	0.44	NA	NA	NA	NA
Jensen et al., 2016 (US), Pilot study	Start T	1.85	0.44	NA	NA	NA	NA
	End T (12 w)	1.74	0.49	NA	NA	NA	NA
	End M (12 w after T)	1.78	0.49	NA	NA	NA	NA
	After 1-y FU (12 m after start T)	1.78	0.38	NA	NA	NA	NA
Larsen et al., 2016 (Denmark), RCT	Start T	1.99	0.46	NA	NA	NA	NA
	After T (6 w)	1.45	0.58	NA	NA	NA	NA
	After M (46 w after end T)	1.53	0.63	NA	NA	NA	NA
Rifas-Shiman et al., 2016 (US), RCT	Start T	1.88	0.69	NA	NA	NA	NA
	After T (1 y)	1.73	0.74	NA	NA	NA	NA
	After M (1 y after end T)	1.67	0.67	NA	NA	NA	NA

Abbreviations: B, behavioural intervention; BMI, body mass index; CT, clinical trial; D, dietary intervention; EF, executive functioning; m, months; M, maintenance; NA, not applicable; NR, not reported; OC, outpatient clinic; P, physical activity intervention; RCT, randomised controlled trial; SMSMT, short message service maintenance treatment; T, treatment; U, unknown; w, weeks

Study drop-out

In line with the divergent intervention designs, the definition of retention to the intervention varied widely between the studies. Generally, adherence to intervention activities was low. Furthermore, at least five studies reported follow-up data of less than 75% of the initial study sample.[20,23,24,26,27] Missing data were handled appropriately by most studies, performing analyses comparing those lost to follow-up with those retained in the study and paying attention to the possibility of differential attrition between the groups. However, in three studies, the incomplete outcome data were not clearly addressed.[26]

Assessment of reporting bias

A Doi plot for the outcome BMI Z-score was generated (Figure 3). Inspection of the Doi plot revealed a mild asymmetrical shape. The LFK index was 0.94.

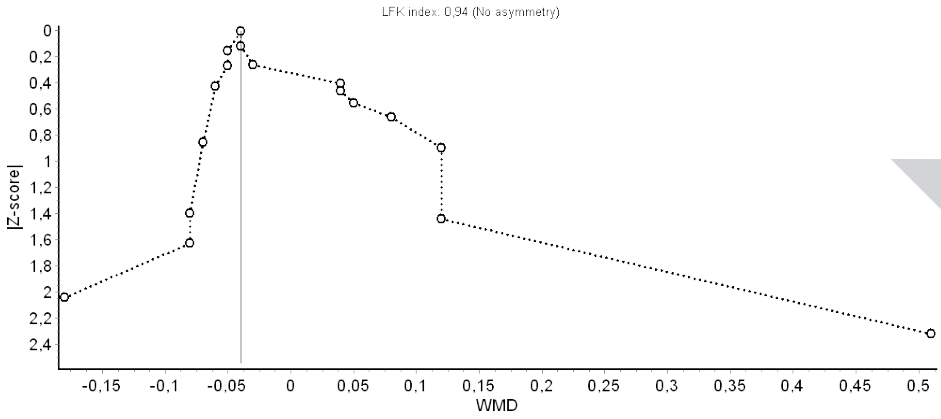


Figure 3. Doi plot including Luis Furuya-Kanamori (LFK) index for the assessment of reporting bias.

DISCUSSION

Childhood overweight and obesity have increased globally. Although several intervention programmes for children result in weight loss or stabilisation in the short-term, preventing relapse remains an important challenge.[40–43] This systematic review summarises the existing evidence about maintenance interventions in childhood obesity.

Overall, a favourable effect of maintenance interventions was detected: pooled analysis showed a stable BMI Z-score in maintenance intervention participants, whereas a slight increase in BMI Z-score was observed in control participants. Essentially, this means no clinically meaningful reduction in overweight in children and adolescents[44] but rather overall stabilisation of treatment effect. This observation is in line with literature on the effectiveness of maintenance interventions in adults.[10,45,46] However, the 11 studies included in our review showed considerable clinical and methodological diversity. Furthermore, only two studies included a control condition.[13,33] In one of these studies, the maintenance interventions provided additional effect compared with the control group in the short-term[13], the other showed no beneficial effect of the maintenance intervention.[33] Other studies were RCTs comparing two different maintenance interventions or cohort studies, some of them with small sample sizes. Moreover, divergent maintenance treatments effects were found. Considering these inconsistent results, in addition to further limitations in the quality of the studies (particularly the risk of bias) reducing the confidence in the pooled estimates, this evidence should be interpreted with caution.

Maintenance interventions: structure and content

The small number of studies, the high heterogeneity and the generally poor methodological quality withholds us from ascertaining which kind of maintenance intervention is more effective than another. The suggestion from literature is that intensive maintenance interventions with a longer duration are more successful.[10,20,33,37,47] However, this was not confirmed in this review. Due to the high clinical and methodological heterogeneity and the inconsistent maintenance treatment effects, it remains unclear whether it is the maintenance content, the frequency or the duration of treatment contact, which contribute to maintenance treatment efficacy. The important observation by Wilfley et al.[13], showing waning of effects over follow-up after maintenance therapy, emphasises the need for sustainable treatment modalities.

'Face-to-face' interventions tend to be more effective than 'on distance' interventions (WMD -0.03 versus 0.02, respectively). Whereas some researchers pose that newsletters as opposed to group classes may suffice as follow-up maintenance programme[35], others advocate for interdisciplinary outpatient follow-up care in groups. In adults, Tsai et al.[48] showed that continued in-person visits during the weight loss maintenance phase led to greater weight loss than contact by mail. Focus groups among children to study what strategies would be helpful in facilitating maintenance of weight loss post-intervention brought forward that

maintenance intervention contacts should be scheduled, personalised rather than automated, and with a familiar member of the intervention team.[49] More extensive and/or tailored care may be necessary to promote continued improvement in weight status.[50]

Continuous motivation, especially after the initial weight reduction phase, was identified as the strongest predictor of successful weight maintenance.[51] Primary motivating factors for adolescent weight loss may be intrinsic rather than extrinsic.[52] Many studies included in this review (although with divergent results) applied a theoretical framework based on self-determination and goal setting, pursuing the performance of behaviour out of a sense of volition, choice and self-endorsed reasons, as opposed to non-self-determined motivation. Both in children and adults, successful weight maintainers generally show the characteristic of high self-efficacy, high internal motivation (i.e. concerning physical activity) and do have profound self-management skills concerning food intake.[51,53,54] Furthermore, peer and parental encouragement and instrumental support were widely endorsed as central to success.[52] Concerning the role of parents in the therapy process, the general relationship between parents and their children seems to be more important in predicting treatment success than higher parental involvement, especially concerning the issues of responsibility.[51] Finally, weight-related teasing during childhood and adolescence might lead to emotional eating, which in turn impairs long-term weight loss maintenance.[55] This highlights the need for interventions aiming at reducing weight stigmatisation and targeting emotional eating for successful long-term weight loss maintenance.

Use of 'on distance' technologies

Commitment devices in the study of Kulendran et al.[25] helped adolescents to maintain their recent weight loss. Furthermore, Fry et al.[56] showed a similar short-term result in adults, with enhanced effectiveness when prompts were frequent and personal contact with a counsellor was included. However, pooled analysis in this review showed a slight preference for 'face-to-face' therapy when compared with 'on distance' interventions. Additionally, in two studies adjunctive 'on distance' intervention provided no additional therapeutic benefit to booster group sessions.[20,37] Although, generally taken, solely an 'on distance' interventions might be insufficiently effective, the use of technology may at least increase the likelihood of programme engagement among adolescent patients.[57] For example, De Niet et al.[38] showed no benefit of SMS maintenance treatment (SMSMT) on treatment outcomes, but children who received SMSMT were less likely to withdraw from the family-based behavioural lifestyle treatment than children who did not receive the SMSMT. Patient retention remains a significant barrier to effective paediatric weight management.[58,59] Structured weight management programmes should increase their efforts to engage patients and families at the initial visit and identify and address barriers to follow-up.[60,61] Given that these populations may be at increased risk for programme dropout, additional supports or tailoring of programmes to these families' needs may be required to reach optimal outcomes. The use of new technologies, such as

smartphone-assisted self-monitoring and feedback, could be helpful in this. As mentioned in the previous discussion, also in intervention texts personalisation should be applied as much as possible to minimise feelings of guilt and shame in overweight and obese adolescents.[62]

Limitations

As mentioned in the previous discussion, our search revealed studies with considerable clinical and methodological heterogeneity. Furthermore, only two studies included a control condition.[13,33] The maintenance treatment effects varied widely, the heterogeneity indicating that there are (unknown) factors that give a credible explanation for the inconsistency of effects. Additional limitations in the quality of the studies (particularly the small sample sizes and the risk of bias) may explain part of the effect variability and further reduce the strength of the evidence. Furthermore, data were handled differently between the studies, with studies presenting results of intention-to-treat analyses with adequate handling of missing data while others suffice with less robust statistical methods.

Generally, the attrition rate was high in the included studies. Although missing data were handled appropriately by most studies, there is a significant risk of attrition bias. Furthermore, adherence to the interventions differed between the studies, a problem faced by many longitudinal clinical research studies.[63] Different reasons for non-compliance were provided by the study authors (i.e. time limitations, practical difficulties and motivation). It could have been that participants with more fidelity to an intervention have had greater improvement in their behaviours, with consequently a greater magnitude of effect.

Finally, visually there is mild BMI Z-score Doi plot asymmetry. Although the LFK index is 0.94 (indicating no asymmetry), the presence of reporting bias cannot be ruled. Publication bias could have attributed to the presence of reporting bias, failing to include all relevant trials because they were not published. Furthermore, although a very broad search has been performed for this review, citations could have been missed. Relevant studies could have been excluded during the eligibility assessment because it was not clear from the title or abstract that a paper described a maintenance intervention. Finally, a language filter has been used in our search, meaning that studies published in a language other than English, Spanish, German or Dutch were not captured.

Conclusions and implications for research and practice

There is limited quality data to recommend one maintenance intervention to be favoured over another. However, this systematic review shows that, in general, continued treatment does have a stabilising effect on BMI Z-score after obesity treatment. Considering the magnitude of the problem of childhood overweight and obesity, associated with significant health and psychosocial consequences, this is an important finding that highlights the need for further research on weight loss maintenance.

Equal to adults, early weight loss (or stabilisation in growing children) may be used as an indicator to identify treatment non-responders and intervention strategies could be modified to improve outcomes.[64] Consideration of social and environmental barriers and time pressures in the design and implementation of future child weight management interventions may help to increase the acceptability and effectiveness of programmes.[65] As stated by Wilfley et al.[13], a comprehensive maintenance programme combining both behaviourally and socially based treatment targets is likely to maximise children's long-term weight control success. Where possible, including an individual component in a group-based intervention could produce optimal outcomes.[50] Self-monitoring[9] and personalised feedback are important items to include, possibly by using new technologies. Furthermore, additional 'on distance' interventions might be used for their beneficial effect on treatment adherence. Future research could focus on facilitators and barriers to the achievement of healthy lifestyle goals.[66] Furthermore, one could examine patient reported outcomes (i.e. quality of life) as outcome parameters and adherence as a mediator of outcome. Studies are needed to examine how biological, behavioural and relational associated factors affect retention in long-term treatment programmes and treatment response, and how these factors can be influenced. Next, the optimal intensity and duration of maintenance therapy remain an area of future research. Finally, although children with overweight, obesity and morbid obesity benefit equally from an ongoing, outpatient, tailored lifestyle intervention[67], future research could evaluate the effectiveness of combined pharmacological and behavioural interventions in severely obese children, as well as the potential risks or harms associated with these interventions. But eventually, every success story starts with the patient's own intrinsic motivation, and healthcare professionals face the challenge to convey this.

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ADDITIONAL INFORMATION (APPENDIX D)

S1 Table

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CHAPTER 7

General Discussion

The objective of this thesis is to look below the tip of the childhood obesity iceberg, and to dive into a few important issues encountered in daily clinical practice. Within this scope a range of studies was carried out. **PART I** of this thesis focused on consequences of childhood obesity: ***Childhood obesity and beyond***. We investigated the health-related quality of life in children and adolescents at the start of hospital-based obesity treatment (**Chapter 2**), studied the expression of adiponectin and leptin receptors on circulating immune cells in obese children pre- and post-lifestyle intervention compared to normal weight control children (**Chapter 3**), and evaluated ambulatory blood pressure measurement patterns in a population of overweight and obese children and adolescents (**Chapter 4**). Subsequently, in **PART II** of this thesis we elaborated on the treatment of childhood obesity: ***Way beyond weight***. We described the effects of our multidisciplinary weight loss intervention, specifically comparing overweight or obese (young) children and adolescents (**Chapter 5**). Additionally, a systematic review and meta-analysis was performed summarising the existing knowledge on programmes and initiatives aimed at long-term maintenance of a healthy or reduced weight in children and adolescents following initial treatment of overweight (**Chapter 6**).
In Table 1 the main findings of the studies are summarised. This General Discussion starts with a critical discussion of several overarching theoretical, practical, and methodological issues derived from these chapters, followed by implications for clinical practice, directions for future research, and an overall conclusion.

Table 1. Overview of the main findings of the research presented in this thesis.

PART I: Childhood obesity and beyond

Health-related quality of life - Chapter 2

Study design	Findings	Conclusions
Cross-sectional	Both parent-proxy reports and child self-reports (when applicable) showed a lower HRQoL in children with an increasing degree of obesity, especially in the physical domains of HRQoL. Parent-reported psychosocial HRQoL scores were not consistently different across weight categories.	Overweight/obesity is associated with an impaired HRQoL. Understanding and assessing the HRQoL of overweight children is essential, as it can guide future health policy and treatment optimalization.
	Significant differences exist between parent-proxy reports and child self-reports on 'Bodily Pain/ Discomfort' and 'General Health Perceptions' (lower child scores), and 'Behaviour' and 'Family Cohesion' (higher child scores).	To gain a complete picture of functioning, it is preferable to obtain HRQoL data from children's point of view supplemented with data from the parents' perspective, as children and parents may not necessarily share similar views about the overall impact of overweight.

Cardiometabolic risk, a 'bench' study: Adipokine receptor expression - Chapter 3

Study design	Findings	Conclusions
Observational cohort	Circulating leukocyte subsets showed distinct adipokine receptor expression profiles.	The distinct adipokine receptor profiles may partly explain the differential impact of adipokines on leukocyte subsets.
	Leukocyte subset numbers and adipokine receptor expression profiles were largely similar in obese children and controls.	Adipokine signalling in childhood obesity is primarily modulated by circulating adipokine levels, instead of adipokine receptor expression.

Cardiometabolic risk, a 'bedside' study: Blood pressure measurement in childhood obesity - Chapter 4

Study design	Findings	Conclusions
Cross-sectional	A high prevalence of abnormal ABPM patterns (WCH, elevated BP, MH, ambulatory HTN) was detected in our population of overweight and obese children and adolescents, with only 54.9% of the population classified as normal BP using ABPM.	
	OBP measurement is often poorly correlated with a subject's actual ABPM pattern.	Random measurement of BP in the office does not suffice in diagnosing HTN in overweight children. Routine incorporation of ABPM into the evaluation would permit accurate detection of the highly prevalent abnormal ABPM patterns.
	Abnormal circadian variation was highly prevalent: isolated night-time BP load ≥25% with normal daytime ABPM was found in almost 25% of the participants, and 40.2% of the participants lacked the physiologic nocturnal SBP dip.	
	A high prevalence of MetS and obesity-related comorbidities was detected in children with elevated BP and (severe) ambulatory HTN, as well as in non-dippers.	

PART II: Way beyond weight

Treatment of childhood obesity: young children versus adolescents - Chapter 5

Study design	Findings	Conclusions
Prospective cohort	Children showed significant larger BMI Z-score differences than adolescents - BMI Z-score difference end versus start of treatment -0.35 (SD 0.49) in children, -0.09 (SD 0.27) in adolescents - and more often a clinically relevant BMI Z-score decrease of >0.25 (48% versus 26%, P=0.10). The prevalence of abnormal blood pressure, disturbances in glucose homeostasis, and metabolic syndrome decreased in the total group (in children more than in adolescents).	Treatment of overweight or obesity should be started at early age.
	There was a high dropout rate in children and adolescents of respectively 29.5% and 40.5%.	A careful assessment of initial expectations is needed, including the identification of barriers to follow-up, as a screening before treatment commences.

Maintenance of treatment result - Chapter 6A/B

Study design	Findings	Conclusions
Protocol	Study protocol for a systematic review	This review will give an overview of the existing knowledge on programmes and initiatives aimed at long-term maintenance of a healthy or reduced weight in children and adolescents following initial treatment of overweight.
Systematic review and meta-analysis	The BMI Z-score of maintenance intervention participants remained stable, whereas control participants experienced a slight increase. No differences were observed regarding intensity and duration of therapy. A slight preference for 'face-to-face' versus 'on distance' interventions was shown.	Continued treatment does have a stabilising effect on BMI Z-score. There is limited quality data to recommend one maintenance intervention over another.

ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure in mmHg; DBP, diastolic blood pressure; HRQoL, health-related quality of life; HTN, hypertension; MH, masked hypertension; MetS, metabolic syndrome; OBP, office blood pressure; SBP, systolic blood pressure; WCH, white coat hypertension

THEORETICAL, PRACTICAL, AND METHODOLOGICAL CONSIDERATIONS

1. *Looking behind the doors of the individual patient* – Participants

In this first part of the General Discussion, the world of our participants will be explored, by discussing participant-related factors that could have influenced the results of our studies. We will focus on our participants as a group, with obesity as the common denominator, and on our participants at individual level, by reviewing factors that affect our patients individually.

This thesis is centred around children and adolescents with overweight or obesity referred to the paediatric outpatient clinic of our hospital by their general practitioner or youth health care physician. All were offered a multidisciplinary multicomponent obesity treatment programme as described in the General Introduction of this thesis.
In Chapter 5 we determined the effect of this hospital-based treatment programme, specifically comparing (young) children and adolescents. Age has been found to be an important factor in treatment success, with children responding better to treatment than adolescents. BMI Z-score of the total group significantly decreased (BMI Z-score -0.27, SD 0.46), with children showing significant larger BMI Z-score differences than adolescents (-0.35, SD 0.49, versus -0.09, SD 0.27) and more often a clinically relevant BMI Z-score decrease of >0.25 (49% versus 24%). But before analysing the effect of treatment in different groups of children, we need to carefully consider the patient population that seeks help. Several studies determined what factors drive participation in a family-based weight management programme.[1] First of all, the child and his or her carers have to recognise the presence of overweight or obesity. Parents are likely to misperceive their child's weight status, especially in the preschool age group.[2–4] This is particularly true for parents who are themselves overweight.[2,5] The recognition of overweight and obesity is even more difficult in the current obesogenic world, were we all get used to overweight and obesity in the environment around us. If parents do not recognise their child as at risk for of having overweight or obesity, they are

Overweight and obesity are sensitive issues to address with patients during any visit, but essential in the overall health of our paediatric patients.

not likely to seek treatment or enroll in intervention opportunities to diminish the risk factors for paediatric obesity and its related complications. Also in adolescents themselves the accurate perception of body size is limited, although on the other side the majority indicated dissatisfaction with their body size, suggesting more self-awareness than would be assumed based on the self-perception assessment of body size alone.[6,7] Another limiting factor that we faced in our outpatient clinic, especially in the youngest children, is the

parental misperception that the child will automatically grow out of his or her obesity. This points to the importance of weight screening initiatives.[8] In addition, in our opinion healthcare workers have the responsibility to discuss weight status with parents and children on every clinical encounter. Although weight is a sensitive issue for both parents and health professionals[9], studies show that parents do want to know this information, as long as it is given in an non-jugdmental manner.[10]

Childhood overweight is often not recognised by children and their parents. Or many other priorities exist behind a families' front door that may divert the attention from a healthy lifestyle and the presence of overweight. These priorities need to be addressed first before someone is receptive to obesity treatment.

To be able to see the obesity problem and subsequently seek and commence treatment, children and parents need to be receptive for it. Conflicting family priorities and needs often make it diffcult to adhere to healthy lifestyles and to commence on obesity treatment.[11] Studies indicate that the environment provided by the parent is central to the development of the child's eating and exercise habits. Often, families report that they have trouble finding enough time to help their children. Parents and caregivers exert varying amounts of control and discipline, depending on parenting style, skill level, and involvement. Other factors, such as financial problems, unemployment, family issues including important life-events such as divorce or disease, may divert the attention away from a healthy lifestyle. In our outpatient obesity clinic, we encountered divergent problems behind several families' front door that claimed more priority than the child's weight.
In conclusion, the *obese childhood population that seeks help* is a selected group of patients. Indeed, we do see obese children in our direct environment every day, but we don't see them all in healthcare settings.

Next, the patients that we ultimately encounter in our clinic may diverge from other children with obesity. Part of them may be sent by their healthcare physician, without feeling urgency or intrinsic motivation by themselves; these patients can be considered as 'non-treatment seeking'. Generally, these patients were not included in our studies, because they did not commence our treatment programme, or together with the paediatrician or multidisciplinary team decided to choose another way of care more suitable for that individual patient or family. Our study population consisted of the treatment-seeking population, and this group likely differs from the average obese child. Thus, we need to be careful with generalising our study results to all children with overweight.[12] For example, in Chapter 2, we determined the HRQoL of overweight and obese children at the start of our hospital-based treatment. One can speculate that the HRQoL in this study population is lower than in non-treatment seeking children, with low HRQoL acting as a reason to search for treatment. As described in Chapter 2, both parent-proxy reports and child self-reports showed a lower HRQoL in children aged

5-18 years with an increasing degree of obesity. Additionally, the HRQoL of our population was lower when compared to the general paediatric population[13–15] and comparable with or worse than children with other chronic conditions (i.e. asthma, eczema, dyslexia, ADHD, or migraine/severe headache).[14,15] In view of what we have discussed, our study population consisting of a treatment-seeking population, we have to consider that the HRQoL measured in our study population might be lower than in the general obese paediatric population.
As a second example, in Chapter 4 we studied the prevalence of abnormal ABPM patterns in our overweight paediatric population. It could be argued that our population has been referred to secondary care because of a perceived high likelihood for comorbidities. A recent study showed that obesity treatment-seeking youth are more adversely affected by cardiometabolic risk factors than the general population of youth with obesity.[16] Hence, it cannot be excluded that in our study population the prevalence of abnormal BP patterns is higher than in the general population of children with obesity.
Other factors, such as degree of obesity, having an additional somatic or psychosocial reason other than 'just' a BMI in the obese range, or pressure from the parents forcing a referral to the paediatrician, could also have influenced the constitution of our study population.
Thus, *the obese childhood population that we encounter in our clinic* is a self-selected group of patients.

The constitution of our study population, with the divergent reasons for referral and treatment commencement, undoubtedly has influenced the attrition rate in our effect study (Chapter 5). In general, the success of obesity treatment is significantly hampered by high attrition rates.[17,18] Before our treatment commenced, all referred children were screened by a child psychologist. Despite this screening a high dropout rate was detected, partly due to emerging psychosocial problems during treatment. We have discussed this drop-out issue in Chapter 5. It is known from literature that both child factors and parental factors influence attrition rate. Several studies tried to identify factors that may predict participation and attrition.[19–22] Social and environmental barriers, i.e. lack of support from family and environment, work commitments, financial problems, food provided at school, low parental self-efficacy, and time pressures were important obstacles to the achievement of healthy lifestyle goals and to compliance with follow-up scheduling.[23,24] Increasing the effort to engage patients and families at the first visit, to assess initial expectations (i.e. about the treatment content, the desired and expected treatment effect, the role of child/parent/caregivers) and to identify and address barriers to follow-up may help to tailor the treatment to the families' needs.[25,26] Participants and their family need to be intensively supported during and after treatment in order to increase adherence to the treatment and to reduce dropout.

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Early weight loss is consistently identified as a strong predictor of long-term weight loss[27,28], and may be used as an indicator to identify treatment non-responders. Participants without early weight loss may benefit from additional support during the intervention, or transition to another intervention could be considered.

A qualitative study of how overweight adolescents managed their weight in the transition to adulthood showed some evidence of more consistent use of exercise, self-monitoring of diet and exercise, and of lifestyle changes becoming habitual or part of identity in the group who slimmed.[6] In another study using qualitative interviews and focus groups in overweight and obese teens and their parents immediately and 12 months post-intervention, several practical strategies and considerations emerged for use in future community programmes, including management of expectations, the cyclical nature of behaviour change in adolescents, the translation of knowledge into behaviour change, the successful implementation of practical goal-setting strategies, and increasing intrinsic motivation.[29] Generally, weight-related concerns and desire to lose weight are important factors in the motivation to implement behavioural changes.[6,30] The use of technology, such as apps on smartphone, accelerometers, fitness websites, might be useful to increase the likelihood of programme engagement or to enhance treatment success, but is not indisputably established.[31] A last important factor to consider is the higher prevalence of obesity and a reduced treatment response in racial and ethnic minorities.[32–34] Cultural differences among ethnic groups may argue for different intervention approaches targeted to each group. In addition, disparities in obesity prevalence exist by socioeconomic position.[32,35–38]

The relevance of a treatment programme depends on external validity or generalisability. In other words, whether the results can be reasonably applied to a definable group of patients in a particular clinical setting in routine practice.[39] In Chapter 5 we showed that our treatment programme improved both anthropometric and metabolic measures in our population of overweight and obese children and adolescents. Note that we have chosen for a pre-test post-test design, for a study that reflects real practice instead of a perfectly designed randomised controlled trial which may not well represent clinical practice, as will be discussed later. Despite this, we need to be careful when generalising our results to other obese paediatric populations. Validation studies are needed to confirm the effectiveness of the treatment programme.

In conclusion, by diving into the world of our participants, we have shown that obesity is actually the only common denominator of our participants. All other variables, including child-, family- and environmental-related factors, diverge between the individual patients. Of course these individual differences are of consequence for childhood obesity treatment, and they immediately show why obesity treatment is such a complex matter. In the next paragraph we will more widely discuss the treatment of childhood obesity.

2. *Fighting fat* – Considerations with regard to childhood obesity treatment

As described in the General Introduction of this thesis, the treatment programmes facilitated in our hospital are in line with the existing evidence: *multidisciplinary*, involving a paediatrician, child psychologist, paediatric dietician, and child physiotherapist, and *multicomponent*, with behavioural modification techniques to change dietary intake and physical activity. The development and process evaluation of one of our treatment programmes (*AanTafel!*) has been described before.[40] In literature, innumerable treatment options for paediatric obesity have been reported[41], but little attention has specifically been given to intervention formats. With regard to intervention format, group sessions comprise the mainstay of our treatment programmes. As summarised by Martin et al., there is compelling evidence that interventions based on sound group dynamics principles are particularly effective for both compliance and adherence.[42] For example, interpersonal learning and imitative behaviour are unique therapeutic factors of group settings. Indeed, when evaluating our treatment programme with the children and their parents, most of them considered the group environment as valuable, especially appreciating the peer support from others and the ability to share experiences. However, inherent to group treatment is the limited attention to individual needs. Including an individual component in a group-based intervention may produce optimal outcomes.[43,44] In contrast, others were not able to show increased cost-effectiveness of a group treatment plus individual format versus group treatment alone.[45] In our treatment programmes evaluated in Chapter 5, three individual meetings are incorporated. During these meetings subjects specific to the child and the family are discussed, i.e. personal and family treatment goals, plans for managing daily life difficulties and challenging moments with regard to a healthy lifestyle, treatment results, etcetera. Furthermore, a physical examination is performed and the presence of comorbidity is evaluated including laboratory tests. The aim of these meetings, in addition to group meetings, is tailoring the treatment to the individual child and family.

Next to face-to-face formats, 'on distance' technologies are increasingly used in the treatment of childhood obesity. Given the modest outcomes and the limited reach of current obesity treatment programmes, novel strategies are needed to enhance reach and effectiveness. As summarised by Tripicchio et al., technology based approaches may provide easier access to treatment services and could reinforce strategies that support behaviour change, such as goal setting, immediate feedback, and increased intervention contact. In our treatment programmes, face-to-face contacts are supported by a personal and secured digital workbook on the internet. Additional information is provided here and assignments can be fullfilled to prepare the group sessions. A secure message system allows the interchange of individually tailored information between participants and healthcare professionals, and encourages adherence to the treatment. Whether this ditigal workbook contributed to the effect of our treatment programmes as described in Chapter 5 is unknown. In general, studies on technology-based counseling in the management of weight and lifestyles of obese

or overweight children and adolescents, on the use of technology adjuncts (i.e. internet, tablets, or mobile phones) to family-based paediatric obesity treatment, and on the use of smartphone interventions for weight treatment and behavioural change in pediatic obesity show contradictory results.[46–48] Thus, until know the effectiveness of on distance technologies in paediatric programmes remains equivocal. From a healthcare organisational perspective, technology can be used to enhance healthcare-community communication as a means to decrease the barriers to collaboration and to create a web of connection between the community and healthcare providers that promote wellness and a healthy weight status.[49] Next to intervention format, intervention setting is relevant to discuss. As mentioned before, family and environmental barriers exist to engagement in obesity treatment. Especially minority and low-income families may experience difficulties with transportation to and from the clinic. Also time pressures are know to prevent family participation in clinic-

Transfer from a clinic-based intervention to the community setting may be helpful in overcoming barriers to engagement in obesity treatment.

based interventions. To overcome these barriers, transfer from a clinic-based intervention to the community setting may be helpful.[11,50] Limited research exists to indicate the effects of transition from a secondary to a primary care setting. In their study investigating factors influencing parental engagement in an early childhood obesity prevention programme, Love et al. used the categorisation of enablers and barriers to engagement into personal, organisational and programme factors.[51] Personal (family, parent) factors include socio-demographics; physical, financial and emotional resources; and social supports. Organisational (service provider) factors include workforce capacity; organisational culture and leadership; and implementation readiness. Programme (process, therapist) factors include the content, delivery and design of the intervention. To learn more about the opportunities and barriers of programme transition from secondary to primary care, we performed a pilot study with *AanTafel!*. We transferred this hospital-based treatment programme to the community setting in Veenendaal, to a district where people with diverse ethnicity live, and where the socio-economic status is generally low (the JES-district: Jan Roeckplantsoen, Engelenburg-Noord, Schrijverspark). The programme was run by local healthcare workers, and local facilities were used. During the individual meetings, a paediatrician from the hospital was present. In order to study the transition of our intervention, a process evaluation was performed.[52] Different ways to evaluate a transition process have been published. Green and Glasgow proposed a set of questions to review the applicability of research or interventions to a specific setting, subdivided in four different themes: reach and representativeness, programme or policy implementation and adaptation, outcomes for decision-making, and maintenance and institutionalisation. Saunders et al. developed constructs for a process evaluation for health programme implementation including fidelity, dose delivered, dose

received, reach, recruitment, and context. According to Koelen and Van den Ban an efficiency evaluation emphasises on the achievement of behavioural and environmental objectives.[53] In the theoretical framework we created, a combination of abovementioned models and theories was used, with the fundamental principle being the change in setting. In short, we focused on 1) intervention adaptation and implementation, 2) participant and setting features, and 3) outcomes for decision making (setting-related costs and setting-related behavioural outcomes). With regard to intervention adaptation and implementation, in order to implement an intervention in a primary care setting, the intervention should often be adapted to this new setting.[54] One of the challenges of intervention adaptation is to maintain elements that are essential for the effectiveness, but at the same time adapt the intervention to be applicable for the setting.[55] In our pilot, the content of the programme remained the same, but it was delivered by local healthcare professionals. Several meetings with the developers and implementers of *AanTafel!* were organised to train the local healthcare workers. Next, the participant recruitment process was organised differently, with the additional possibility to apply for the programme without interference of the hospital.

To improve intervention transition, healthcare professionals and a group of participants should participate in the adaptation and implementation process.

The literature and desk research we performed on transition of care in general, and more specific on the components of abovementioned theoretical framework, revealed that main advantages of transition of interventions to primary care are the use of local knowledge and facilities, the increased involvement of healthcare professionals in patient's health processes, and increased patient satisfaction.[52] Main barriers are the increased complexity of intervention organisation, difficulties in realising the transition, and the potential influence of transition on the external validity of the programme. In addition to literature and desk research, we performed qualitative research to further evaluate the transition process, by semi-structured interviews with the staff and participants of the transferred *AanTafel!* programme, and unstructured observations during the meetings of *AanTafel!* by an independent researcher. Identical conclusions with regard to the opportunities and barriers were drawn here, with the main advantage according to the participants being the decreased physical distance (between participants and setting, with the focus on decreased travelling times and expenses) and social distance (between participants and staff members, and increased social cohesion of the group). Opportunities mentioned by the staff were: the possibility to inform participants about local facilities and initiatives tailored to the child and family, and the social interaction between the group members (also outside the meetings). Barriers according to the staff were related to the transition process itself and the organisation complexity, i.e. getting used to collaborate in a new multidisciplinary team, the lack of a common location to meet, and the difficulty to find a balance between maintaining key elements of the programme and adapting the content to the specific setting (i.e. elaborating

on Ramadan in this multicultural community). At this moment, *AanTafel!* is being transferred to other local community settings, using the knowledge obtained from this process evaluation. Outcome data (BMI Z-score, quality of life) are ready to be analysed, to evaluate the effect of the transferred *AanTafel!* programme, but the sample size is still too small.
In conclusion, community-based interventions may be especially valuable to minority and low-income families, where difficulty with transportation to and from the clinic and time pressures can prevent familty participation in clinic-based interventions.

As a third relevant factor to discuss, we will more widely discuss issue of intervention duration. In literature, the duration of childhood obesity interventions and follow-up periods differs greatly. Generally, intervention duration ranges between 6 weeks and 2 years. (cochrane reviews) There is no consensus about the ideal dosage (i.e. number and length of sessions), duration, and intensity of treatments for long-term sustainability of healthy weight management.[56] Treatments considered efficacious are multicomponent interventions that include dietary and physical activity modifications and utilise behavioural strategies. Among components for weight maintenance, self-efficacy and self-regulation strategies are considered as two effective determinants.[57] However, the high clinical and methodological heterogeneity makes it difficult to compare different treatment modalities.[31] High intensity interventions with extended contact are promising, with a focus on building self-regulation skills and strategies to overcome potential barriers to weight maintenance. In Chapter 6 we presented our systematic review and meta-analysis on maintenance interventions in childhood obesity. Although there is limited high-quality data to recommend one maintenance intervention over another, pooled analysis showed that the BMI Z-score of maintenance intervention participants remained stable, whereas control participants experienced a slight increase. Thus, continued treatment does have a stabilising effect on BMI Z-score after obesity treatment. However, the optimal intensity and duration of maintenance therapy remain an area of future research. Studies are needed to examine how biological, behavioural and relational associated factors affect retention in long-term treatment programmes and treatment response, and how these factors can be influenced. In a recently published parallel-group randomised clinical trial in 172 children aged 7-12 years, Wilfley et al. found that following family-based behavioural weight loss treatment, specialised intervention content (social facilitation maintenance treatment supplemented with self-regulatory skills) enhanced children's weight outcomes.[58] Sustained monitoring and goal setting, support from the family and home environment, and healthy peer interactions explained outcome differences in this study, highlighting key treatment targets.[58] Roughly mapped, long-term behaviour change is influenced by treatment-related factors (content, technique) and participant characteristics. Several studies investigated the association of these factors and characteristics with successful weight reduction and maintenance in response to lifestyle interventions.[20,59–62] With regard to participant characteristics, psychosocial determinants have been widely discussed in a previous section of this General Discussion.

Next, psychological factors can influence the occurrence of weight (loss) maintenance. For example, weight loss maintenance is less favourable in individuals who had suffered from weight-related teasing during childhood and adolescence.[63] Finally, there is a physiological tendency toward weight regain after obesity treatment.[64] Zooming out to a more conceptual model of behaviour change, Dolan et al. presented two ways of thinking about individual behaviour and how to influence it.[65] The first is the 'cognitive' (reflective) model; starting from the presumption that we will analyse incentives offered to us, and act in ways that reflect our best interests, we can influence behaviour by 'changing minds', through conscious reflection on the surrounding environment. The second is the 'context' (automatic) model, which focuses on the more automatic processes of judgement and influence, the way we simply respond to the environment. This shifts the focus of attention away from facts and information, and towards the context within which people act. Until now, probably we have predominantly focused on the first model as a route to behaviour change in childhood obesity. However, given the earlier mentioned important influence of the physical and psychosocial environment of an obese child, we might have to focus more on the automatic and often context-based drivers of behaviour.

Involvement of children's and adolescents' peer networks in intervention efforts may be critical for promoting and maintaining positive behavioural health trajectories.

As the childhood obesity prevalence remains continuously high[66,67], despite all efforts and initiatives to tackle this global medical and public health threat, the time is there again to reconsider our treatment approaches. Kelly et al. found substantial gaps in knowledge regarding the basic behavioural, psychosocial, and biological mechanisms driving the development of severe obesity and the influence of these factors on treatment response.[68] This knowledge is indispensable to better understand the heterogeneous aetiology of obesity and explain the high degree of variability observed with interventions. In addition, future research could be directed at the effectiveness of combined pharmacological and behavioural interventions in appropriate age groups. Focus groups to study what strategies would be helpful in facilitating maintenance of weight loss post-intervention from the perspective of the child/adolescent/parent could be helpful.[69,70] Another approach to obesity management could be to identify innovative strategies from 'positive outliers'. Positive outliers are defined as individuals who have succeeded where many others have not, to change their health behaviours, reduce their body mass index, and develop resilience in the context of adverse built and social environments.[71–73] Finally, focusing action and policy at the individual, environmental and societal levels, and across multiple sectors, would help family-based programmes to be embedded in a social and fiscal environment, which would be supportive of behaviour change. Examining the effectiveness of a systems approach is a very important area of research, and needs to include the development of new evaluation methods.[74]

In Hospital Gelderse Vallei, two-year multidisciplinary maintenance programmes have been developed following each treatment programme described in the General Introduction. They are practice- and science-based using the best available evidence obtained from our systematic review and meta-analysis as described in Chapter 6. The maintenance programmes use a cognitive-behavioural approach to weight maintenance with the focus on motivation and capacity to continue weight maintenance behaviour over time. The family-based programme comprises extended education of self-regulatory skills and planning techniques and focuses on relapse prevention and social support. Challenges of establishing and sustaining new eating and activity behaviours are discussed in groups and individually. The programmes extensively use multimedia approaches to complement face-to-face contacts, for example by using a digital workbook on the internet including a secure message system that allows the interchange of individually tailored information between participants and health care professionals, and encourages adherence to the programme. Effect analysis will be performed when the sample size has become larger.

Our final comment is on intrinsic motivation. As known from literature[62], we experienced that continuous intrinsic motivation is a central concept in behavioural change, and associated with improved well-being and sustained behavioural change. Autonomy, competence, and relatedness have been found to be the most powerful influences on intrinsic motivation. Deci et al. stated that social contexts supportive of the needs for competence, autonomy, and relatedness maintain or enhance intrinsic motivation, facilitate the internalisation and integration of extrinsic motivation, and promote or strengthen aspirations or life goals that ongoingly provide satisfaction of basic needs.[75] In turn, these were associated with positive affective experiences. Events such as positive feedback that foster perceived competence tend to enhance intrinsic motivation, as it has been proposed that intrinsically motivated behaviours are based in people's needs to feel competent and self-determined. In our opinion, this important knowledge from psychological research can be admitted by healthcare workers for use in daily practice. Because eventually, in our clinic every success story started with the participants' own motivation. In the fight against childhood obesity, the lack of motivation is a first Mount Everest to be overcome.

Can we 'nudge' our patients toward healthier behaviour? Unfortunately, no we cannot. We can try to enhance intrinsic motivation, but people must feel responsible for the competent performance in order for perceived competence to have positive effects on intrinsic motivation.[75] On the other hand, and that is what I pursue, yes we can. Automatic decisions can be systematically triggered to improve health outcomes. After knowing that a particular behaviour is driven by specific type of goal, impulse, or habit, we can determine what behaviour change techniques are most effective in the specific circumstances.[76] If we thereby switch thoughts from obesity being a personal, straightforward problem to obesity as a multifaceted worldwide phenomenon, we might also be able to change our mindset from 'personal health ailment' to 'many embedded societal contexts that need to be unveiled', which open doors for 'nudging'.

In view of the prevalence, health consequences, and costs associated with childhood obesity, should we increasingly switch to prevention instead? Bleich et al. recently summarised evidence from randomised controlled trials, quasi-experimental studies, and natural experiments that test the effect of interventions focused on obesity prevention.[77] The effectiveness of school-based interventions with combined diet and physical activity components and a home element had greatest effectiveness, which suggests that they hold promise for childhood obesity prevention worldwide. More research with rigorous evaluation and consistent reporting is needed in non-school settings and in combinations of settings. The most effective efforts to prevent or reduce childhood obesity worldwide will probably require multi-setting and multicomponent approaches.

3. *Beyond first sight* – Childhood obesity, more than being chubby!

Childhood obesity is of concern because of short- and long-term health consequences.[78,79] In this General Discussion the focus is on cardiovascular obesity-related comorbidity including hypertension. Subsequently, we will briefly discuss the psychosocial correlates of childhood obesity.

Future research should focus on the link between ABPM patterns and TOD, preferably in larger prospective studies. Furthermore, establishing a standardised practice guideline for the diagnosis, evaluation, management, and follow-up of the more complex abnormal ABPM patterns (i.e. WCH, MH, abnormal dipping status) would be of additional value for clinic and research purposes. Finally, robust normative data for ABPM would be of benefit.

In our study population described in Chapter 5, 68.6% of the children and adolescents presented with at least one obesity-related comorbidity. The number of obesity-related comorbidities was calculated by the sum of the presence of disordered glucose metabolism, abnormal blood pressure, dyslipidaemia, and eGFR <80 ml/min/m2. Our prevalence is in line with prevalences observed by others[80–82], although the heterogeneity in scores limits comparability across studies.

Of the abovementioned obesity-related comorbidities, abnormal blood pressure (BP) was the most prevalent (46.0%) in our effect study. Our abnormal BP prevalence is slightly higher than reported in previous studies in overweight and obese children (20-40.2%) and summarised by l'Allemand et al.[80] This could be due to differences in study population, including the relatively small sample size of our study, but also because of the high prevalence of the white coat phenomenon in our study (4.9%: WCH; 9.8%: OBP hypertension but elevated BP on ABPM, suggesting white coat phenomenon; 7.3% elevated BP in the office and normal ABPM, classified as normal BP but one could argue to classify as WCH), as described in Chapter 4.

Office blood pressure measurement is often poorly correlated with a subject's actual ambulatory blood pressure measurement (ABPM) pattern. Routine incorporation of ABPM into the evaluation of overweight children and adolescents would permit accurate detection of the highly prevalent and often clinically 'hidden' abnormal ABPM patterns.

Obesity-related hypertension is associated with a significantly increased cardiovascular morbidity and mortality.[83] Considering these consequences of abnormal BP in childhood, careful and accurate diagnostics on HTN is indispensable. Therefore, in the study presented in Chapter 4, we evaluated ambulatory blood pressure measurement (ABPM) patterns in a population of overweight and obese children and adolescents referred to our paediatric obesity clinic, and compared these ABPM patterns with regular office BP (OBP) measurements. Nearly half of the participants showed an abnormal ABPM pattern, including (severe) ambulatory HTN, masked hypertension (MH), white coat hypertension (WCH), and elevated BP. Furthermore, a quarter of the participants showed an isolated night-time BP load >25%, and up to 40% of the participants lacked physiologic nocturnal SBP dipping. Almost one quarter of the participants with normal OBP turned out to have either elevated BP or MH on ABPM, emphasising the usefulness of ABPM as a diagnostic tool in the overweight population. The importance of performing ABPM in the obese paediatric population has also been brought forward by others.[84,85]

The high prevalence cardiometabolic risk factors in childhood obesity, even at young age, confirms the importance of early attention to weight and weight-related problems, and early start of intervention. By identifying children with multiple risk factors, healthcare workers are able to apply the most intensive intervention efforts to the children and adolescents in greatest need of risk reduction.[86]

Being overweight or obese can have significant impact on the physical and psychosocial well-being of children, affecting their everyday (quality of) life.

Next to cardiovascular obesity-related comorbidity, other obesity-related conditions deserve attention in the paediatric obesity clinic. For example, multiple sleep concerns (i.e. snoring, daytime sleepiness/fatigue/difficulty waking, mouth breathing/nasal congestion) and comorbidities including obstructive sleep apnoea (OSA) were reported in children aged 8-16 years with a BMI ≥95th centile who were undergoing polysomnography.[87] In literature, OSA has been associated with high BP independent of obesity.[88–90] Next, mental health disorders are highly prevalent in the obese paediatric population. Both physical and mental comorbidity can severely affect the psychosocial well-being of children and their daily life functioning. Understanding and assessing the health-related quality of life (HRQoL) of overweight children is essential, as it can guide future health policy and treatment optimalisation. In the study

described in Chapter 2, both parent-proxy reports and child self-reports showed a lower HRQoL in children with an increasing degree of obesity, especially in the physical domains of HRQoL. In contrast to many studies limiting themselves to reporting the parent-proxy HRQoL, our study includes self-reported HRQoL of children. The observed discordance between parent and child reports underscores the importance of using a combination of parent-proxy and child self-reports to assess HRQoL. An important obstacle in comparing parent-reported (CHQ-PF50) and child self-reported (CHQ-CF87) HRQoL is the different set-up of the CHQ questionnaires. Not all scales are built up evenly. However, the impact of this in our study was considered low, as we only matched scales with the same wording and intent.

To gain a complete picture of functioning, it is preferable to obtain HRQoL data from children's point of view supplemented with data from the parents' perspective, as children and parents may not necessarily share similar views about the impact of overweight.

A compromised HRQoL constitues a critical part of the overweight- and obesity-related psychosocial complications in children and adolescents. In addition, overweight and obesity are associated with a significant reduction in psychosocial functioning, underscoring the relevance of measuring and addressing this in the obese child. Children with chronic conditions, including obesity, are at increased risk for psychosocial maladjustment.[91,92] Higher rates of anxiety and depressive symptoms have been identified as consequences of overweight in children and adolescents.[93–97] Extremely obese adolescents and young adults who seek long-term inpatient treatment have a high lifetime prevalence for affective, anxiety, somatoform and eating disorders.[98] Higher problematic eating attitudes and behaviours were related to less improvement in eating attitudes and behaviours at follow-up.[99] Executive functions play a critical role in regulating eating behaviours and have been shown to be associated with overeating which over time can result in overweight and obesity.100 Working memory and sustained attention decrements have been shown to exist among overweight adolescent girls.[101] Furthermore, overweight children and adolescents often suffer from poor self-esteem.[102–105] In mid-adolescent girls, the influence of overweight and obesity on the development of self-image is substantial.[106,107] Body image dissatisfaction has shown to be an important mechanism linking obesity and decreased HRQoL among adolescents.[108,109] Next, a significant association between internet addiction and obesity has been reported, including a higher tendency to stay up late and more daytime sleepiness compared with non-obese adolescents.[110] Finally, bullying and social stigma are serious problems associated with childhood overweight and obesity.[111,112] Stigmatisation of people with obesity is widespread and causes harm, i.e. by dramatically impairing qualiy of life.[113] All these problems are again associated with low self-esteem, body dissatisfaction, poor psychosocial adjustment, depression, low HRQoL, and eating disorders.[102,114–119] In turn, psychosocial complications

and reduced HRQoL may influence the effect of obesity treatment: in adults, psychological quality of life is associated even with modest amounts of weight loss in the long run.[120] In children, attention and hyperactivity/impulsivity are linearly associated with reduced short- and long-term weight loss.[121,122]
In our study in Hospital Gelderse Vallei, questionnaires on behavioural and emotional problems and skills, eating behaviour, self-image and competency experience, coping, and eating disorders are filled-out at the start of treatment. These data are currently being analysed.

4. *Measuring success beyond the scale* - Outcome measures

A shift away from drastic weight-control measures toward the long-term implementation of healthful eating and physical activity behaviours is needed to treat obesity.

As mentioned in the previous section, obesity is a multifactorial problem with a large diversity of associated physical and psychosocial comorbidities. In line with this multifactorial nature, multidisciplinary and multicomponent treatment programmes are developed, in order to widely approach obesity and take into account the context in which a person is located. Effect evaluation of these treatment programmes would logically be directed at these different components as well. However, traditionally weight-related outcomes have generally been used in the effect evaluation of obesity interventions.[123–125] Nowadays, there is an increasing trend in obesity research and care from weight management to health promotion[126], from weight-based terminology to health-based terminology[127,128], and from the conventional weight focus to a broader range of outcome measures.[129] Statistically and clinically relevant improvements in physiological measures (e.g. blood pressure), health behaviours (e.g. eating and activity habits, dietary quality), and psychosocial outcomes (e.g. quality of life, self-esteem, body image) become more important than weight or BMI.[129] A good development, as improvements on physiological, health behaviour, and psychosocial measures may not necessarily go along with improvements in weight status[130,131], and focus on weight-related outcomes, dieting, and unhealthful weight-control behaviours may have unintended negative psychological consequences.[129,132]
In this paragraph we will shortly elaborate on weight-related outcomes, and subsequently switch to a few other indicators that may be of additional value for the evaluation of the effectiveness of a treatment programme.

Growing evidence suggests that outcome parameters other than the conventional weight-related measures may be of additional value in determining treatment effect.

The World Health Organization (WHO) defines obesity as a disorder of excess body fatness that is associated with increased risk of disease.[133] However, direct measurement of body fatness in children is not possible in most clinical settings. An objective candidate index

of body fatness in children and adolescents includes BMI Z-score, accounting for height, age, and sex.[134] Therefore, in our effect study described in Chapter 5 BMI Z-score has been chosen as the primary outcome measure. Our systematic review and meta-analysis (Chapter 6) was also directed at weight-related outcome measures. But what reduction in BMI Z-score is required in obese children and adolescents to improve body composition and cardiometabolic health? Ford et al. studied the impact of BMI Z-score improvement through lifestyle modification on metabolic risk and body composition in a prospective cohort study over 12 months, including 88 adolescents of median age 12.4 years (range 9.1-17.4).[135] They found that reducing BMI Z-score by ≥0.5 achieved significant improvements in important measures of body composition (mean waist circumference Z-score and body fat Z-score), while also leading to significant reductions in key metabolic risk factors (triglycerides, LDL, hsCRP). A lesser reduction of ≥0.25 improved insulin sensitivity, total cholesterol/ high-density lipoprotein ratio and BP. In other studies successful weight reduction and maintenance was defined as a reduction in BMI-SDS of ≥0.2 by the end of the follow-up period, based on definitions according to the national consensus statement of Böhler et al.: a reduction in BMI Z-score of at least −0.2 was defined as treatment success, a reduction in BMI Z-score of at least −0.5 as good treatment success.[136,137] Hunt et al. concluded that, for BMI Z-score, a reduction of between 0.5 and 0.6 is required to be relatively certain of actually reducing adiposity.[134] In Chapter 5, we considered a BMI Z-score decrease of >0.25 as clinically relevant. But in the end, it is important to realise that for a given reduction in BMI Z-score, the range of percentage fat loss is wide[134], and that BMI Z-score remains at most a proxy for body fatness.

With regard to other weight-related outcome measures, waist circumference has been proposed as a valuable marker in addition to BMI Z-score, as it can provide additional information, for example in the case of a stable BMI Z-score when fat mass decreased and fat free mass increased.[138] Distribution of body fat has been shown to be an important determinant of cardiovascular disease risk. Where BMI has been shown to be a poor proxy for central fatness[139], underestimating the prevalence of obesity in young people, waist circumference provides a simple yet effective measure of truncal adiposity in children and adolescents[140], providing the best simple measure of fat distribution since it was least affected by gender, race, and overall adiposity, comparing most favourably with dual-energy x-ray absorptiometry.[141] Therefore, waist circumference was added as outcome measure in our effect study described in Chapter 5. Skinfold measures were also taken in our study. The sum of the four (biceps, triceps, subscapular, supra-iliacal) skinfold thicknesses (SSFT) Z-score was significantly higher in children compared to adolescents (SSFT Z-score 8.0 versus 6.2, respectively) at baseline. This suggest the presence of more subcutaneous fat in children compared to adolescents, using SSFT as an estimate of body fat mass. However, it is known for years that estimating the body fatness from skinfolds in chidren and adolescents is difficult.[142] For example, estimates of body fatness may reflect the changing fat-free body composition through puberty rather than

change in actual fat content. On the other side, skinfold thickness (as a proxy for subcutaneous fat) during adolescence has been shown to be a better predictor of high body fatness during adulthood than BMI during adolescence, the latter not distinguishing between fat mass and lean body mass.[143] Analysing our data about children and adolescents separately, in both groups a significant decrease in SSFT Z-score was observed during our treatment. This effect could be relevant in light of the tracking of body fatness and the associated risk of cardiovascular morbidity. However, we need to be careful when drawing conclusions from these data, as the skinfold thickness measurements were difficult to perform in our population. As an example of this, a few young children were not cooperative to the measurements because of fear for the skinfold caliper, which led to missing values in some cases. In addition, a number of adolescents presented with skinfolds >40 mm, which is more than the limit of the skinfold caliper. Therefore, skinfold measurements were not included as outcome parameter in our study described in Chapter 5.

Inclusion of HRQoL assessments in regular patient evaluations and in future research, preferably a combination of generic and disease-specific questionnaires and both parent and self-reports, could guide the development of broad healthcare policies that recognise the bio-psychosocial impact of the growing obesity epidemic.

Beyond the conventional weight focus, as a psychosocial outcome we have studied QoL (Chapter 2). Overweight and obese children have low scores for several HRQoL domains, as has been outlined in Chapter 2. In literature, improvements in QoL have been described to occur even in children and adolescents who increased or only slightly decreased their BMI Z-score during treatment.[130,144] These improvements of HRQoL during obesity treatment, which are not exclusively attributable to reductions in BMI Z-score, confirm the value of adding HRQoL parameters as intervention outcomes. The other way around, as far as we know, there are no studies that evaluated the effect of HRQoL on treatment outcomes in childhood obesity. One could speculate that a decreased HRQoL can cause people to seek healthcare, or initiate behavioural change that might lead to a healthier BMI, feeling the urge to attack the problem of overweight. People might be more motivated to improve their lifestyle. Improvement in HRQoL might subsequently serve as a first step in treatment success, ensuring an increase in self-confidence that stimulates further treatment enhancement and ultimately causes the desired effect on weight-related outcomes.

Next to weight-related and psychosocial outcomes, change in health behaviours can be used as measures of treatment success. For example, physical activity, sedentary behaviour and healthy eating behaviours can be evaluated. These outcomes are relevant to the patient, not at least because they not only contribute to obesity but also have important independent health implications.[145]

Researchers should aim to reach a consensus for the best way to evaluate the impact of obesity and weight loss on HRQoL in future studies, to facilitate comparison of results across studies.

In our study, three day nutritional diaries were collected to study dietary quality including daily consumption of fruits and vegetables, eating breakfast, and consumption of sweets and sweetened beverages: at start of the treatment, after the intensive phase of treatment, and at the end of treatment. In addition, questionnaires on eating behaviour were filled out at these time points (Child Eating Behaviour Questionnaire [CEBQ], Dutch Eating Behaviour Questionnaire [DEBQ]). In their study evaluating the effect of *AanTafel!*, Van Hoek et al. showed that the median energy intake per day significantly decreased (-300 kcal). Also the intake of sugar-containing sweet drinks decreased (from 2.5 drinks/day to 1.2 drinks/day). The use of breakfast increased from 82% of the children to 100%.
Physical activity (PA) was measured using the tri-axial accelerometer Actigraph (GT3x) on four consecutive days, also at the three abovementioned time points. Children were instructed to record physical activity and wearing time, to make it possible to link accelerometer data with clinical data. In adults, longitudinal exercise training studies demonstrated a long-term anti-inflammatory effect.[146] Additionally, in adults it has been hypothesised that physical activity has a BMI-independent positive effect on HRQoL, as outlined in Chapter 2. Generally, in children and adolescents the role of PA in decreasing adverse health outcomes independently of BMI remains poorly studied. Results of a few studies point to the notable role of physical activity in improving HRQoL, even without a substantial change in body composition, and thus the importance of attention to physical fitness as part of obesity treatment. It is known from literature that during adolescence PA declines in the general population.[147] Therefore, interventions that attempt to attenuate the PA decline, even without an increase in PA levels, might be considered as effective. Accelerometer data of our study population showed a non-significant increase in median counts per minute during treatment (from 241 counts/min at baseline to 258 counts/minute at the end of treatment).[148] In general, the evaluation of the abovementioned health behaviour outcomes is significantly hampered by missing or incomplete data, which is unfortunately a common reported problem in this kind of research.

Finally, we will shortly elaborate on physiological measures. In a previous section of this General Discussion, we have already mentioned cardiometabolic risk and obesity-related comorbidities, the more or less 'bedside' physiologic measures that can be followed in time and co-determine treatment effect. Instead, we would like to focus on the 'bench' part of this thesis, and more specifically on low-grade inflammation.
Low-grade inflammation has been addressed to play an important role in the relationship between obesity and cardiovascular risk factors.[149,150] Over the last years, the perception of adipose tissue as an inert energy storage tissue has evolved to that of an active metabolic and

It has been shown that visceral adipose tissue is a highly active endocrine organ that secretes numerous adipokines that have both pro- and anti-inflammatory properties contributing to inflammation, appetite regulation, insulin resistance, and cardiovascular risk.

endocrine organ.[151–153] Adipose tissue releases a cluster of bioactive peptides, known as adipokines, which act at both the local and the systemic level and induce a state of chronic low-grade systemic inflammation.[154] This low-grade inflammation process contributes to systemic metabolic dysfunction and is associated with the development of obesity-linked disorders, including glucose intolerance, hyperlipidaemia, and hypertension.[155–157] Together, these conditions are directly linked to the development of cardiovascular disease.[158–161] Both in adults and in children, lifestyle interventions may cause reductions in systemic inflammation[162–164], and therefore these interventions may be valuable in lowering the risk of obesity-related cardiovascular disease. In addition to their role in inflammation, metabolism, and cardiovascular disease, adipokines have profound effects on appetite and energy balance, and are involved in the regulation of neuroendocrine and immune function. As it is now believed that adipokines released from adipose tissue act in a paracrine and systemic manner in the body, 'bench' research has been directed at the molecular interaction of these adipokines with target cells, i.e. via adipokine receptors. In Chapter 3 we have studied the differential impact of circulating adipokine levels and adipokine receptor expression on adipokine signalling in childhood obesity. Our finding that circulating leukocyte subsets showed distinct adipokine receptor expression profiles may partly explain the differential impact of adipokines on leukocyte subsets. This provides an exciting starting point for future studies to the role of adipokine receptors in leukocyte differentiation and function.

In the near future, the role of adipokines in the pathophysiology of diabetes and atherosclerosis should remain a prominent focus of research, including the therapeutic options that could arise from the manipulation of the signalling pathways both in humans and in translational models.[169] The application of network analysis has shown to be helpful in generating hypotheses that not only test the efficacy of established novel pharmaceuticals, but the benefits of structured lifestyle change as well.[166]

But how does this 'bench' research relate to our daily clinic?

When adipose tissue inflammation and dysfunction are established, adipokine secretion is significantly changed toward a diabetogenic, pro-inflammatory and atherogenic pattern.

Many studies and reviews have been published that focus on the link between obesity, inflammation and metabolic dysfunction.[165–168]

Studying the biology of adipose tissue derived cytokines and adipokines in human represents a first step, as to date, although in vitro and animal models strongly suggest a critical role of adipokines in atherosclerosis, the picture is less clear when the impact of adipokines as a predictive marker or player in CVD is investigated in humans.[158] It is difficult to dissect out

whether adipokines take part in the evolution of vascular remodelling and atherosclerotic process or whether simply mark the progression of the disease. For example, changes in leptin and adiponectin levels might not directly reflect in deteriorated or improved cardiometabolic profile. The emerging concept of 'adipokine-resistance', consisting in the disruption of the cell signalling pathway beyond adipokines receptor activation could help in explaining this.[158]

In conclusion, with regard to outcome measures of obesity treatment, the traditionally used weight-related outcomes are important, but even more relevant are clinically relevant improvements in physiological measures, health behaviours, and psychosocial outcomes. In this childhood obesity epidemic, we have to search for outcomes that are valuable to the individual patient and his or her environment. Recently, Mechanick et al. proposed a new diagnostic term for obesity that explicitly identifies a chronic disease, alludes to a precise pathophysiologic basis, and avoids the stigmata and confusion related to the differential use and multiple meanings of the term 'obesity': Adiposity-Based Chronic Disease (ABCD).[170] In line with this new diagnostic term, interventions should focus on health, not weight, and should be referred to as 'health promotion' and not marketed as 'obesity prevention/ treatment'. Outcomes measured in obesity research need to reflect overall health and wellbeing of participants, truly measuring the health of the individual in a person-centred care approach.

In addition to these patient-related outcome measures, we would like to add research-related outcome measures. As widely enumerated above, 'bench' research is indispensable to the broadening of our knowledge about the pathophysiological basis of obesity and obesity-related comorbidity, and the development of improved or new therapeutic approaches. Ultimately, these research-related outcome measures will be translated into knowledge relevant for daily clinical practice.

5. *Where research meets practice* – Final remarks on study design

In the final part of this dissertation we would like to comment more generally on performing research in the field of obesity.

Data collection for the studies presented in this thesis was performed in the longitudinal observational Pro- and Anti-Inflammatory Marker (PAIM)-study. Children and adolescents with overweight or obesity were enrolled in this study. Participants were referred by their general practitioner, youth health care physician, or paediatrician to the paediatric outpatient clinic of Hospital Gelderse Vallei (Ede, the Netherlands). All were offered a multidisciplinary obesity treatment programme as described in the General Introduction.

One of the main aims of our study was to evaluate the effect of obesity treatment at our hospital. We performed our study in daily clinical practice, in other words in a 'real world' setting. There have been many difficulties of translating intervention effectiveness in controlled

RCT's are especially adequate for efficacy studies, and less suitable for effectiveness studies evaluaitng the effect of interventions in real-life settings.

settings to real world contexts.[171] The high prevalence of lifestyle-related health issues calls for urgent, society-wide actions by health practitioners and policy makers, often in the absence of complete or definitive research evidence applicable to all segments of the population. Generally, researchers pay more attention to the internal validity, by providing insight into what is effective (preferably using the 'gold standard' RCT) but not into how it can be made effective in a real-world setting, than the external validity, i.e. the applicability and generalisability of the results to other populations and settings.[172] This results in a major gap in our understanding of how to implement and sustain intervention programmes in the real world, and for us was one of the reasons to perform a study as close as possible related to common clinical practice. The RCT is especially adequate for efficacy studies, designed in order to make valid inferences about the intervention and its effect. However, they are less suitable for effectiveness studies[172], which are aimed at evaluating the effect of interventions in real-life settings and require designs in which the internal and external validity are more equally balanced.[173] In the PAIM-study, a one-group pre-test post-test design was used to assess the observed change in the situation after the intervention compared to the situation before the intervention. The lack of a control group, due to financial- and time-related reasons but also because we deemed it unethically to withhold patients from our best-practice and best-evidence based treatment, makes this design vulnerable. The only thing we can conclude from the effect analysis presented in Chapter 5, is that there is a difference between the situation before and after, but we are not sure whether this change is being caused by the intervention.[174] However, attention should be focused not only on the improvement of the (scientific) quality of the information, but also on its relevance for public health policy and its translation into relevance for the local context.[173] In our opinion, in obesity research it is essential to move thoughts from a scientifically relevant problem (i.e. explaining problems and adding to the body of knowledge based on existing theory) to practically relevant problem (i.e. corresponding to the public's or patient's requests or needs due to problems that are modifiable and tractable)[128,172], to mind the gap between what practice needs and what is delivered by science. The studies presented in this thesis are examples of clinically relevant problems translated into research projects and questions, and connecting 'bench' to 'bedside'.

THE DAY AFTER – IMPLICATIONS FOR CLINICAL PRACTICE

Many implications for clinical practice can be extracted from the work presented in this thesis. In the previous text boxes, those especially important or relevant to this thesis, or main factors encountered during the conduct of the studies, have been presented. They are summarised in Table 2.

Table 2. Implications for clinical practice.

In daily clinic	
	Overweight and obesity are sensitive issues to address with patients during any visit, but essential in the overall health of our paediatric patients.
	Childhood overweight is often not recognised by children and their parents. Or many other priorities exist behind a families' front door that may divert the attention from a healthy lifestyle and the presence of overweight. Generally, important steps have to be taken before someone is receptive to treatment.
Consequences of childhood obesity including obesity-related comorbidities	
	Office blood pressure measurement is often poorly correlated with a subject's actual ambulatory blood pressure measurement (ABPM) pattern. Routine incorporation of ABPM into the evaluation of overweight children and adolescents would permit accurate detection of the highly prevalent and often clinically 'hidden' abnormal ABPM patterns.
	Being overweight or obese can have significant impact on the physical and psychosocial well-being of children, affecting their everyday (quality of) life.
	To gain a complete picture of functioning, it is preferable to obtain HRQoL data from children's point of view supplemented with data from the parents' perspective, as children and parents may not necessarily share similar views about the impact of overweight.
	It has been shown that visceral adipose tissue is a highly active endocrine organ that secretes numerous adipokines that have both pro- and anti-inflammatory properties contributing to inflammation, appetite regulation, insulin resistance, and cardiovascular risk.
Obesity treatment	
	RCT's are especially adequate for efficacy studies, and less suitable for effectiveness studies evaluating the effect of interventions in real-life settings.
	Increasing the effort to engage patients and families at the first visit, to assess initial expectations, and to identify and address barriers to follow-up may help to tailor the treatment to the families' needs.
	Involvement of children's and adolescents' peer networks in intervention efforts may be critical for promoting and maintaining positive behavioural health trajectories.
	A shift away from drastic weight-control measures toward the long-term implementation of healthful eating and physical activity behaviours is needed to treat obesity.
	Growing evidence suggests that outcome parameters other than the conventional weight-related measures may be of additional value in determining treatment effect.
	Transfer from a clinic-based intervention to the community setting may be helpful in overcoming barriers to engagement in obesity treatment.
	To improve intervention transition, healthcare professionals and a group of participants should participate in the adaptation and implementation process.

WHICH DOORS SHOULD BE OPENED? – DIRECTIONS FOR FUTURE RESEARCH

A few recommendations for future research that relate to studies presented in PART I of this thesis have already been mentioned in the text boxes. They are summarised in Table 3. In this paragraph I would like to mention a few additional recommendations that can serve as food for thought in the development of future studies. These recommendations specifically relate to PART II of this thesis, including this General Discussion, supplemented with some general thoughts about the field of childhood obesity. One of the common denominators of these directions for future research is: *Obesity is actually the only common denominator of our participants*.

Table 3. Directions for future research related to studies presented in PART I of this thesis.

Health-related quality of life	
	- Inclusion of HRQoL assessments in regular patient evaluations and in future research, preferably a combination of generic and disease-specific questionnaires and both parent and self-reports, could guide the development of broad healthcare policies that recognize the biopsychosocial impact of the growing obesity epidemic.
	- Researchers should aim to reach a consensus for the best way to evaluate the impact of obesity and/or weight loss on HRQoL in future studies, to facilitate comparison of results across studies.
Adipokine receptor expression	
	- In the near future, the role of adipokines in the pathophysiology of diabetes and atherosclerosis should remain a prominent focus of research, including the therapeutic options that could arise from the manipulation of the signalling pathways both in humans and in translational models.[169] The application of network analysis has shown to be helpful in generating hypotheses that not only test the efficacy of established novel pharmaceuticals, but the benefits of structured lifestyle change as well.[166]
Blood pressure measurement in childhood obesity	
	- Future research should focus on the link between ABPM patterns and TOD, preferably in larger prospective studies.
	- Establishing a standardised practice guideline for the diagnosis, evaluation, management, and follow-up of the more complex abnormal ABPM patterns (i.e. WCH, MH, abnormal dipping status) would be of additional value for clinic and research purposes.
	- Robust normative data for ABPM would be of benefit.

ABPM, ambulatory blood pressure monitoring; HRQoL, health-related quality of life; MH, masked hypertension; TOD, target organ disease; WCH, white coat hypertension

In the future, it would be valuable to broaden our knowledge regarding the basic behavioural, psychosocial, and biological mechanisms driving the development of severe obesity and the influence of these factors on treatment response, with the aim to better understand the heterogeneous aetiology of obesity and explain the high degree of variability observed with interventions. Next, it would be of added value to study the drivers of participation in obesity treatment and treatment adherence, including the facilitators and barriers to the achievement of healthy lifestyle goals, thereby considering the patient population that seeks help. Important factors to take into account in this are the frequently observed misperception

of a child's weight status, and the existence of divergent problems (i.e. conflicting family priorities, environmental obstacles) behind several families' front door that claim priority and causes people to be less receptive to see the obesity problem and subsequently seek and commence treatment. Additionally, with the aim to develop tailored treatment strategies, a better understanding of individual differences in genetic endowment, clinical, metabolic, psychological, and behavioural phenotypes, and response to environmental exposures would be helpful. How do these factors affect retention in long-term treatment programmes and treatment response? And how can these factors be influenced?

With regard to treatment content, it would be valuable to study the involvement of children's and adolescents' peer networks in intervention efforts, as they may be critical for promoting and maintaining positive behavioural health trajectories. Furthermore, we need to investigate how to optimise the involvement of parents and family members in treatment in different age groups, especially when it comes to long-term weight maintenance. Moreover, knowledge is lacking on the optimal intensity and duration of (maintenance) therapy. Next, future research may elaborate on the value of intervention setting in overcoming family and environmental barriers that exist to engagement in obesity treatment. The effectiveness, feasibility of widespread implementation, and sustainability of interventions need to be evaluated in various settings. In addition, studies could be directed at the use of technology to enhance treatment effect and programme engagement, as until now the effectiveness of on distance technologies in paediatric programmes remains equivocal. Finally, the effectiveness of combined pharmacological and behavioural interventions in severely obese children in appropriate age groups should be investigated, as well as the potential risks or harms associated with these interventions.

In the evaluation of treatment effectiveness, I think we have to focus on clinically relevant improvements in physiological measures (e.g. blood pressure), health behaviours (e.g. eating and activity habits, dietary quality), and psychosocial outcomes (e.g. quality of life, self-esteem, body image), in addition to the conventional weight outcomes.

But how can this be accomplished?

We must be aware of the gap between what practice needs and what is delivered by science. Let us search for the topics where science meets practice, i.e. by:

Moving thoughts from a scientifically relevant problem (i.e. explaining problems and adding to the body of knowledge based on existing theory) to practically relevant problem (i.e. corresponding to the public's or patient's requests or needs due to problems that are modifiable and tractable).

Focusing the attention not only on the improvement of the (scientific) quality of the information, but also on its relevance for public health policy and its translation into relevance for the local context.

Aiming at action and policy at the individual, environmental and societal levels, and across multiple sectors, involving appropriate stakeholders from the first minute, as this would help family-based programmes to be embedded in a social and fiscal environment, which would be supportive of behaviour change.
In addition, I am in the opinion that we can learn more from the obese paediatric population, by focusing on specific patient subpopulations:
– Map the non-treatment seeking population
– Perform focus groups to study what strategies would be helpful from the perspective of the child/adolescent/parent
– Extensively compare treatment responders with non-responders
– Identify innovative strategies from 'positive outliers', defined as individuals who have succeeded where many others have not, to change their health behaviours, reduce their body mass index, and develop resilience in the context of adverse built and social environments.

Finally, I would like to advocate for a trend towards network medicine: from multidisciplinary teams on islands in clinic and laboratory, to more extensive collaboration in large networks with coordinated initiatives and shared knowledge, involving all stakeholders in the field.

BEHIND THE DOORS OF THE EPIDEMIC – OVERALL CONCLUSION

We aimed to dive into a few important childhood obesity-related issues encountered in daily clinical practice.
First, we focused on consequences of childhood obesity. We showed that children with an increasing degree of obesity present with a lower HRQoL, especially in the physical domains. Significant differences exist between parent-proxy reports and child self-reports. Next, we demonstrated that circulating leukocyte subsets showed distinct adipokine receptor expression profiles, and that leukocyte subset numbers and adipokine receptor expression profiles were largely similar in obese children and controls. In another study, we found that office blood pressure measurement is poorly correlated with a subject's actual ABPM pattern. A high prevalence of abnormal ABPM patterns was detected, as well as a high prevalence of abnormal circadian variation.
Second, we elaborated on the treatment of childhood obesity. Childhood obesity treatment in Hospital Gelderse Vallei improved both anthropometric and metabolic measures in a population of overweight and obese children and adolescents. From our systematic review and meta-analysis summarising the existing knowledge on programmes and initiatives aimed at long-term maintenance of a healthy or reduces weight, we concluded that the BMI Z-score of maintenance intervention participants remained stable, whereas control participants experienced a slight increase. No differences were observed regarding intensity and duration

of therapy. A slight preference for 'face-to-face' versus 'on distance' interventions was shown. Finally, we demonstrated that there are many aspects to consider when performing research in the field of childhood obesity. The obese childhood population that seeks help and that we encounter in our clinic is a selected group of patients that might not exactly reflect the general obese paediatric population. Additionally, we showed that a complex set of factors from multiple contexts (as summarised in the ecological model) interact with each other to place a child at risk of overweight, and at least partly determine the effect of obesity treatment. Obesity is actually the only common denominator of our participants. All other variables, including child-, family- and environmental-related factors and associated comorbidities, diverge between the individual patients. Childhood obesity treatment has to comprise all these variables, and we have discussed this in relation to intervention format, design, and duration. We elaborated on the increasing trend in obesity research and care from weight management to health promotion, from weight-based terminology to health-based terminology, from a conventional weight focus to a broader range of outcome measures including physiological, health behavioural, and psychosocial outcomes. Finally, we commented more generally on performing research in the field of obesity, by discussing study design and the gap between what practice needs and what is delivered by science.

In conclusion, childhood obesity remains a challenging subject, from different points of view, both for research and in clinical practice. Although a few doors have been opened in this dissertation, behind the doors of the epidemic many topics remain that need careful attention in future research and practice.

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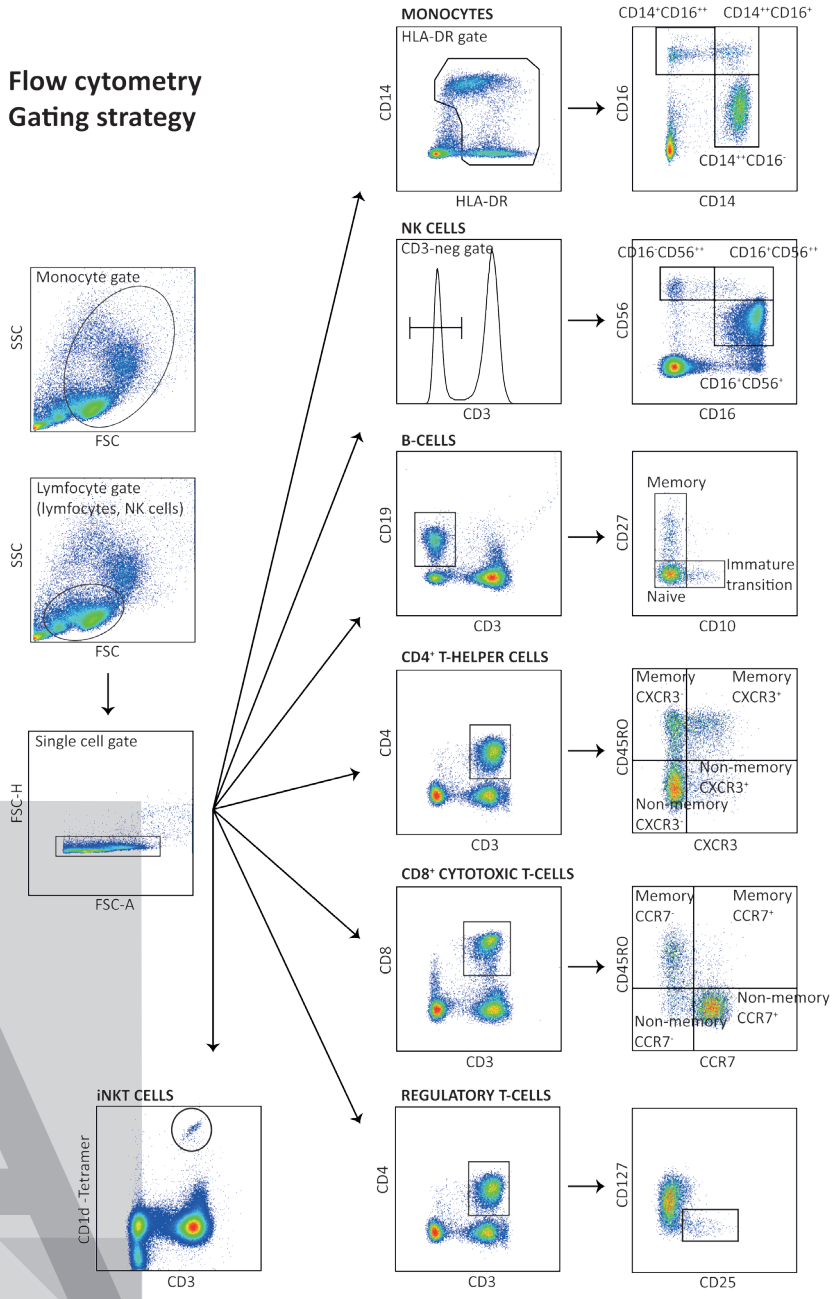
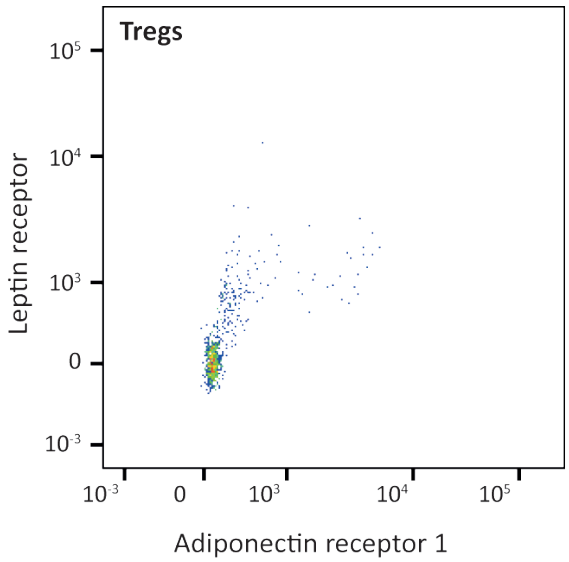
APPENDIX A

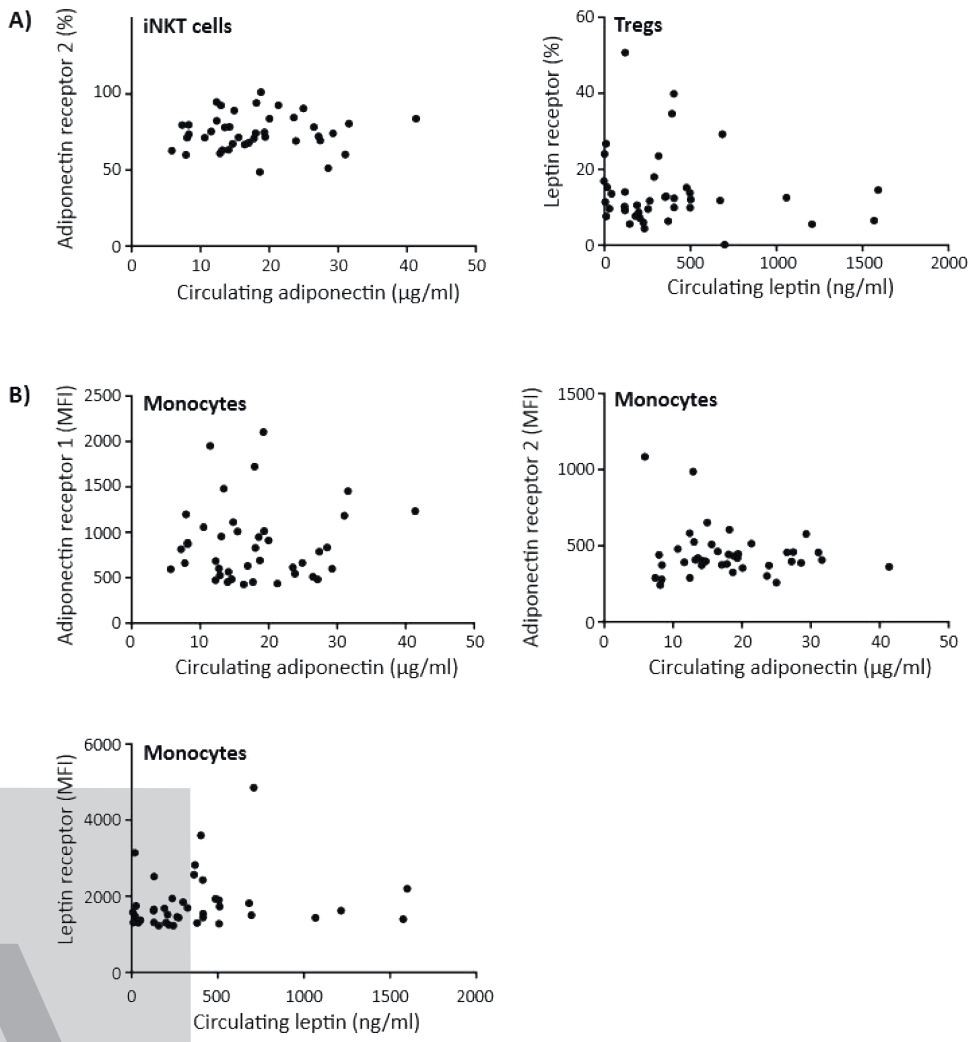
Additional information Chapter 3



S1 Figure. Gating strategy of the leukocyte subsets.
First, forward scatter (FSC) and sideward scatter (SSC) profiles were used to roughly distinguish monocytes and lymphocytes/NK cells. Second, doublet cells were excluded using FSC-Area (FSC-A) and FSC-Height (FSC-H) gating. Finally, leukocyte subsets were gated on their marker expression.



S2 Figure. Combined adiponectin receptor 1 and leptin receptor expression on regulatory T-cells (Tregs). Focusing on the CD25hiCD127lowCD4+ T-cells (regulatory T-cells), the adiponectin receptor 1-positive subset also expresses the leptin receptor.



S3 Figure. Circulating adipokine levels and adipokine receptor expression. A) Circulating adiponectin levels versus percentage of adiponectin receptor 2 expressing iNKT cells (Pearson's correlation coefficient 0.048, p = 0.764), and circulating leptin levels versus percentage of leptin receptor expressing regulatory T-cells (Pearson's correlation coefficient -0.130, P=0.416). B) Circulating adiponectin levels versus median fluorescence intensity (MFI) of adiponectin receptor 1 and 2 expression (Pearson's correlation coefficient AdipoR1 0.052, P=0.746; AdipoR2 -0.172, P=0.284), and circulating leptin levels versus median fluorescence intensity (MFI) of leptin receptor expression (Pearson's correlation coefficient 0.126, P=0.431).

S1 Table. Adiponectin receptor 1 expression.

	Lean controls	Obese-pre	Obese-post
Innate immunity			
Monocytes (total)	583 (465-769)*#	931 (582-1306)*	866 (656-1104)#
CD14++	405 (354-522)	403 (342-479)	433 (377-461)
CD14++CD16++	737 (606-1036)	935 (738-1164)	835 (745-1063)
CD14+CD16++	812 (549-1456)*	1317 (1014-2379)*	1232 (968-1885)
Natural Killer cells (CD16+CD56+)	335 (262-453)	399 (321-510)	406 (336-517)
CD16+CD56++	297 (261-396)	322 (280-366)	328 (293-390)
CD16-CD56++	225 (220-270)	236 (207-266)	215 (211-265)
Bridging immunity			
Natural Killer T cells	236 (221-395)	317 (239-333)	273 (241-366)
Adaptive immunity			
B cells			
Naive (CD10-CD27-)	249 (230-279)	242 (225-264)	236 (231-264)
Memory (CD10-CD27+)	228 (219-234)#	224 (218-232)	217 (215-225)#
Immature transition (CD10+CD27+)	224 (197-251)#	217 (202-240)	249 (224-496)#
CD4+ T helper cells			
CD45RO- CXCR3-	255 (242-348)	278 (251-381)	258 (245-304)
CD45RO- CXCR3+	297 (285-383)	339 (320-457)$	308 (299-339)$
CD45RO+ CXCR3-	259 (241-332)	245 (234-370)	249 (239-314)
CD45RO+ CXCR3+	279 (263-347)	299 (262-382)	286 (262-315)
CD8+ cytotoxic T cells			
CD45RO- CCR7-	230 (228-233)#	244 (225-251)	236 (228-252)#
CD45RO- CCR7+	246 (230-306)	241 (224-356)	241 (231-231)
CD45RO+ CCR7-	225 (224-228)	229 (222-244)	229 (225-233)
CD45RO+ CCR7+	279 (273-365)	354 (255-426)	310 (275-375)
Regulatory T cells (CD25+CD127-)	282 (240-314)	248 (210-277)	257 (224-271)

Median Fluorescence Intensity (MFI) of adiponectin receptor 1 on leukocyte subsets of lean controls compared to obese children pre-lifestyle intervention (pre) and post-lifestyle intervention (post). Data are presented as median (interquartile range). * P<0.05 for lean controls compared to obese-pre. # P<0.05 for lean controls versus obese-post. $ P<0.05 for obese-pre compared to obese-post.

S2 Table. Adiponectin receptor 2 expression.

	Lean controls	Obese-pre	Obese-post
Innate immunity			
Monocytes (total)	460 (401-518)	410 (376-535)	392 (326-434)
CD14++	455 (394-515)#	405 (369-515)	378 (321-419)#
CD14++CD16++	641 (499-752)	507 (433-1100)	491 (414-648
CD14+CD16++	487 (417-553)	445 (381-561)	421 (372-482)
Natural Killer cells (CD16+CD56+)	370 (358-417)	351 (296-437)	352 (291-377)
CD16+CD56++	690 (617-858)	690 (579-753)	631 (548-726)
CD16-CD56++	752 (695-941)	705 (613-778)	668 (594-771)
Bridging immunity			
Natural Killer T cells	378 (376-602)	399 (354-418)	392 (353-419)
Adaptive immunity			
B cells			
Naive (CD10-CD27-)	306 (286-318)#	294 (281-310)	290 (268-299)#
Memory (CD10-CD27+)	308 (289-317)	301 (282-313)	305 (271-312)
Immature transition (CD10+CD27+)	444 (389-474)	454 (395-504)	423 (357-454)
CD4+ T helper cells			
CD45RO- CXCR3-	294 (282-345)	297 (273-346)	283 (278-324)
CD45RO- CXCR3+	348 (328-409)	345 (314-467)	341 (308-365)
CD45RO+ CXCR3-	308 (293-347)	304 (280-360)	298 (282-356)
CD45RO+ CXCR3+	333 (305-448)	332 (292-397)	331 (291-391)
CD8+ cytotoxic T cells			
CD45RO- CCR7-	293 (278-304)	291 (279 319)	291 (286-317)
CD45RO- CCR7+	331 (285-901)	321 (281-530	314 (290-698)
CD45RO+ CCR7-	290 (275-314)	295 (280 -318)	291 (286-308)
CD45RO+ CCR7+	535 (471-1086)	600 (393-769)	833 (505-964)
Regulatory T cells (CD25+CD127-)	297 (286-617)	297 (263-419)	320 (280-437)

Median Fluorescence Intensity (MFI) of adiponectin receptor 2 on leukocyte subsets of lean controls compared to obese children pre-lifestyle intervention (pre) and post-lifestyle intervention (post). Data are presented as median (interquartile range). * P<0.05 for lean controls compared to obese-pre. # P<0.05 for lean controls versus obese-post. $ P<0.05 for obese-pre compared to obese-post.

S3 Table. Leptin receptor expression.

	Lean controls	Obese-pre	Obese-post
Innate immunity			
Monocytes (total)	1451 (1317-1699)	1670 (1439-2326)	1705 (1454-1932)
CD14++	1467 (1302-1699)	1677 (1405-2451)	1532 (1393-1872)
CD14++CD16++	2236 (1715-2433)	2524 (1827-4133)	2227 (2008-2893)
CD14+CD16++	1188 (1141-1529)	1402 (1139-1999)	1467 (1467-1971)
Natural Killer cells (CD16+CD56+)	387 (370-416)	384 (362-426)	388 (367-416)
CD16+CD56++	380 (350-409)	365 (342-381)	374 (356-403)
CD16-CD56++	376 (356-403)	377 (365-401)	378 (350-424)
Bridging immunity			
Natural Killer T cells	483 (403-774)	577 (462-774)$	440 (415-603)$
Adaptive immunity			
B cells			
Naive (CD10-CD27-)	465 (445-487)	467 (449-479)	460 (434-480)
Memory (CD10-CD27+)	521 (502-546)	527 (492-560)	507 (481-523)
Immature transition (CD10+CD27+)	470 (447-500)	477 (451-529)	468 (449-516)
CD4+ T helper cells			
CD45RO- CXCR3-	417 (409-487)	410 (405-504)	419 (407-430)
CD45RO- CXCR3+	597 (562-737)	646 (562-846)	582 (571-648)
CD45RO+ CXCR3-	421 (406-441)	426 (412-529)	424 (409-451)
CD45RO+ CXCR3+	504 (444-727)	527 (437-632)	577 (502-607)
CD8+ cytotoxic T cells			
CD45RO- CCR7-	410 (398-424)	402 (388 -464)	414 (403-445)
CD45RO- CCR7+	463 (424-624)	457 (415-691)	443 (432-537)
CD45RO+ CCR7-	412 (395-470)	429 (400-481)	436 (417-464)
CD45RO+ CCR7+	676 (583-753)	886 (545-1063)	737 (631-1006)
Regulatory T cells (CD25+CD127-)	410 (401-494)	426 (410-489)	451 (429 -566)

Median Fluorescence Intensity (MFI) of leptin receptor on leukocyte subsets of lean controls compared to obese children pre-lifestyle intervention (pre) and post-lifestyle intervention (post). Data are presented as median (interquartile range).
* P<0.05 for lean controls compared to obese-pre. # P<0.05 for lean controls versus obese-post. $ P<0.05 for obese-pre compared to obese-post.

APPENDIX B

Additional information Chapter 5

S1 Table. Baseline characteristics of study participants separately for boys and girls.

	Boys (n=46)	Girls (n=91)	P value
Age	9.7 (4.1)	9.3 (4.4)	0.53
BMI	26.3 (4.9)	26.3 (6.4)	0.57
BMI Z-score	3.6 (0.9)	3.1 (0.7)	0.002
WC*	89.0 (19.5)	87.5 (19.9)	0.65
WC Z-score*	3.1 (0.7)	3.1 (0.6)	0.88
Overweight / obesity			0.03
Normal weight	1 (2.2)	0 (0.0)	
Overweight	3 (6.5)	17 (18.7)	
Obesity grade 1	17 (37.0)	35 (38.5)	
Obesity grade 2	12 (26.1)	29 (31.9)	
Obesity grade 3	13 (28.3)	10 (11.0)	
Excess adiposity*	44 (95.7)	85 (96.6)	0.79
Casual blood pressure			
Normal BP	27 (58.7)	47 (51.6)	0.43
Elevated BP	10 (21.7)	17 (18.7)	0.67
Hypertension	9 (19.6)	27 (29.7)	0.20
Glucose metabolism**			
Prediabetes	6 (14.0)	7 (8.0)	0.29
Provisional diagnosis of diabetes	0 (0.0)	2 (2.3)	0.32
Lipid profile**			
Elevated TC	2 (4.7)	4 (4.6)	0.99
Elevated LDL-C	2 (4.7)	3 (3.4)	0.74
HDL-C below cut-off	7 (16.3)	8 (9.2)	0.23
Elevated TG	3 (7.0)	8 (9.2)	0.67
MetS***	4 (9.1)	14 (16.3)	0.26
Components of MetS†			0.28
0	16 (36.4)	36 (40.4)	
1	24 (54.5)	39 (43.8)	
2	2 (4.5)	12 (13.5)	
3	1 (2.3)	2 (2.2)	
4	1 (2.3)	0 (0.0)	

Number (%), except for age, BMI, BMI Z-score, WC, WC Z-score (mean, SD)

* Girls: n=88

** Boys: n=43; Girls: n=87

*** Boys: n=44; Girls: n=86

† Boys: n=44; Girls: n=89

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TC, total cholesterol; TG, triglycerides; WC, waist circumference

APPENDIX C

Additional information Chapter 6A

ADDITIONAL FILE 1

Search strategy. Detailed description of search strategy using the following electronic databases: PubMed, Embase, Cochrane Library, CINAHL, Web of Science, PsycINFO, Scopus, and SocINDEX.

Pubmed

Filters activated: Dutch, English, Spanish, French, German.

#1 "Overweight"[Mesh] OR "Obesity"[Mesh:noexp] OR "Obesity, Morbid"[Mesh] OR "Obesity, Abdominal"[Mesh] OR "Adiposity"[Mesh:noexp] OR overweight[Title/Abstract] OR obesity[Title/Abstract] OR obese[Title/Abstract] OR obesitas[Title/Abstract] OR adiposity[Title/Abstract] OR adipositas[Title/Abstract] OR excessive weight[Title/Abstract]

#2 child[Title/Abstract] OR children[Title/Abstract] OR childhood[Title/Abstract] OR adolescent[Title/Abstract] OR adolescents[Title/Abstract] OR teen[Title/Abstract] OR teens[Title/Abstract] OR teenager[Title/Abstract] OR teenagers[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract] OR adolescence[Title/Abstract] OR youngster[Title/Abstract] OR youngsters[Title/Abstract] OR schoolchildren[Title/Abstract] OR pediatric[Title/Abstract] OR pediatrics[Title/Abstract] OR paediatric[Title/Abstract] OR paediatrics[Title/Abstract] OR girl[Title/Abstract] OR girls[Title/Abstract] OR boy[Title/Abstract] OR boys[Title/Abstract] OR "Child"[Mesh] OR "Adolescent"[Mesh] OR "Minors"[Mesh]

#3 #1 AND #2

#4 therapy[Title/Abstract] OR therapies[Title/Abstract] OR treatment[Title/Abstract] OR treatments[Title/Abstract] OR intervention[Title/Abstract] OR interventions[Title/Abstract] OR program[Title/Abstract] OR programs[Title/Abstract] OR programme[Title/Abstract] OR programmes[Title/Abstract] OR strategy[Title/Abstract] OR strategies[Title/Abstract] OR care[Title/Abstract] OR approach[Title/Abstract] OR approaches[Title/Abstract] OR "therapy"[Subheading]

#5 maintenance[Title/Abstract] OR follow-up[Title/Abstract] OR followup[Title/Abstract]

#6 #4 AND #5

#7 post-treatment[Title/Abstract] OR posttreatment[Title/Abstract] OR aftercare[Title/Abstract]

#8 #6 OR #7

#9 #3 AND #8

#10 #9 NOT "Animals"[Mesh]) NOT ("Animals"[Mesh]) AND "Humans"[Mesh])

The Cochrane Library (Wiley)

#1 MeSH descriptor: [Overweight] explode all trees
#2 MeSH descriptor: [Obesity] this term only
#3 MeSH descriptor: [Obesity, Abdominal] explode all trees
#4 MeSH descriptor: [Obesity, Morbid] explode all trees
#5 MeSH descriptor: [Adiposity] this term only
#6 MeSH descriptor: [Child] explode all trees
#7 MeSH descriptor: [Adolescent] explode all trees
#8 MeSH descriptor: [Minors] explode all trees
#9 overweight or obesity or obese or obesitas or adiposity or adipositas or excessive weight:ti,ab,kw
#10 #9 or #1 or #2 or #3 or #4 or #5
#11 child or childhood or adolescent or teen or teenager or youth or adolescence or youngster or schoolchildren or pediatric or pediatrics or girl or boy:ti,ab,kw
#12 #11 or #6 or #7 or #8
#13 therapy or treatment or intervention or program or strategy or care or approach:ti,ab,kw
#14 maintenance or follow-up or followup:ti,ab,kw
#15 #13 and #14
#16 post-treatment or posttreatment or aftercare:ti,ab,kw
#17 #15 or #16
#18 #10 and #13
#19 #17 and #18

CINAHL, PsycINFO, SocINDEX (EBSCO)

S1. TI overweight OR AB overweight OR TI obesity OR AB obesity OR TI obese OR AB obese OR TI obesitas OR AB obesitas OR TI adiposity OR AB adiposity OR TI adipositas OR AB adipositas
S2. TI excessive weight OR AB excessive weight
S3. S1 OR S2
S4. TI child OR AB child OR TI children OR AB children OR TI childhood OR AB childhood OR TI adolescent OR AB adolescent OR TI adolescents OR AB adolescents OR TI teen OR AB teen
S5. TI teens OR AB teens OR TI teenager OR AB teenager OR TI teenagers OR AB teenagers OR TI youth OR AB youth OR TI youths OR AB youths OR TI adolescence OR AB adolescence

S6. TI youngster OR AB youngster OR TI youngsters OR AB youngsters OR TI schoolchildren OR AB schoolchildren OR TI pediatric OR AB pediatric OR TI pediatrics OR AB pediatrics TI paediatric OR AB paediatric

S7. TI paediatrics OR AB paediatrics OR TI girl OR AB girl OR TI girls OR AB girls OR TI boy OR AB boy OR TI boys OR AB boys

S8. S4 OR S5 OR S6 OR S7

S9. TI therapy OR AB therapy OR TI therapies OR AB therapies OR TI treatment OR AB treatment OR TI treatments OR AB treatments OR TI intervention OR AB intervention OR TI interventions OR AB interventions

S10. TI program OR AB program OR TI programs OR AB programs OR TI programme OR AB programme OR TI programmes OR AB programmes OR TI strategy OR AB strategy OR TI strategies OR AB strategies

S11. TI care OR AB care OR TI approach OR AB approach OR TI approaches OR AB approaches

S12. TI maintenance OR AB maintenance OR TI follow up OR AB follow up OR TI followup OR AB followup

S13. S9 OR S10 OR S11

S14. S12 AND S13

S15. TI post-treatment OR AB post-treatment OR TI posttreatment OR AB posttreatment OR TI aftercare OR AB aftercare

S16. S14 OR S15

S17. S3 AND S8

S18. S16 AND S17

S19. S18 Limiters – Human; Language: Dutch/Flemish, English, French, German, Spanish

EMBASE

#1. 'overweight'/exp OR 'obesity'/exp OR 'adiposity'/exp

#2. overweight:ab,ti OR obesity:ab,ti OR obese:ab,ti OR obesitas:ab,ti OR adiposity:ab,ti OR adipositas:ab,ti OR 'excessive weight':ab,ti

#3. #1 OR #2

#4. 'child'/exp OR 'adolescent'/exp OR 'minors'/exp

#5. child:ab,ti OR children:ab,ti OR childhood:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR teen:ab,ti OR teens:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR youth:ab,ti OR youths:ab,ti OR adolescence:ab,ti OR youngster:ab,ti OR youngsters:ab,ti OR schoolchildren:ab,ti OR pediatric:ab,ti OR pediatrics:ab,ti OR paediatric:ab,ti OR paediatrics:ab,ti OR girl:ab,ti OR girls:ab,ti OR boy:ab,ti OR boys:ab,ti

#6. #4 OR #5
#7. #3 AND #6
#8. therapy:ab,ti OR therapies:ab,ti OR treatment:ab,ti OR treatments:ab,ti OR intervention:ab,ti OR interventions:ab,ti OR program:ab,ti OR programs:ab,ti OR programme:ab,ti OR programmes:ab,ti OR strategy:ab,ti OR strategies:ab,ti OR care:ab,ti OR approach:ab,ti OR approaches:ab,ti
#9. maintenance:ab,ti OR 'follow up':ab,ti OR followup:ab,ti
#10. #8 AND #9
#11. 'post treatment':ab,ti OR posttreatment:ab,ti OR aftercare:ab,ti
#12. #10 OR #11
#13. #7 AND #12
#14. #13 AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim OR [spanish]/lim) AND [humans]/lim

Web of Science

1. TOPIC: (overweight) OR TOPIC: (obesity) OR TOPIC: (obese) OR TOPIC: (obesitas) OR TOPIC: (adiposity) OR TOPIC: (adipositas OR TOPIC: ('excessive weight)
2. TOPIC: (child) OR TOPIC: (children) OR TOPIC: (childhood) OR TOPIC: (adolescent) OR TOPIC: (adolescents) OR TOPIC: (teen) OR TOPIC: (teens) OR TOPIC: (teenager) OR TOPIC: (teenagers) OR TOPIC: (youth) OR TOPIC: (youths) OR TOPIC: (adolescence) OR TOPIC: (youngster) OR TOPIC: (youngsters) OR TOPIC: (schoolchildren) OR TOPIC: (pediatric) OR TOPIC: (pediatrics) OR TOPIC: (paediatric) OR TOPIC: (paediatrics) OR TOPIC: (girl) OR TOPIC: (girls) OR TOPIC: (boy) OR TOPIC: (boys)
3. #1 AND #2
4. TOPIC: (therapy) OR TOPIC: (therapies) OR TOPIC: (treatment) OR TOPIC: (treatments) OR TOPIC: (intervention) OR TOPIC: (interventions) OR TOPIC: (program) OR TOPIC: (programs) OR TOPIC: (programme) OR TOPIC: (programmes) OR TOPIC: (strategy) OR TOPIC: (strategies) OR TOPIC: (care) OR TOPIC: (approach) OR TOPIC: (approaches)
5. TOPIC: (maintenance) OR TOPIC: (' follow up') OR TOPIC: (followup)
6. TOPIC: (post-treatment) OR TOPIC: (posttreatment) OR TOPIC: (aftercare)
7. #4 AND #5
8. #6 OR #7
9. #3 AND #8
10. #9 Refined by: LANGUAGES=(ENGLISH OR GERMAN OR FRENCH OR SPANISH OR DUTCH)

Scopus

#1. TITLE-ABS-KEY(overweight) OR TITLE-ABS-KEY(obesity) OR TITLE-ABS-KEY(obese) OR TITLE-ABS-KEY(obesitas) OR TITLE-ABS-KEY(adiposity) OR TITLE-ABS-KEY(adipositas) OR TITLE-ABS-KEY('excessive weight')

#2. TITLE-ABS-KEY(child) OR TITLE-ABS-KEY(children) OR TITLE-ABS-KEY(childhood) OR TITLE-ABS-KEY(adolescent) OR TITLE-ABS-KEY(adolescents) OR TITLE-ABS-KEY(teen) OR TITLE-ABS-KEY(teens) OR TITLE-ABS-KEY(teenager) OR TITLE-ABS-KEY(teenagers) OR TITLE-ABS-KEY(youth) OR TITLE-ABS-KEY(youths) OR TITLE-ABS-KEY(adolescence) OR TITLE-ABS-KEY(youngster) OR TITLE-ABS-KEY(youngsters) OR TITLE-ABS-KEY(schoolchildren) OR TITLE-ABS-KEY(pediatric) OR TITLE-ABS-KEY(pediatrics) OR TITLE-ABS-KEY(paediatric) OR TITLE-ABS-KEY(paediatrics) OR TITLE-ABS-KEY(girl) OR TITLE-ABS-KEY(girls) OR TITLE-ABS-KEY(boy) OR TITLE-ABS-KEY(boys)

#3. #1 AND #2

#4. TITLE-ABS-KEY(therapy) OR TITLE-ABS-KEY(therapies) OR TITLE-ABS-KEY(treatment) OR TITLE-ABS-KEY(treatments) OR TITLE-ABS-KEY(intervention) OR TITLE-ABS-KEY(interventions) OR TITLE-ABS-KEY(program) OR TITLE-ABS-KEY(programs) OR TITLE-ABS-KEY(programme) OR TITLE-ABS-KEY(programmes) OR TITLE-ABS-KEY(strategy) OR TITLE-ABS-KEY(strategies) OR TITLE-ABS-KEY(care) OR TITLE-ABS-KEY(approach) OR TITLE-ABS-KEY(approaches)

#5. TITLE-ABS-KEY(maintenance) OR TITLE-ABS-KEY('follow up') OR TITLE-ABS-KEY(followup)

#6. #4 AND #5

#7. TITLE-ABS-KEY(post-treatment) OR TITLE-ABS-KEY(posttreatment) OR TITLE-ABS-KEY(aftercare)

#8. #6 OR #7

#9. #3 AND #8

ADDITIONAL FILE 2

Risk of Bias Assessment Tool. Risk of Bias Assessment Tool form that will be used to assess the risk of bias in included studies in this systematic review. This tool is based on the 'risk of bias' tool developed by The Cochrane Collaboration to assess risk of bias in randomised controlled trials[1], supplemented with items extracted from the Newcastle-Ottawa quality assessment tool[2] and from the Agency for Healthcare Research and Quality (AHRQ) publication of Viswanathan et al.[3]

Risk of Bias Assessment Tool

First author: Year:	Journal: ID:	Judgement (high/ low risk)		Support for judgement
		RCT	**Cohort**	
Selection bias *Systematic differences between baseline characteristics of the groups that are compared.*				
1 Random sequence generation: Did the investigators describe a random component in the sequence generation process?			X	
2 Allocation concealment: Were participants and investigators enrolling participants able to foresee assignment?			X	
3 Participants analyzed within groups they were originally assigned to?				
4 Did study apply inclusion/exclusion criteria uniformly to all comparison groups?		X		
5 Did strategy for recruiting participants into study differ across study groups?		X		
6 Does design or analysis control account for important confounding and modifying variables though matching, stratification, multivariable analysis, or other approaches?				
7 In cohort studies, is the exposed cohort representative of average in community?		X		
Performance bias *Systematic differences between groups in the care that is provided, or in exposure to factors other than interventions of interest.*				
1 Blinding of participants and personnel?	Outcome 1			
	Outcome 2			
	Outcome 3			
2 Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?				
3 Did study maintain fidelity to intervention protocol?				

Detection bias *Systematic differences between groups in how outcomes are determined.*				
1	Blinding of outcome assessment or exposure status?	Outcome 1		
		Outcome 2		
		Outcome 3		
2	In prospective studies, was length of follow-up different between groups?			
3	Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?			
4	Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?			
5	Confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?	Outcome 1		
		Outcome 2		
		Outcome 3		
Attrition bias *Systematic differences between groups in withdrawals from a study.*				
1	Incomplete outcome data addressed?	Outcome 1		
		Outcome 2		
		Outcome 3		
2	If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?			
3	Follow-up long enough for outcomes to occur?			
Reporting bias *Systematic differences between reported and unreported findings.*				
1	Selective reporting (e.g. protocol, analysis plan, all pre-specified and expected outcomes have been reported in the pre-specified way)	Outcome 1		
		Outcome 2		
		Outcome 3		
Other bias *Bias due to problems not covered elsewhere in the table.*				
1				
2				

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APPENDIX D

Additional information Chapter 6B

S1 Table. Details of included studies.
Abbreviations: A, all; C, control; DM, diabetes mellitus; FU, follow-up; ITT, intention-to-treat analysis; GLM, generalised linear model; NA, not applicable; NR, not reported; M, maintenance; min, minutes; m, months; y, years; T, treatment; vs, versus; w, weeks
Participants: of maintenance phase unless otherwise indicated.

Van Egmond-Fröhlich et al., 2006

Country		Germany
Objective		Development and longer-term evaluation of a programme for structured outpatient follow-up care by primary care physicians after inpatient rehabilitation of obese children and adolescents
Methods	Study design	Multicentre, randomised, parallel controlled clinical trial
	Selection	Children and adolescents who applied for inpatient medical rehabilitation in one of the cooperating hospitals were checked against the inclusion criteria. If they met the criteria, they were asked to participate. Subsequently, the outpatient physician was informed and asked to participate.
	Inclusion criteria	Approval of an inpatient medical rehabilitation in one of the cooperating hospitals; adiposity as primary indication for the inpatient medical rehabilitation; BMI >p97 (Kromeyer-Hauschild K et al., Monatschrift Kinderheilkunde 2001); age 9-16 years; willingness to participate (child, parents, doctor)
	Exclusion criteria	Secondary cause for overweight / obesity; DM type 1; psychiatric disturbance; treatment duration <28 days; disability or language barrier that would interfere with group training
Participants	Sample	n=521 (T n=777); M1 n=250, C n=271
	Age (years), mean (SD)	9-16 years; M1 13.2 (1.8), C 13.5 (1.7)
	Gender (female), number (%)	M1: 144 (58); C: 148 (55)
	Race/Ethnicity, number (%)	NR
	SES	Sonderschule, Hauptschule, Grundschule, Orientierungsstufe, Gesamtschule, Realschule, Gymnasium; number (%) M1: 28 (11.2), 44 (17.4), 45 (17.8), 22 (8.8), 75 (29.8), 30 (12.0) C: 33 (13.0), 49 (19.4), 44 (17.4), 33 (12.8), 64 (25.4), 37 (14.6)
	Retention, number (%)	*Intervention* M1: 22.4% not started, 16.8% loss to FU (no information about use of aftercare), 16.8% no aftercare arranged, 8.8% ≤6 consultations, 35.2% 7-13 consultations. Duration of consultations on average 28±11 min. *Measurements* Halfway M: M1 115 (46), C 135 (54) End M: M1 194 (78), C 229 (84) Analysis: ITT including all patients with FU data at the end of M (regardless of retention to the intervention)
Intervention	T	Inpatient medical rehabilitation for 6 w (mean 5.9 w, SD 1.2), based on individual treatment goals
	Duration	6 w
	M general	NA
	M1	Check-up 6 m and 12 m after inpatient rehabilitation + 10-12 times in 12 m (= every 4 w) structured outpatient aftercare (consultations) with own physician, based on the SanaReha ('strukturierten ambulanten Nachbetreuung von adipösen Kindern und Jugendlichen nach stationärer Reha') consultant guidelines --> information about relevant basic knowledge and key points of the modern treatment strategies, including checklists, examples, and homework
	M2	NA
	C	Only check-up 6 m and 12 m after inpatient rehabilitation
	Duration	12 m
	Follow-up	6 w (T) + 12 m (M)

Wilfley et al., 2007

Country		US
Objective		To determine the short-term and long-term efficacy of 2 distinct weight maintenance approaches vs no continued treatment control following standard family-based behavioural weight loss treatment for childhood overweight, and to examine children's social functioning as a moderator of outcome

Methods	Study design	Parallel-group RCT
	Selection	Children aged 7 to 12 years who were 20-100% overweight and had at least 1 parent with BMI >25 were recruited through media announcements or advertisements and physician referrals
	Inclusion criteria	See Selection
	Exclusion criteria	Either child or parent was currently involved in psychological or weight loss treatment, was using appetite or weight affecting medications, or had a psychiatric condition (e.g., eating disorder, psychosis) that would interfere with participation
Participants	Sample	n=150 (T n=204); M1 n=51, M2 n=50, C n=49
	Age (years), mean (SD)	7-12 years; M1 9.9 (1.4), M2 9.9 (1.4), C 9.8 (1.2)
	Gender (female), number (%)	M1 37 (72.5), M2 35 (70.0), C 32 (65.3)
	Race/Ethnicity, number (%)	Black, white (non-Hispanic), white (Hispanic), other M1: 5.9 (3), 70.6 (36), 21.6 (11), 2.0 (1) M2: 14.0 (7), 64.0 (32), 16.0 (8), 6.0 (3) C: 2.0 (1), 77.6 (38), 18.4 (9), 2.0 (1)
	SES	Hollingshead Socioeconomic Status Index, mean (SD) M1: 47.9 (9.7) M2: 47.0 (9.7) C: 47.0 (13.8)
	Retention, number (%)	*Intervention:* end M1 n=48 (94), end M2 n=48 (96). Randomised participants had attended a median 17 of 20 weight loss sessions (85%), with no significant differences across maintenance conditions. *Measurements* End M: M1 47 (92), M2 47 (94), C 46 (94) After 1-y FU: M1 44 (86), M2 43 (86), C 42 (86) After 2-y FU: M1 43 (84), M2 43 (86), C 38 (78) Analysis: mixed-model, repeated-measures analysis of variance. Missing data at postweight maintenance (n=4), 1-y FU (n=7), or both time points (n=1) were linearly interpolated based on observed values at immediately preceding and subsequent time points. Outliers (n=2) were removed. To ensure that the primary analyses were robust, 3 additional ITT analyses were conducted. Start M: M1 50 (1 outlier), M2 50, C 48 (1 outlier) End M: M1 48, M2 49, C 46 After 1-y FU: M1 45, M2 47, C 43 After 2-y FU: M1 42, M2 43, C 37
Intervention	T	Weekly 20-minute family treatment (to reinforce the content of group session topics and provide opportunities for individualised behaviour therapy) and 40-minute separate child and parent groups. Dietary modification: improve dietary quality and reduce caloric intake to approximately 1200 to 1500 calories per day. Physical activity increases: maximum goal of 90 minutes of at least moderate-intensity activity per day for at least 5 days per week, while also encouraging decreased sedentary activities. Behaviour change skills: using self-monitoring to set and evaluate behaviour change goals, and a family-based reinforcement system.
	Duration	5 m
	M general	Maintain a 3-lb (1.35-kg) weight range, 1.5 lb (0.675 kg) above or below their absolute weight at the outset of the weight maintenance treatment. Modify caloric intake from weight loss treatment levels to an individualised level consistent with weight maintenance. Participate in the frequency, duration, and intensity of physical activity necessary to bring about energy balance, which was increased from the weight loss phase and individualised to partially compensate for increased caloric intake.
	M1	16 weekly group sessions: 20-minute family treatment + 40-minute separate child and parent groups. BSM-approach: cognitive-behavioural approach to weight maintenance, emphasising self-regulation behaviours and relapse-prevention strategies.
	M2	16 weekly group sessions: 20-minute family treatment + 40-minute separate child and parent groups. SFM-approach: empirically supported techniques to help parents facilitate child peer networks that support healthy eating and physical activity.
	C	Discontinued contact after the weight loss programme. Only follow-up assessments in the clinic at all 3 follow-up time points.
	Duration	4 m
	Follow-up	29 m (T + M + 2 year U after end T)

Davis et al., 2012

Country		US
Objective		To assess the effects of a maintenance programme (monthly newsletters vs monthly group classes and telephone behavioural sessions) on obesity and metabolic disease risk at 1 year in overweight minority adolescents
Methods	Study design	Randomised controlled trial
	Selection	Participants were recruited into the initial 4-month intervention from schools, community centres and health clinics. Any participant who completed the initial 4-month intervention was eligible to participate in the maintenance study.
	Inclusion criteria	For initial 4-month intervention: age- and gender-specific BMI ≥85th percentile, African-American or Latino ethnicity, and grades 9th through 12 th. No additional inclusions in the maintenance programme criteria.
	Exclusion criteria	NR
Participants	Sample	n=61 (initial 4-month intervention n=84); M1 n=28, M2 n=33 Baseline characteristics: of M completers (M1 n= 23, M2 n=30)
	Age (years), mean (SD)	Grades 9th through 12th (14-18 years); M1 15.8 (0.9), M2 15.6 (1.1)
	Gender (female), number (%)	M1 16 (70), M2 13 (43)
	Race/Ethnicity, number (%)	All African-American or Latino ethnicity
	SES	NR
	Retention, number (%)	*Intervention* End M1: 23 (82) End M2: 30 (91). All participants attended at least six of the eight monthly group sessions; 80% all eight classes, 13% seven classes, 7% six classes. Motivational interviewing sessions: all received 4 phone sessions, on average 16±4 min. Parents: 15% attended minimum of two classes. *Measurements:* NR Analysis: GLM repeated measures, with post hoc pairwise comparisons with Bonferroni adjustments
Intervention	T	Culturally tailored dietary intervention once per week (90 min) for 16 w. Two goals: ≤10% of total daily calorie intake from added sugar + consuming at least 14 g/1,000 kcal of dietary fiber a day. D+P: also strength training twice per week (60 min/session) for 16 w. Four individual motivational interviewing (MI) sessions (by trained research staff). Parent(s): same curriculum separately from the participants.
	Duration	4 m
	M general	NA
	M1	Eight, either D+P or D only, monthly newsletters (email) + two calls (to make sure they were receiving the newsletters and that their contact information was still correct). Basic tips on how to continue to eat foods and drink beverages low in sugar and high in fibre and included one or two new low-sugar or high-fibre recipes. D+P: benefits of strength training and sample strength-training exercises. List of community resources.
	M2	Monthly class of 90 minutes, either D+P or D only. Included a cooking component, a snack, and a nutrition lesson. D+P: 45-minute strength training session led by certified personal trainer. Four motivational interviewing (MI) sessions lasting approximately 15 min. Parent(s) were also offered separate monthly classes.
	C	NA
	Duration	8 m
	Follow-up	12 m (T + M)

Nguyen et al., 2013; Nguyen et al., 2012

Country		Australia
Objective		To evaluate the effectiveness of additional therapeutic contact (ATC) as an adjunct to a community-based weight-management programme for overweight and obese 13-16-year-olds
Methods	Study design	Community-based RCT
	Selection	Recruited via the media, schools, health professionals and several community organisations into weight management programme
	Inclusion criteria	Overweight and to moderately obese (i.e., BMI Z-score 1.0-2.5) but otherwise healthy adolescents; age 13.0-16.9 years; available to attend the initial group sessions with one of their parents or caregivers on specified days; ability to access a landline telephone and e-mail and/or a mobile telephone

	Exclusion criteria	Severely obese (i.e.. BMI Z-score >2.5) or with a secondary cause for overweight/ obesity; intellectual disability, significant medical illness, psychiatric disturbance; taking medications that affect weight status; inability to take part in physical activity sessions; poor level of spoken English
Participants	Sample	n=130 (T n=151); M1 n=64, M2 n=66 Baseline characteristics: of participants enrolled in weight-management programme (T1 n=73, T2 n=78)
	Age (years), mean (SD)	13-16 years; T1 14.0 (0.9); T2 14.2 (1.0)
	Gender (female), number (%)	T1 36 (49); T2 42 (54)
	Race/Ethnicity, number (%)	NR
	SES	NR
	Retention, number (%)	*Intervention:* end M1 58 (91), end M2 62 (94) Booster session attendance declined from 69% to 31% between the first and final session. Median (range) number of telephone coaching sessions 12 (2-15), number of SMS or email messages 31 (14-33). *Measurements* Halfway M: M1 57 (89), M2 50 (76) End M: M1 43 (67), M2 50 (76) Analysis: ITT approach with linear mixed models with an unstructured covariance structure to test for time and group effects
Intervention	T	Loozit: 7 weekly group sessions of 75 minutes (facilitated by dieticians) for adolescents and parents/carers. Healthy food choices and eating patterns. Increasing physical activity and reducing sedentary behaviour. Strategies for managing behaviour change with a focus on goal setting, dealing with stress and building self-esteem. Cognitive behavioural approach using behavioural principles to change dietary intake and activity levels, and social cognitive approaches to modify self-efficacy, motivation, perseverance and self-regulation.
	Duration	2 m
	M general	5 booster group sessions of 60 minutes for adolescents once every three m (facilitated by dietitians but could be run by nurses or other health professionals) + 2 outcome assessment. Educational content generally new, although key messages from treatment phase are reinforced.
	M1	ATC (by group facilitator): every three m 2 times telephone coaching call (10 min) + 3 times electronic communication message. Aim: enhance adolescents' knowledge, skills and confidence to initiate and maintain required changes in dietary and activity behaviours.
	M2	No ATC
	C	NA
	Duration	22 m
	Follow-up	24 m (T + M)

de Niet et al., 2012 (1+2); Bauer et al., 2010

Country		The Netherlands
Objective		To analyse whether self-monitoring of lifestyle behaviours through a short message service maintenance treatment (SMSMT) via mobile phones with personalised feedback positively effects weight, lifestyle behaviours and psychological well-being in obese children
Methods	Study design	Multi-centre randomised controlled trial
	Selection	Overweight and obese children participating in the Big Friends Club (BFC) programme in hospitals in the Netherlands
	Inclusion criteria	Being overweight or obese; parent participation in the BFC; a sufficient knowledge of the Dutch language
	Exclusion criteria	Behavioural problems defined as score >70 on the Child Behaviour Checklist (CBCL) and any disease causing overweight that could be treated with drugs and mental retardation
Participants	Sample	n=141 (T n=144); M1 n=73, M2 n=68
	Age (years), mean (SD)	8-12 years; M1 10.0 (1.3), M2 9.8 (1.3)
	Gender (female), number (%)	M1 45 (62), M2 45 (66)
	Race/Ethnicity, number (%)	Dutch: M1 57 (78), M2 48 (71)
	SES	NR
	Retention, number (%)	*Intervention* End T + M1: 61 (84). Discontinued SMSMT but continued with BFC: 12.

		End T + M2: 47 (69) *Measurements:* NR Analysis: mixed modelling, allowing the use of incomplete cases if missing at random; end T + M1 73, end T + M2 67 (1 excluded from analysis)
Intervention	T	11 group sessions in 1 year: 8 during first 3 m (and 3 parent sessions) = treatment, 3 FU group sessions = maintenance (see below). First 90 minutes: healthy eating and exercise behaviour, strategies to deal with difficulties concerning eating or physical activity, psychosocial aspects of obesity. The last part of each session (1 hour): exercise together (led by physiotherapist), meant to improve their physical condition and create positive exercise experiences through games and sports.
	Duration	3 m
	M general	NA
	M1	FU group sessions (6, 9, and 12 months after start T). SMSMT (weekly for 9 m) --> self-monitoring on five-point Likert scale via SMS (on physical activity, healthy eating pattern and mood) and personalised feedback (promoting social support, motivating participants, reinforcing positive changes, suggesting behaviour modification and self-management skills that were learned during T). Enhanced compliance by sending an SMS reminder after 1 week of non-responding.
	M2	Follow-up group sessions only
	C	NA
	Duration	9 m
	Follow-up	12 m (T + M)

Straker et al., 2014

Country		Australia
Objective		To determine the effects of participation in Curtin University's Activity, Food and Attitudes Program (CAFAP), a community-based family-centred behavioural intervention, on the physical activity, sedentary time, and healthy eating behaviours of overweight and obese adolescents
Methods	Study design	Staggered entry, within-subject, waitlist controlled clinical trial
	Selection	Adolescents recruited via the health system, the education system and from the general community. Paediatric specialists, allied health professionals at a tertiary children's hospital, general medical practices close to the study and nurses in schools close to the study were informed about the study and asked to identify potential suitable adolescents.
	Inclusion criteria	Males and females aged 11-16 years; BMI higher than the 85th centile on the standard Centres for Disease Control (CDC) BMI-for-age growth charts (includes children who are typically classified as overweight or obese); have passed medical screening
	Exclusion criteria	Obesity is due to identified genetic, metabolic or endocrine disease; undergoing treatment for psychiatric disorders; reside remotely or are unable to attend twice weekly sessions at the designated community intervention locations; assessed unsafe to participate by general practitioner or paediatrician
Participants	Sample	n=69 (start T); M1 n=44 Baseline characteristics: n=68 (1 participant did not complete baseline testing but entered the study during waitlist period)
	Age (years), mean (SD)	11-16 years; T 14.1 (1.6)
	Gender (female), number (%)	48 (71)
	Race/Ethnicity, number (%)	*NR*
	SES	NR
	Retention, number (%)	*Intervention* End T: 44 (64) End M: 34 (77% of participants starting M) *Measurements: NR* Analysis: mixed linear models with 56 participants who participated in at least 2 assessments. Missing values were accounted for in the linear mixed models, which uses a likelihood-based estimation procedure resulting in non-biased estimates by imputation of missing responses based upon the surrounding responses and modelled covariance structure.

Intervention	T	Intensive 8 week multidisciplinary programme focused on improving activity, food and attitude habits. Run within school terms and delivered by community health professionals following training in the philosophy and approach of the programme. Groups of 12 to 15 adolescents and their parents attended twice weekly, and on each occasion adolescents participated in a 45 minute exercise class involving aerobic, strength and skill stations. They also participated in hour long education sessions covering healthy activity, healthy eating, energy balance, food labelling, preparing meals and snacks, goal setting, problem solving, dealing with mood, family activity and eating and relationship with family. Parents participated in education sessions covering the same issues, but also sessions on understanding adolescence, providing support, relationships with adolescents, community resources, food budgeting and a supermarket visit. Also informal support from other parents and staff in 'walk and talk' sessions. Phone contact was made with participants who missed a session to increase attendance adherence.
	Duration	8 w
	M general	NA
	M1	Tapered FU for 12 months; participants received structured telephone and text message contact at a decreasing frequency (starting with 3 messages per week) based on the same theoretical principles and key messages as during the intensive face-to-face contact period. Contact was based on self-determination theory and goal setting theory and focused on eating more fruits and vegetables, eating less junk food, being less sedentary and being more active. The phone coaching was completed by members of the facilitation/assessment team who were well known to participants and aimed to provide structure, support attempts at change, and promote adolescents' sense of autonomy.
	M2	NA
	C	NA
	Duration	12 m
	Follow-up	8 w (T) + 12 m (M)

Carraway et al., 2014

Country		US
Objective		To evaluate short-term objective changes in all participants' weight status across the 19-day immersion treatment phase as well as long-term changes in weight status in a subset enrolled in a 10-month follow-up programme
Methods	Study design	Cohort intervention study with pre/post design and longitudinal follow-up
	Selection	Though available to self-pay campers, the majority of campers received a full or partial scholarship. Candidates for scholarships were identified through East Carolina University's Paediatric Healthy Weight Research and Treatment Centre, primary care practices, health departments in eastern North Carolina, school nurses, and case management programmes or were self-referral.
	Inclusion criteria	Age 12-18 years; obesity (BMI ≥95th percentile for age and sex)
	Exclusion criteria	Assessed as precontemplative or uninterested in making healthy lifestyle changes, or disruptive and/or potentially violent by a multidisciplinary team (physician, social worker, psychologist, medical family therapist)
Participants	Sample	n=52 (start T); M1 n=33 (based on residency restrictions imposed by the funding foundation)
	Age (years), mean (SD)	12-18 years; T 14.0 (1.5), M1 13.9 (1.4)
	Gender (female), number (%)	T 37 (71), M1 22 (67)
	Race/Ethnicity, number (%)	T: white 15 (29), non-white 37 (71) (31 [59] African American, 1 [2] Asian American, 1 [2] Hispanic, 1 [2] Native American, 3 [6] other) M1: white 7 (21), non-white 26 (79) (22 [67] African American, 1 [3] Asian American, 1 [3] Hispanic, 0 [0] Native American, 2 [6] other)
	SES	NR
	Retention, number (%)	*Intervention* M1: 33.3% attended ≤3 FU meetings, 30.3% attended 4-6 meetings, 36.4% ≥7 meetings. None attended all 10 meetings, 1 did not attend any meetings. *Measurements* End M: M1 23 (70) Analysis: ITT n=33, baseline (start T) carried forward for participants missing final measurements

Intervention	T	3-week (19-day) residential, immersion weight management summer camp, called Take Off 4-Health (TO4H). Major focus: developing autonomous problem-solving and behavioural choice skills that are expected to promote maintenance of healthier behaviours and improved weight status. Specific components: nutrition education, physical activity, cognitive-behaviour modification strategies, self-monitoring, and group therapy.
	Duration	3 w (19 days)
	M general	NA
	M1	Provided by an interdisciplinary team (nutritionist, nurse, and social worker) and consisted of 10 monthly meetings with campers and their families to provide support, reinforcement, accountability, and education. Campers and a parent/guardian were also given the opportunity to exercise at a local wellness facility at very low cost, and case management services were provided as needed. Height and weight were measured at each monthly meeting.
	M2	NA
	C	NA
	Duration	10 m
	Follow-up	3 w (T) + 10 m (M)

Hampl et al., 2016

Country		US
Objective		To determine the 24-month outcomes of a moderate-intensity stage 3 intervention for preadolescents and adolescents with obesity presenting to a tertiary care children's hospital
Methods	Study design	Cohort study
	Selection	Referred to clinic from community primary care provider (PCP) or a hospital-based PCP or subspecialist
	Inclusion criteria	BMI ≥95th percentile for age and sex and availability of an English- or Spanish-speaking parent or caregiver to attend the weight management programme with the child
	Exclusion criteria	Significant intellectual disabilities that prevented age-appropriate participation in group sessions
Participants	Sample	n=124 (T n=173); M1 n=124 Baseline characteristic: completers of T (n=124)
	Age (years), mean (SD)	8-18 years; T 12.3 (2.1)
	Gender (female), number (%)	M1 82 (66.1)
	Race/Ethnicity, number (%)	53 (42.7) African American, 37 (29.8) Caucasian, 31 (25.0) Latino, 3 (2.4) other
	SES	NR
	Retention, number (%)	*Intervention:* Completers of T: attended ≥50% of the 24 weekly sessions *Measurements*: Start T: 124 End T, start M: 110 (88.7) Halfway M: 68 (54.8) End M: 37 (29.8) Analysis: multilevel model (does not require an equal number of observations for each person and allows for management of missing data without the need for data imputation; thus all participant cases were retained in our analyses despite attrition)
Intervention	T	Group-based weight management programme Promoting Health In Teens and Kids (PHIT Kids), including 24 group-format weekly meetings delivered by health educators. Targeted changes to diet and physical activity through a curriculum developed by a multidisciplinary clinical and educational team. In addition to education, each meeting included at least 30 minutes for actual physical activity for families. Behavioural strategies taught included goal setting, self-monitoring, and contingency management, among others.
	Duration	24 w
	M general	NA
	M1	FU visits to the PHIT Kids Weight Management Clinic and monthly group sessions led by the health educators, including educational activities, active games, or group exercise and often a meal or snack demonstration. Focus: provide families with support and a dedicated space to practice behaviour change.
	M2	NA

	C	NA
	Duration	24 m
	Follow-up	24 w (T) + 24 m (M)

Jensen et al., 2016

Country		US
Objective		To examine the efficacy and acceptability of a smartphone assisted adolescent behavioural weight control intervention
Methods	Study design	Pilot study
	Selection	Adolescents were recruited through advertisements posted in schools, paediatricians' offices, and community health centres. School nurses were also provided study advertisements, which they used to refer potential participants. Interested families responded to the advertisement by phone to be screened by research assistants for eligibility and to schedule an in-person intake session with both the participating adolescent and parent.
	Inclusion criteria	Parent/guardian and adolescent consented to participate; age 13-18 years; the adolescent exceeded the 85th BMI percentile for age and sex; the adolescent was living at home with their parent/guardian; did not have any serious mental illnesses of developmental delays; participants consented to video recording during the group treatment sessions
	Exclusion criteria	See Inclusion criteria
Participants	Sample	n=14 (T n=16); M1 n=14 Baseline characteristics: start T
	Age (years), mean (SD)	13-17 years; 38% 13 years, 44% 14 years, 6% 15 years, 6% 16 years, 6% 17 years
	Gender (female), number (%)	12 (75)
	Race/Ethnicity, number (%)	Non-Hispanic white 9 (5), Hispanic/Latino 4 (25), Other 3 (19)
	SES	Parent education level: high school graduate 1 (6), attended college 2 (12), associate's degree 3 (18), college graduate 7 (46), graduate degree 3 (18) Parent monthly income: range $2000-16.666, average $6151,45
	Retention, number (%)	*Intervention* T: on average, participants attended 7.5 (62.5%) out of 12 in-person treatment sessions. Participants monitored at least 2 meals on 48.3% of days and tracked at least 30 min of physical activity on 14.6% of available days. M1: participants monitored at least 2 meals on 16.6% of the available days, and tracked at least 30 min of physical activity on 4.6% of available days. *Measurements* End M: 14 (100) After 1-y FU: M1 10 (71) Analysis: paired samples t tests were used to examine change in BMI Z-score over time and estimates of effect size (Cohen's d) were computed. Participants with insufficient data to calculate BMI Z-score at any given time point were excluded from analyses.
Intervention	T	Group weight control programme led by clinical psychology doctoral students under the supervision of licensed psychologist, with parents and adolescents attending separate group meetings in adjoining rooms. Group meeting duration: 75 min. Standardised by using a 12-week modular behavioural weight control program developed by Jelalian et al. that included important components of weight management including self-monitoring, portion control, problem solving, stimulus control, emotional eating, and physical activity. Each parent/adolescent dyad also received 15 minutes of individual family intervention every 4 weeks after group sessions, with motivational interviewing. Smartphone-based treatment consisted of 2 parts: electronic self-monitoring (record all meals/snacks and physical activity), human-generated text messaging (feedback regarding participant self-monitoring behaviour and progress toward treatment goals + content designed to reinforce principles addressed in the in-person treatment, including seeking social support, expanding diets to include healthier foods, altering food environments. Text messages were selected from a library developed by Woolford et al.. Brief text messages were sent to each participant once per day in the evening.
	Duration	12 w
	M general	NA
	M1	Only smartphone-based treatment as described above
	M2	NA
	C	NA
	Duration	12 w
	Follow-up	12 w (T + M) + 1-y FU after start T

Larsen et al., 2016

Country		Denmark
Objective		To evaluate the effectiveness of a one-year multicomponent immersive day-camp weight-loss intervention for children with overweight and obesity
Methods	Study design	Parallel-group randomised controlled trial
	Selection	Fifth grade primary school children had their body height, -weight, and waist circumference assessed by school nurses as a part of the mandatory health examination. Children with a BMI above the limit for overweight according to the International Obesity Task Force (IOTF) were offered to participate in the Odense overweight intervention study (OOIS).
	Inclusion criteria	See Selection
	Exclusion criteria	Children participated in other intervention research involving cardiovascular risk management; did not attend a regular school due to personal problems of psycho-social nature; taking any medications, during three months prior to entering the study, which are known to affect weight status; known endogenous cause of overweight; motor-control handicap that prohibited normal participation in physical activity
Participants	Sample	T n=106, randomised into T1 (n=55) + T2 (n=51)
	Age (years), mean (SD)	11-13 years; T 12.0 (0.4)
	Gender (female), number (%)	T1 29 (52.7), T2 30 (58.8)
	Race/Ethnicity, number (%)	Ethnic Danish: T1 70.6%, T2 61.8%
	SES	Based on the mothers' education level: group 1, 2, 3 1: male / female --> T1 7/8, T2 4/6 2: male / female --> T1 11/13, T2 7/8 3: male / female --> T1 6/7, T2 6/16
	Retention, number (%)	*Intervention* T1: 50 out of 52 children (96.1) who initiated the camp programme completed the six weeks according to the predetermined acceptable attendance rate (≥85% of the total time) M1: 25 out of 52 children (48.1) attended ≥4 of 6 meetings *Measurements* End T: T1 51, T2 43 End M: T1 48, T2 38 Analysis: linear mixed-effects modelling for repeated measures. A true ITT was not possible to perform as nine children dropped out after the randomisation and before the baseline measurements.
Intervention	T	T1: camp intervention, 7 days a week. Each day minimum 3 hours of exercise with a focus on physical activity enjoyment and motivation, 1 hour of health classes, and 1 hour of homework assignment. Parents received written information about the intervention, healthy cooking in the household, and advice on how best to support the child's health behaviour. T2: weekly exercise session, as well as a single health and lifestyle educational session for the parents, delivered by a dietician and a physical activity specialist
	Duration	6 w
	M general	NA
	M1	Only participants of T1: family-based intervention including 4 joint meetings, led by trained school nurses and instructors from the day-camp intervention
	M2	NA
	C	NA
	Duration	46 w
	Follow-up	52 w (T + M)

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Country		US
Objective		To examine 2-year changes in age- and sex-specific BMI Z-scores and obesity-related behaviours among participants in High Five for Kids
Methods	Study design	Cluster randomised controlled trial in 10 paediatric practices
	Selection	See Inclusion criteria and Exclusion criteria
	Inclusion criteria	Children 2-6 years whose BMI was ≥95th percentile or whose BMI was 85th-<95th percentile if at least one parent was overweight (BMI≥25 kg/m2), and who received their paediatric care at Harvard Vanguard Medical Associates (HVMA) between August 2006 and October 2008

	Exclusion criteria	Children whose parent or guardian could not respond to interviews in English or Spanish; whose families were planning to leave HVMA; families for whom the primary care clinician thought the intervention was not appropriate; children with chronic medical conditions
Participants	Sample	T n=445, randomised into T1 (n=271) + T2 (n=204) Baseline characteristics: T1 253, T2 192 (after T)
	Age (years), mean (SD)	2-6 years; T overall 4.9 (1.2), T1 4.8 (1.2), T2 5.2 (1.1)
	Gender (female), number (%)	T overall 215 (48.3), T1 121 (47.8), T2 94 (49.0)
	Race/Ethnicity, number (%)	White: T overall 252 (56.6), T1 118 (46.6), T2 134 (69.8) Black: T overall 84 (18.9), T1 70 (27.7), T2 14 (7.3) Latino: T overall 74 (16.6), T1 48 (19.0), T2 26 (13.5) Other: T overall 35 (7.9), T1 17 (6.7), T2 18 (9.4)
	SES	Parent education: some college or below --> T overall 171 (38.4), T1 106 (41.9), T2 65 (33.9). College graduate --> T overall 274 (61.6), T1 147 (58.1), T2 127 (66.1). Annual household income: <$50.000 --> T overall 126 (28.7), T1 88 (35.5), T2 38 (19.9). ≥$50.000 --> T overall 313 (71.3), T1 160 (64.5), T2 153 (80.1)
	Retention, number (%)	*Intervention* M1: 62% of participants completed 0 visits, 17% completed one visit and 21% completed two of the two intervention visits *Measurements* End T: T1 253 (93), T2 192 (94) End M: T1 249 (92), T2 192 (94) Analysis: ITT, using unadjusted and multivariable-adjusted linear regression models to estimate differences from baseline tot 2 years between the intervention and usual care groups. In all models, generalised linear mixed models were performed that accounted for clustering by practices.
Intervention	T	T1: intervention. Motivational interviewing by paediatric nurse practitioners in primary care during four, 25 minute, in-person, chronic disease management visits and three, 15 minute telephone calls. Intervention practices received primary care restructuring, and families received motivational interviewing by clinicians and educational modules targeting television viewing and intakes of fast food and sugar-sweetened beverages. T2: usual care. Standard of care offered by their paediatric practice, including baseline and annual well child care visits.
	Duration	1 y
	M general	NA
	M1	Two in-person intervention visits
	M2	NA
	C	NA
	Duration	1 y
	Follow-up	2 y (T + M)

SUMMARY

Childhood obesity is reaching alarming proportions and is currently one of the most important public health problems. It is associated with significant physical and psychosocial health consequences, both in the short and long term. In **Chapter 1** (General Introduction) we provided some general background information about the childhood obesity epidemic. Although much is already known on this topic, important research questions remain to be answered in the field of childhood obesity. Therefore, in this thesis we looked below the tip of the childhood obesity iceberg, and dived into a few important issues encountered in daily clinical practice.

PART I of this thesis focused on consequences of childhood obesity: ***Childhood obesity and beyond.***

In **Chapter 2** we described the results of a cross-sectional study investigating the health-related quality of life (HRQoL) in children and adolescents at the start of hospital-based obesity treatment. We showed that children with an increasing degree of obesity present with a lower HRQoL, especially in the physical domains of HRQoL. By analyzing both self-reports and parent-proxy reports, we concluded that significant differences exist between parent-proxy reports and child self-reports on 'Bodily Pain/Discomfort' and 'General Health Perceptions' (lower child scores), and 'Behavior' and 'Family Cohesion' (higher child scores). Thus, in order to gain a complete picture of functioning, it is preferable to obtain HRQoL data from the children's point of view supplemented with data from the parents' perspective, as children and parents may not necessarily share similar views about the overall impact of overweight.

Chapter 3 covers the results of studying the expression of adiponectin and leptin receptors on circulating immune cells in obese children pre- and post-lifestyle intervention compared to normal weight control children. We demonstrated that circulating leukocyte subsets show distinct adipokine receptor expression profiles. These distinct adipokine receptor profiles may partly explain the differential impact of adipokines on leukocyte subsets. Next, we showed that leukocyte subset numbers and adipokine receptor expression profiles were largely similar in obese children and controls. From this we can conclude that adipokine signalling in childhood obesity is primarily modulated by circulating adipokine levels, instead of adipokine receptor expression.

In **Chapter 4** we described the results of a study conducted to evaluate ambulatory blood pressure measurement (ABPM) patterns in a population of overweight and obese children and adolescents, in order to estimate the prevalence of (hidden) abnormal blood pressure patterns. A high prevalence of abnormal ABPM patterns (white coat hypertension, elevated blood pressure, masked hypertension, ambulatory hypertension) was detected, with only

54.9% of the population classified as normal blood pressure using ABPM. In addition, an abnormal circadian variation was highly prevalent: isolated night-time BP load ≥25% with normal daytime ABPM was found in almost one quarter 25% of the participants, and 40.2% of the participants lacked the physiologic nocturnal SBP dip. Finally, office blood pressure measurement was often poorly correlated with a subject's actual ABPM pattern. Thus, this study confirms the high prevalence of abnormal blood pressure in obese children and adolescents, and it also underscores the unreliability of office blood pressure measurement and the need for blood pressure monitoring by APBM.

Moving to **PART II** of this thesis, we elaborated on the treatment of childhood obesity: ***Way beyond weight.***

In **Chapter 5** we summarised the effects of our multidisciplinary multicomponent weight loss intervention in Hospital Gelderse Vallei, specifically comparing overweight/obese children with overweight/obese adolescents. Children showed significant larger BMI Z-score differences than adolescents (BMI Z-score difference end versus start of treatment -0.33 [SD 0.48] in children, -0.09 [SD 0.28] in adolescents) and more often a clinically relevant BMI Z-score decrease of >0.25 (48% versus 26%, p=0.10). The prevalence of abnormal blood pressure, disturbances in glucose homeostasis, and metabolic syndrome decreased in the total group. Children showed a more favourable effect than adolescents, confirming the importance of early start of treatment. The dropout rate in our study was 30% in children and 41% in adolescents. This points to the need of a careful assessment of initial expectations including identification of barriers to follow-up, as a screening before treatment commences, followed by individualised care.

Although several intervention programmes for children result in a decrease in BMI Z-score in the short term, from literature and experience we know that preventing relapse remains an important challenge. Therefore, we performed a systematic review and meta-analysis on maintenance programmes in childhood obesity, which is presented in Chapter 6 of this thesis. The aim of this review was to summarise the existing knowledge on programmes and initiatives aimed at long-term maintenance of a healthy or reduces weight in children and adolescents following initial treatment of overweight. **Chapter 6A** provides the overview and design of this systematic review, and in **Chapter 6B** we presented the findings. We found that the BMI Z-score of maintenance intervention participants remained stable, whereas control participants experienced a slight increase. No differences were observed regarding intensity and duration of therapy. A slight preference for 'face-to-face' versus 'on distance' interventions was shown. Thus, although there is limited quality data to recommend one maintenance intervention over another, in general continued treatment does have a stabilising effect on BMI Z-score.

Finally, in **Chapter 7** (General Discussion) we contemplated on the main findings of this thesis and critically discussed theoretical, practical, and methodological issues derived from this thesis. We demonstrated that there are many aspects to consider when performing research in the field of childhood obesity. The obese childhood population that seeks help and that we encounter in our clinic is a selected group of patients that might not exactly reflect the general obese pediatric population. Additionally, we showed that a complex set of factors from multiple contexts (as summarised in the ecological model) interact with each other to place a child at risk of overweight, and at least partly determine the effect of obesity treatment. Obesity is actually the only common denominator of our participants. All other variables, including child-, family- and environmental-related factors and associated comorbidities, diverge between the individual patients. Childhood obesity treatment has to comprise all these variables, and we have discussed this in relation to intervention format, design, and duration. We elaborated on the increasing trend in obesity research and care from weight management to health promotion, from weight-based terminology to health-based terminology, from a conventional weight focus to a broader range of outcome measures including physiological, health behavioural, and psychosocial outcomes. Finally, we commented more generally on performing research in the field of obesity, by discussing study design and the gap between what practice needs and what is delivered by science. By moving thoughts from scientifically relevant problems to practically relevant problems, not only focusing on the improvement of (scientific) quality of the information, but also on its relevance for public health policy and its translation into relevance for the local context, we might shorten the distance between science and practice. We highlighted the implications of our research for daily clinic, with regard to consequences of childhood obesity including obesity-related comorbidities, and with regard to obesity treatment. Additionally, we mentioned directions for future research. In general, it would be valuable to broaden our knowledge regarding the basic behavioural, psychosocial, and biological mechanisms driving the development of severe obesity and the influence of these factors on treatment response, with the aim to better understand the heterogeneous aetiology of obesity and explain the high degree of variability observed with interventions. Next, drivers of participation and factors that affect retention in treatment programmes have to be more extensively studied. In addition, both treatment content and involvement of family and environment in the treatment of children of different age groups remains an important area of research. We might learn more from children with obesity, by more specifically focusing on patient subpopulations. Last but not least, I would like to advocate for a trend towards network medicine: from multidisciplinary teams on islands in clinic and laboratory, to more extensive collaboration in large networks with coordinated initiatives and shared knowledge, involving all stakeholders in the field.

SUMMARY IN DUTCH / NEDERLANDSE SAMENVATTING

Overgewicht op de kinderleeftijd komt momenteel alarmerend vaak voor. Het is wereldwijd een van de belangrijkste gezondheidsproblemen. In Nederland is de prevalentie van jongens met overgewicht gestegen van 9% in 1997 tot 13% in 2009. De prevalentie van obesitas in deze groep steeg van 0.9% in 1997 tot 1.8% in 2009. Bij meisjes is een vergelijkbare trend zichtbaar: de prevalentie van overgewicht was 12% in 1997 en 15% in 2009, en de prevalentie van obesitas steeg van1.6% in 1997 tot 2.2% in 2009. Overgewicht en obesitas ontstaan op steeds jongere leeftijd, en de prevalenties variëren sterk binnen verschillende etnische groepen. Bij kinderen van Turkse en Marokkaanse afkomst komen overgewicht en obesitas vaker voor dan bij kinderen met een Nederlandse achtergrond. Ook zien we meer overgewicht en obesitas bij kinderen van ouders met een laag opleidingsniveau.

In **Hoofdstuk 1** (Algemene Introductie) van dit proefschrift wordt achtergrondinformatie gegeven over de obesitasepidemie bij kinderen. Bij volwassenen wordt overgewicht gedefinieerd als een body mass index (BMI, berekend door het gewicht te delen door de lengte in het kwadraat) ≥25, en obesitas als een BMI ≥30. Bij kinderen verandert de BMI substantieel met de leeftijd. Daarom zijn leeftijd- en geslachtsspecifieke afkapwaarden voor BMI vastgesteld door de International Obesity Task Force. Mede vanwege de veranderende BMI wordt bij kinderen vanaf de leeftijd van 2 jaar gebruik gemaakt van BMI standaarddeviatiescores (BMI-SDS of BMI Z-scores), waarbij de BMI-waarde van het kind wordt afgezet tegen die van leeftijds- en seksegenoten. Een BMI Z-score van 0 betekent gemiddeld, een normaal gewicht. In de literatuur wordt gesproken over een effectieve behandeling wanneer een BMI Z-score daling optreedt van ≥0.25.

Hoewel er steeds meer bekend is over overgewicht[1] bij kinderen, zijn er ook nog veel vragen. Daarom worden in dit proefschrift een aantal belangrijke onderwerpen op het gebied van overgewicht bij kinderen verder bestudeerd.

In **DEEL I** van dit proefschrift wordt gefocust op de consequenties van overgewicht bij kinderen. Overgewicht is geassocieerd met belangrijke lichamelijke, psychische en sociale gevolgen, zowel op de korte als op de lange termijn.

In **Hoofdstuk 2** worden de resultaten beschreven van een studie waarbij de kwaliteit van leven van kinderen en tieners met overgewicht is onderzocht op het moment dat zij startten met een van de behandelprogramma's in Ziekenhuis Gelderse Vallei (zie hieronder). Uit deze studie blijkt dat kinderen met een toenemende mate van overgewicht zich presenteren met een slechtere kwaliteit van leven, in het bijzonder als het gaat over fysiek welbevinden. Daarnaast zijn kwaliteit van leven vragenlijsten ingevuld door ouders (als afgeleide van hun kind), vergeleken met vragenlijsten ingevuld door de kinderen zelf (vanaf een leeftijd van 10 jaar). Hieruit blijkt dat op het gebied van 'Lichamelijke pijn/discomfort' en 'Algemene gezondheidsbeleving' kinderen significant lager scoren dan hun ouders, en op het gebied van 'Gedrag' en 'Familiecohesie' significant hoger.

1 In deze samenvatting wordt de term overgewicht gebruikt voor zowel overgewicht als obesitas.

Om een compleet beeld te verkrijgen over het functioneren van een kind met overgewicht, is het dus van belang dat kwaliteit van leven wordt gemeten vanuit het perspectief van het kind, aangevuld met data van ouders. Dit omdat kinderen en ouders dus niet noodzakelijkerwijs een gelijke mening hebben over de impact van overgewicht op de kwaliteit van leven van het kind.

Overgewicht op de kinderleeftijd vergroot de kans op het optreden van hart- en vaatziekten op vroege en latere leeftijd. Op moleculair niveau is aangetoond dat laaggradige ontsteking (inflammatie) een belangrijke rol speelt in de relatie tussen overgewicht en het toegenomen cardiovasculaire risico, door een cascade van effecten. Deze cascade start met de ontwikkeling van een excessieve hoeveelheid vetcellen (adipocyten). Adipocyten produceren signaaleiwitten, ook wel adipokines genoemd. Er zijn pro-inflammatoire adipokines (die ontsteking veroorzaken, een voorbeeld hiervan is leptine) en anti-inflammatoire adipokines (die ontsteking tegengaan, bijvoorbeeld adiponectine). Bij overgewicht worden er relatief meer pro-inflammatoire adipokines geproduceerd, waardoor laaggradige ontsteking ontstaat. Hierbij worden cellen van het immuunsysteem, namelijk witte bloedcellen, betrokken. Uiteindelijk draagt deze laaggradige ontsteking bij aan het ontwikkelen en progressief zijn van aan overgewicht gerelateerde complicaties zoals hart- en vaatziekten.
Bij overgewicht is de hoeveelheid adiponectine verlaagd en de hoeveelheid leptine verhoogd. Adiponectine en leptine werken onder andere doordat zij zich binden aan een receptor op de witte bloedcellen. Er zijn verschillende soorten witte bloedcellen. De adipokines hebben op elke witte bloedcel een ander soort effect, maar we weten niet zo goed hoe dit komt. In **Hoofdstuk 3** worden de resultaten beschreven van onderzoek naar de expressie van receptoren voor adiponectine en leptine op de witte bloedcellen van kinderen met overgewicht. Deze expressie is gemeten op twee tijdstippen bij 13 kinderen met overgewicht: voor start van de behandeling en na de behandeling. Tevens zijn kinderen met overgewicht vergeleken met kinderen met een gezond gewicht. Uit deze studie komt naar voren dat bepaalde witte bloedcellen een ander profiel hebben van adipokine receptor expressie. Deze verschillen in receptor profielen zouden, op zijn minst deels, de verschillende impact die adipokines hebben op de diverse witte bloedcellen kunnen verklaren. Verder laat dit onderzoek zien dat het aantal witte bloedcellen en de adipokine receptor expressie profielen gelijk zijn bij kinderen met overgewicht en kinderen met gezond gewicht. Hieruit kunnen we concluderen dat de signaaloverdracht die plaatsvindt via adipokines bij kinderen met overgewicht voornamelijk wordt gemoduleerd door de hoeveelheid circulerende adipokines, in plaats van de hoeveelheid receptoren die tot expressie komt op de witte bloedcellen.

Het volgende hoofdstuk van dit proefschrift gaat over bloeddruk. Overgewicht kan een te hoge bloeddruk (hypertensie) veroorzaken. Hypertensie is een risicofactor voor het ontwikkelen van hart- en vaatziekten. Daarom wordt bij kinderen met overgewicht de bloeddruk gecontroleerd. Het meten van de bloeddruk op de polikliniek is een momentopname. Daarnaast schommelt de bloeddruk over de dag. Het is bekend dat bij mensen met hypertensie de bloeddruk in de nacht minder daalt (dipping) dan bij mensen met een normaal gewicht. Het niet voldoende dalen van de bloed-

druk in de nacht is een voorloper van het ontwikkelen van hypertensie. Om een indruk te krijgen van de bloeddruk gedurende dag en nacht wordt bij alle kinderen met overgewicht in Ziekenhuis Gelderse Vallei een 24-uurs bloeddrukmeting verricht. Met een 24-uurs bloeddrukmeting kunnen bloeddrukpatronen worden ontdekt die niet gedetecteerd worden met een eenmalige meting op de polikliniek. Een voorbeeld hiervan is witte-jassen-hypertensie (waarbij de eenmalige meting op de polikliniek een te hoge bloeddruk laat zien, maar de 24-uurs meting normaal is), gemaskeerde hypertensie (waarbij de meting op de polikliniek normaal is, maar er bij 24-uurs bloeddrukmeting toch sprake blijkt te zijn van hypertensie) en nachtelijke hypertensie. In **Hoofdstuk 4** worden de resultaten beschreven van de 24-uurs bloeddrukmetingen die zijn verricht bij 82 kinderen met overgewicht. Deze evaluatie is gedaan om te bekijken of het verrichten van een 24-uurs bloeddrukmeting meerwaarde heeft boven het verrichten van een bloeddrukmeting op de polikliniek, onder andere ook omdat een 24-uurs bloeddrukmeting voor sommige kinderen best belastend kan zijn. Daarnaast is bestudeerd hoe vaak er sprake is van een abnormaal 24-uurs bloeddrukpatroon. Uit deze studie bljkt dat verhoogde bloeddruk, hypertensie, en abnormale bloeddrukpatronen als witte-jassen-hypertensie en gemaskeerde hypertensie vaak vóórkomen bij kinderen met overgewicht. Slechts 54.9% van deze populatie kinderen met overgewicht had een normale bloeddruk bij 24-uurs bloeddrukmeting. Daarnaast komt een verhoogde bloeddruk 's nachts (met overdag een normale bloeddruk) voor bij bijna een kwart van de kinderen met overgewicht, en ruim 40% van de kinderen heeft geen nachtelijke dip in hun bovendruk. Tenslotte is de bloeddruk die wordt gemeten op de polikliniek vaak niet goed te correleren aan het 24-uurs bloeddrukpatroon van het kind. Dus, deze studie bevestigt dat een abnormale bloeddruk vaak voorkomt bij kinderen met overgewicht, en dat het niet voldoende is om alleen een bloeddruk op de polikliniek te controleren (momentopname) maar dat er een noodzaak bestaat voor monitoring van de bloeddruk door middel van een 24-uurs bloeddrukmeting.

In **DEEL II** van dit proefschrift wordt ingegaan op de behandeling van kinderen met overgewicht. In Ziekenhuis Gelderse Vallei zijn drie behandelprogramma's ontwikkeld: *AanTafel!* voor kinderen van 3 t/m 7 jaar, *Basta* voor kinderen van 8 t/m 12 jaar, en *Toppers* voor kinderen van 13 t/m 17 jaar. Deze behandelprogramma's zijn multidisciplinair (kinderarts, psycholoog, fysiotherapeut en diëtist) van aard en volgen een cognitief gedragsmatige benadering. Ze hebben een totale duur van negen maanden (*Toppers*) tot 1 jaar (*AanTafel!* en *Basta*) en bestaan uit drie individuele bijeenkomsten (t=0, start behandeling; t=1, 3-4 maanden na start behandeling; t=2, eind behandeling, dit 9-12 maanden na start behandeling) en meerdere groepsbijeenkomsten met als hoofdthema een gezonde leefstijl (fysieke activiteit en gezond eten). Daarnaast zijn er een aantal beweegbijeenkomsten met de fysiotherapeut. In de eerste 3-4 maanden van de behandeling zijn er meer bijeenkomsten (intensieve gedeelte) dan in de resterende maanden van het programma (minder intensieve gedeelte). Afhankelijk van de leeftijdsgroep is het programma vooral gericht op ouders (*AanTafel!*), op zowel ouders als kind (*Basta*), of met name op het kind zelf (*Toppers*). Face-to-face contacten worden ondersteund door een persoonlijk en beveiligd digitaal werkboek op internet. In dit werkboek kan men extra

achtergrondinformatie vinden (teksten, video's) die aansluiten bij de structuur van het programma (informatie o.a. over gedragsverandering, fysieke activiteit, en gezond eten). Daarnaast dienen de ouders en/of kinderen opdrachten te maken (waaronder het invullen van eet- en beweegdagboeken) als voorbereiding op de bijeenkomsten. Na elke bijeenkomst gaat een nieuwe module open in het digitale werkboek. Het werkboek is verbonden met het elektronisch patiëntendossier van het kind. De behandelaren kunnen de ingevulde opdrachten bekijken en de uitkomsten bediscussiëren met de deelnemers tijdens de eerstvolgende bijeenkomst. Een beveiligd berichtensysteem zorgt ervoor dat deelnemers en behandelaren digitaal kunnen communiceren, en moedigt deelnemers aan het programma vol te houden.

De programma's zijn gebaseerd op zelfmonitoring en zelfevaluatie. Deelnemers worden uitgedaagd doelen voor zichzelf en hun gezin te stellen, en een persoonlijk plan te ontwikkelen voor moeilijke momenten die zij in het dagelijks leven tegenkomen als het gaat om een gezonde leefstijl (bijv. verjaardagen, feestdagen, ongezonde keuzes in de supermarkt, enzovoorts). Zelfregulerende vaardigheden worden onderwezen met als doel een permanente leefstijlverandering te bewerkstelligen. In alle programma's worden de drie componenten van de interventie (gedragsverandering, fysieke activiteit, gezond eten) met de deelnemers doorgenomen, waarbij rekening wordt gehouden met de leeftijd van het kind en de uitdagingen die binnen de desbetreffende leeftijdscategorie spelen.

De behandelprogramma's worden allen gevolgd door een bestendigingsprogramma met een duur van twee jaar. In deze vervolgprogramma's wordt gefocust op motivatie en capaciteit om de gezonde leefstijl vol te houden. De bestendigingsprogramma's bestaan uit vier keer per jaar een groepsbijeenkomst, waarbij het vooral gaat over moeilijke momenten die ouders en kinderen tegenkomen in hun dagelijks leven als het gaat over het volhouden van een gezonde leefstijl. Daarnaast is er extra aandacht voor gedragsverandering en planning. Tijdens de bestendigingsprogramma's worden lokale zorgverleners en initiatieven uit de buurt betrokken om te streven naar een naadloze transfer naar de eigen omgeving van het kind.

In **Hoofdstuk 5** wordt het effect van de behandelprogramma's in Ziekenhuis Gelderse Vallei beschreven, waarbij we het effect bij kinderen met overgewicht (3 t/m 12 jaar) hebben vergeleken met het effect bij tieners met overgewicht (13 t/m 17 jaar). Kinderen lieten een significant grotere daling in BMI Z-score zien dan tieners: een afname in BMI Z-score van 0.33 bij kinderen versus 0.09 bij tieners. Daarnaast werd bij kinderen vaker een klinisch relevant verschil van ≥0.25 gezien in BMI Z-score dan bij tieners (48% versus 26%). Gedurende de behandeling nam de prevalentie van abnormale bloeddruk, verstoringen in het glucosemetabolisme en metabool syndroom af in de totale groep (alle kinderen en tieners bij elkaar). Bij kinderen werd meer effect gezien dan bij tieners, hetgeen het belang van een vroege start van behandeling, dus op jonge leeftijd al, bevestigt. Het percentage deelnemers wat het behandelprogramma niet heeft afgemaakt was 30% bij de kinderen en 41% bij de tieners. Redenen voor uitval waren onder andere een gebrek aan motivatie, problemen met het tijdstip van de bijeenkomsten of de planning van het programma, psychologische factoren en een belaste familiesituatie. Deze grote uitval benadrukt de noodzaak om nauwgezet, voor start van de behandeling, de wederzijdse verwachtingen en mogelijke barrières bij het afmaken van het

programma te bespreken. Daarnaast geeft dit aan dat het belangrijk is om de zorg te individualiseren.

Hoewel verschillende behandelprogramma's voor kinderen met overgewicht resulteren in een afname van BMI Z-score op de korte termijn, weten we uit de literatuur en uit eigen ervaring dat het voorkómen van een terugval (opnieuw een stijging in BMI Z-score, of een ongezondere leefstijl) na behandeling een grote uitdaging is. Daarom hebben wij in de literatuur gezocht naar wat er bekend is over bestendigingsprogramma's (programma's na initiële behandeling) voor kinderen met overgewicht, en deze kennis hebben we samengevat in een systematische review en meta-analyse. In **Hoofdstuk 6A** wordt beschreven hoe we in de literatuur hebben gezocht naar relevante studies en vervolgens deze kennis hebben gebundeld. In **Hoofdstuk 6B** presenteren we onze bevindingen. We concludeerden dat de BMI Z-score van kinderen die meededen aan een bestendigingsprogramma stabiel blijft, terwijl bij kinderen in de controlegroep (dus kinderen die geen bestendigingsprogramma hebben gevolgd na hun behandeling voor overgewicht) een lichte stijging in BMI Z-score werd gezien bij follow-up. Het maakt hierbij niet uit hoe intensief het bestendigingsprogramma is of hoe lang het programma duurt. Wel bestaat er een lichte voorkeur voor 'face-to-face' behandeling versus behandeling op afstand (bijv. online of via SMS). Echter, de kwaliteit van de studies die we hebben gebruikt voor onze samenvatting was niet altijd even goed. Meer studies waren er niet beschikbaar. Samengevat: hoewel er maar weinig kwalitatief goede data beschikbaar zijn om één manier van bestendigen aan te bevelen boven een ander, heeft een voortgezette behandeling een stabiliserened effect op de BMI Z-score.
De kennis uit deze systematische review en meta-analyse is gebruikt bij het ontwikkelen van de bestendigingsprogramma's in Ziekenhuis Gelderse Vallei.

Tot slot wordt in **Hoofdstuk 7** (Algemene Discussie) een beschouwing gegeven over de belangrijkste bevindingen beschreven in dit proefschrift. Kritisch worden de diverse theoretische, praktische en methodologische punten bediscussieerd die naar voren zijn gekomen in de hoofdstukken. Er zijn veel aspecten om rekening mee te houden wanneer onderzoek wordt verricht op het gebied van overgewicht bij kinderen. Bijvoorbeeld als het gaat om de populatie die wordt bestudeerd. De groep kinderen met overgewicht die wij hebben gevraagd voor onze studies heeft hulp gezocht. Deze groep is een geselecteerde groep van patiënten die naar alle waarschijnlijkheid niet de algemene populatie kinderen met overgewicht reflecteert. Tevens beschrijven we dat er veel verschillende factoren zijn binnen diverse contexten, bijvoorbeeld het kind zelf, zijn/haar familie, de omgeving van het kind, die er samen voor zorgen dat een kind een verhoogd risico heeft op overgewicht. Deze factoren bepalen ook op zijn minst deels het effect van de behandeling van overgewicht bij deze kinderen. Overgewicht is eigenlijk het enige wat de kinderen als gemeenschappelijke factor hebben. Allerlei andere factoren, waaronder kind-, familie- en omgevingsgerelateerde factoren en de gevolgen van overgewicht die zich bij een kind kunnen presenteren (lichamelijk, psychisch, sociaal), verschillen tussen de individuele patiënten. De behandeling van overgewicht

dient met al deze variabelen rekening te houden. Dit wordt bediscussieerd in relatie tot het soort behandeling, de opbouw en de duur van de behandeling. Verder is er een toenemende trend, zowel in wetenschappelijk onderzoek als in de zorg, om bij de aanpak van overgewicht meer te focussen op gezondheidsbevordering in het algemeen dan op een te hoog gewicht. Bijvoorbeeld door over te gaan van op gewicht gebaseerde terminologie naar op gezondheid gebaseerde terminologie, en van het geïsoleerde focus op gewicht naar een breder arsenaal aan uitkomstmaten waaronder fysiologische, leefstijlgerelateerde en psychosociale uitkomsten (bijvoorbeeld kwaliteit van leven).

Tenslotte wordt de opzet van wetenschappelijke studies bediscussieerd en het gat tussen wat de praktijk nodig heeft en wat aan kennis wordt geleverd door de wetenschap. Door niet zozeer te denken in wetenschappelijk relevante problemen maar meer in praktisch relevante problemen is het wellicht mogelijk om de afstand tussen wetenschap en praktijk te verkleinen. In dit kader bediscussiëren we de implicaties die ons onderzoek heeft voor de dagelijkse praktijk. Daarnaast worden richtingen benoemd voor toekomstig wetenschappelijk onderzoek. Het zou bijvoorbeeld waardevol zijn om onze kennis te verbreden als het gaat om de basale gedragsmatige, psychosociale en biologische mechanismen die de ontwikkeling van ernstige obesitas drijven, en de invloed die deze factoren hebben op het effect van behandeling. Daarmee kunnen mogelijk de diverse ontstaansmechanismen van overgewicht beter worden begrepen, en kan wellicht worden verklaard waarom de ene patiënt wel en de andere patiënt niet op een bepaalde behandeling reageert. Verder zouden we de drijfveren van deelname aan behandeling beter kunnen onderzoeken, inclusief de factoren die van invloed zijn op het wel of niet volhouden van een behandeling. Daarnaast blijft het belangrijk om verder uit te zoeken welke soort behandeling qua inhoud het beste is, en hoe het gezin en de omgeving van de patiënt het beste betrokken kunnen worden in de behandeling van kinderen van verschillende leeftijden met overgewicht. Tot slot is netwerkgeneeskunde onmisbaar. Er bestaan diverse goede initiatieven op het gebied van overgewicht bij kinderen, maar vaak weet men niet van elkaar waar men mee bezig is. Samenwerken in grote netwerken met gecoördineerde initiatieven en gedeelde kennis, waarbij alle stakeholders in het veld worden betrokken, zal uiteindelijk resulteren in betere zorg.

Concluderend: overgewicht op de kinderleeftijd is en blijft een uitdagend onderwerp, vanuit verschillende gezichtspunten, zowel als het gaat over het verrichten van wetenschappelijk onderzoek op dit gebied als over hoe we in de dagelijkse praktijk de zorg voor kinderen met overgewicht het beste kunnen vormgeven. Hoewel we in dit proefschrift op een aantal gebieden binnen het onderwerp overgewicht bij kinderen weer wat meer kennis hebben opgedaan, blijven er achter de deuren van de obesitasepidemie veel onderwerpen over die persisterend aandacht behoeven in toekomstig wetenschappelijk onderzoek en in de zorg voor de kinderen met overgewicht.

ABBREVIATIONS

ABCD	Adiposity-Based Chronic Disease
ABPM	ambulatory blood pressure monitoring
ADA	American Diabetes Association
AdipoR1	adiponectin receptor 1
AdipoR2	adiponectin receptor 2
AHA	American Heart Association
BMI	body mass index
BMI-SDS	body mass index standard deviation score
BP	blood pressure in mmHg
CDC	Centers for Disease Control and Prevention
CEBQ	Child Eating Behaviour Questionnaire
CHQ-CF87	Child Health Questionnaire Child Form 87
CHQ-PF50	Child Health Questionnaire Parental Form 50
CI	confidence interval
cIMT	carotid intimal-medial thickness
CVD	cardiovascular disease
DBP	diastolic blood pressure
DEBQ	Dutch Eating Behaviour Questionnaire
ECHO	Commission on Ending Childhood Obesity
eGRF	estimated glomerular filtration rate
FU	follow-up
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostasis model assessment of insulin resistance
HRQoL	health-related quality of life
HTN	hypertension
IDF	International Diabetes Federation
IL	interleukin
iNKT	invariant Natural Killer T-cells
IOTF	International Obesity Task Force
ITQOL-97	Infant Toddler Quality of Life Questionnaire 97
ITT	intention-to-treat analysis
IQR	interquartile range
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
LDL-C	low-density lipoprotein cholesterol
MFI	median fluorescence intensity
MH	masked hypertension
MetS	metabolic syndrome
OBP	office blood pressure
OGTT	2-h oral glucose tolerance test

PA	physical activity
PBMC	peripheral blood mononuclear cells
PPARγ	peroxisome-proliferator-activated receptor γ
PWV	pulse wave velocity
RCT	randomised controlled trial
SBP	systolic blood pressure
SE	standard error
SSFT	sum of the four (biceps, triceps, subscapular, supra-iliacal) skinfold thicknesses
TC	total cholesterol
TG	triglycerides
TNF	tumor necrosis factor
TOD	target-organ disease
T2D	type 2 diabetes
SD	standard deviation
WC	waist circumference
WCH	white coat hypertension
WHO	World Health Organization

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ABOUT THE AUTHOR

CURRICULUM VITAE

Laila Bernadette van der Heijden was born in Apeldoorn, the Netherlands, on the 23th of June 1987. After graduating from secondary school in Apeldoorn in 2005, she started her study Medicine at Utrecht University. She completed her foundation year cum laude in 2006. During the subsequent years of her medical training Laila was involved in several research projects. In the context of the Excellent Traject, Laila developed a multicentre study on chronic immune thrombocytopenia (ITP) in children (CIN-KID study) in the Netherlands, under the supervision of Dr M.C.A. Bruin and Dr K.M.J. Heitink-Pollé. During her final year research internship she performed a laboratory study using the collected CIN-KID data and blood samples, investigating the correlation between platelet function parameters and clinical bleeding tendency in children with chronic ITP. During another research elective, Laila effectuated a retrospective research project on the treatment of fetal supraventricular tachycardia, under the supervision of Dr M. Freund. In the last year of her medical study, Laila lived in London for five months where she conducted a clinical audit on the antenatal detection of transposition of the great arteries at the Royal Brompton Hospital, as a research fellow under the supervision of Dr H.M. Gardiner. In addition to these research projects, Laila went abroad for two clinical internships during her study Medicine: Ophthalmology (University of Malaya, Malaysia) and Obstetrics and Gynecology (Queen Elizabeth Hospital, Blantyre, Malawi).

After graduation from medical school in 2012, Laila started working as a paediatric resident at Hospital Gelderse Vallei in Ede, the Netherlands. In 2013 she commenced on her PhD studies as an external PhD student at the Division of Human Nutrition and Health, Wageningen University, in collaboration with Hospital Gelderse Vallei, under the supervision of Prof. Dr E.J.M. Feskens and Dr A.J. Janse. As a PhD student, Laila attended several national and international conferences. Additionally, she was involved in the supervision of bachelor and master students from Wageningen University and Utrecht University. Parallel to the PhD research leading to this thesis, Laila started her specialist training in paediatrics at the Wilhelmina Children's Hospital, University Medical Centre in Utrecht, the Netherlands (Prof. Dr J. Frenkel) in 2015. The first part of her paediatric training she worked at St. Antonius Hospital in Nieuwegein, the Netherlands (Dr W.A.F. Balemans).

Since 2016 Laila has been a member of the board of the Dutch Paediatric Society (NVK), and the president of the board representing all paediatric residents in the Netherlands. Additionally, she is involved in several other committees of the Dutch Paediatric Society, including the council for paediatric training and education (Concilium Paediatricum).

Laila lives in Utrecht, together with Antoine Kuijpers and their son Tjebbe (March 2018).

LIST OF PUBLICATIONS

Publications in peer reviewed journals

Publications included in this thesis are marked by an asterisk (*)

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** contributed equally to this study

Gardiner HM, Kovacevic A, van der Heijden LB, Pfeiffer PW, Franklin RCG, Gibbs JL, LaRovere JM. Prenatal screening for major congenital heart disease: assessing performance by combining national cardiac audit with maternity data. Heart. 2014; 100(5):375-82

van der Heijden LB, Oudijk MA, Manten W, ter Heide H, Pistorius L, Freund MW. Sotalol as first line treatment in fetal tachycardias and neonatal follow-up. Ultrasound Obstet Gynecol. 2013; 42(3):285-93

Submitted for publication

Publications included in this thesis are marked by an asterisk (*)

* Van der Heijden LB, Feskens EJM, Janse AJ. The effects of a multidisciplinary, multicomponent, family-based childhood obesity treatment programme – comparing results in young children and adolescents. Accepted for publication in BMC Pediatrics.

* van der Heijden LB, Feskens EJM, Raat H, Janse AJ. Quality of life of children and adolescents with clinical obesity. Submitted.

* van der Heijden LB, Groothoff JW, Feskens EJM, Janse AJ. Office blood pressure versus ambulatory blood pressure measurement in childhood overweight and obesity. Submitted.

OVERVIEW OF COMPLETED TRAINING ACTIVITIES

Discipline specific activities

- NVK congress, Nederlandse Vereniging voor Kindergeneeskunde (NVK, Dutch Paediatric Society), 2012 (Veldhoven, The Netherlands)
- National Congress on Childhood Obesity, Alliantie Voeding Gelderse Vallei (AVGV)/Ziekenhuis Gelderse Vallei (ZGV, Hospital Gelderse Vallei)/ Wageningen University and Research (WUR), 2013 (Ede, The Netherlands)
- NASO Annual meeting, Netherlands Association for the Study of Obesity (NASO), 2013 (Utrecht, The Netherlands)
- Introduction to Data Analysis, Netherlands Institute for Health Sciences (NIHES) Erasmus Summer Programme, 2013 (Rotterdam, The Netherlands)
- Principles of Research in Medicine and Epidemiology, NIHES Erasmus Summer Programme, 2013 (Rotterdam, The Netherlands)
- Masterclass Public Health Research in Practice, WUR, 2013 (Wageningen, The Netherlands)
- Symposium 'Fibres in food and feed', WUR, 2013 (Wageningen, The Netherlands)
- Young Investigators Day, Training Upcoming Leaders in Paediatric Science (TULIPS), 2013 (Veldhoven, The Netherlands)
- NVK congress, NVK, 2013 (Veldhoven, The Netherlands)
- NASO Silver Jubilee meeting, NASO, 2014 (Oosterbeek, The Netherlands)
    - Poster presentation (1x)
- Congress on Severe Obesity in Childhood, SCEM, 2014 (Ede, The Netherlands)
- Young Investigators Day, TULIPS, 2014 (Veldhoven, The Netherlands)
- NVK congress, NVK, 2014 (Veldhoven, The Netherlands)
- National Congress on Childhood Obesity, AVGV/ZGV/WUR, 2015 (Ede, The Netherlands)
- Minisymposium Kinderobesitas Barneveld, Gemeente Barneveld, 2015 (Barneveld, The Netherlands)
    - Oral presentation (1x)
- NVK congress, NVK, 2015 (Veldhoven, The Netherlands)
- NVK congress, NVK, 2017 (Papendal, The Netherlands)
- European Congress on Obesity (ECO), European Association for the Study of Obesity (EASO), 2018 (Vienna, Austria)
    - Oral presentation (1x)
- NVK congress, NVK, 2018 (Papendal, The Netherlands)
- ECO, EASO, 2019 (Glasgow, Scotland)
    - Poster presentation (2x)

General courses

- Competence Assessment, Wageningen Graduate Schools (WGS), 2013 (Wageningen, The Netherlands)
- PhD week, VLAG, 2013 (Wageningen, The Netherlands)
- Project and Time Management, WGS, 2013 (Wageningen, The Netherlands)
- PhD Workshop Carrousel, WGS, 2014 (Wageningen, The Netherlands)
- Scientific Writing, WGS, 2014 (Wageningen, The Netherlands)

Optionals

- Preparation of Research Proposal, WUR, 2012 (Wageningen, The Netherlands)
- Rothman Lunches, WUR, 2013-2015 (Wageningen, The Netherlands)
- PaperClip research meetings, WUR, 2014-2015 (Wageningen, The Netherlands)
- Staff seminars, WUR, 2012-2016 (Wageningen, The Netherlands)
- Food for Thought, AVGV/ZGV/WUR, 2012-2016 (Wageningen, The Netherlands)
    - Oral presentation (1x)
- Journal Club Paediatrics, ZGV/St. Antonius Ziekenhuis Nieuwegein/ Wilhelmina Kinderziekenhuis Utrecht, 2012-2019 (Ede, Nieuwegein, Utrecht; The Netherlands)
- PhD committee, WUR, 2014-2015 (Wageningen, The Netherlands)

Colophon

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