Esther van Hoek

Young Children and Obesity

Development and Evaluation of
FAMILY-ORIENTED TREATMENT

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Development and Evaluation of Family-oriented Treatment

Esther van Hoek

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Thesis committee

Promotor
Prof. Dr E.J.M. Feskens
Professor of Nutrition and Health over the life course
Wageningen University

Co-promotors
Dr A.J. Janse
Pediatrician and Clinical Epidemiologist, Department of Pediatrics
Gelderse Vallei Hospital, Ede

Dr L.I. Bouwman
Assistant professor, Health and Society
Wageningen University

Other members
Prof. Dr C. de Graaf, Wageningen University
Dr M.P. l'Hoir, TNO Quality of Life, Leiden
Dr T.L.S. Visscher, Windesheim University of Applied Sciences, Zwolle
Dr A.C.E. Vreugdenhil, Maastricht University Medical Centre

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Abstract

Introduction
The prevalence of childhood obesity has increased rapidly during the last decades. Childhood obesity is a multisystem disease with serious consequences such as hypertension, dyslipidemia, chronic inflammation, endothelial dysfunction and hyperinsulinemia. In addition, obese children have a decreased health-related quality of life (HRQoL).
The age interval of 3 to 7 years is a critical growth period. Fast increase of weight in this period is associated with obesity later in life. Furthermore, starting treatment at younger age is associated with a larger reduction in overweight. At the start of this project in 2009, there was no evaluated treatment program available for young obese children (defined as 3 to 8 years).
The risk of cardiovascular diseases and type 2 diabetes (i.e. cardiometabolic risk) can be assessed by measuring conventional risk factors (for example blood pressure). Other markers, such as pro-inflammatory markers, are part of the cardiometabolic risk profile. Epicardial adipose tissue is a metabolically active cardiac fat depot. In obese adults, the epicardial adipose tissue thickness (EATT) is increased, this is correlated to atherosclerosis. It is unknown whether young overweight children have already increased EATT.
The aim of this thesis is to develop, implement and evaluate a treatment program for obese young children. Furthermore, it aims to assess whether EATT is increased in obese young children and is correlated with the cardiometabolic risk profile, and with treatment.

Methods
The treatment program for obese young children is developed based on a review of the clinical guidelines, a literature review (including a systematic review with meta-analysis and an extended literature review) and target group interviews. The findings were integrated with professional judgement. To evaluate the resulting program called *AanTafel!,* a pilot study was performed (n=7 children), including a process evaluation based on parental interviews and questionnaires with the therapists. The effectiveness of *AanTafel!* was evaluated with a pre-post-test design including 40 children with a median BMI z-score of 3.4 (standard deviation 1.0) in secondary care. The BMI-z-score was the main outcome measure. Secondary outcome measures were components of the metabolic syndrome, markers of cardiometabolic risk, and HRQoL. Outcome measures were assessed at baseline and at the end of treatment (1 year). The BMI z-score was also evaluated 3 years after baseline in the first 23 children who finished treatment. EATT was measured by

echocardiography in 25 obese, 8 overweight, and 15 normal weight young children. In the obese and overweight children the EATT, as well as cardiometabolic risk factors, and the markers adiponectin and high sensitive CRP (hsCRP) were measured at baseline and after treatment.

Results

Meta-analysis showed that multicomponent treatment programs of moderate or high intensity (> 26 hours) were the most effective and resulted in a decrease of BMI z-score of 0.5. During the development of the treatment program, the gaps in evidence in clinical guidelines for childhood obesity treatment were overcome by insights from an additional literature review, target group interviews and professional judgement. The resulting treatment program *AanTafel!* has the following key characteristics: multicomponent, multidisciplinary, family-based with focus on parents, age-specific, tailored to individual children and families, a duration of one year and a combination of individual and group sessions and a web-based learning module. The pilot study showed that to improve parental involvement, peer support, family tailoring, and highly participative elements (such as self-monitoring) are important. The treatment program *AanTafel!* resulted in a change of mean BMI z-score of -0.5 directly after finishing treatment. This clinical relevant result persisted 2 years after baseline. Furthermore, a significant increase in HDL cholesterol and a reduction in the number of components of metabolic syndrome were found. Regarding markers of cardiometabolic risk, an overall significant decrease was seen in IL18, e-selectin, and sICAM. The HRQoL showed a non-significant improvement in most domains, with a clinically relevant improvement in the physical summary score. EATT was higher in overweight and obese young children compared to their normal weight peers. EATT was inversely correlated with adiponectin, but correlations with other cardiometabolic risk factors were not statistically significant. EATT did not change during treatment (n=17).

Conclusion

During the development process of an obesity treatment program, it was important to add the views of the target group and therapists to the evidence from clinical guidelines and literature review. The resulting treatment program *AanTafel!* is effective with a clinically relevant decrease of BMI z-score, an improvement of cardiometabolic risk profile, and a clinically relevant increase in the physical summary score of HRQoL. EATT is increased in obese young children; this is inversely correlated with adiponectin.

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Chapter 1

General introduction

Obesity in children is a common health problem in the Global North and an upcoming problem in the Global South [1]. The high and increasing prevalence of childhood obesity puts an increasing pressure on health systems [2]. Childhood obesity often has serious short- and long-term consequences for almost all organ systems [3]. With regards to the cardio-metabolic system, these consequences are dyslipidemia, hypertension, insulin resistance, chronic low-grade inflammation, and atherosclerosis. Consequences related to the pulmonary system, childhood obesity can result in obstructive sleep apnea (OSAS), asthma and exercise intolerance. Gastrointestinal consequences are fatty liver disease, gastro-esophageal reflux, and cholelithiasis. Furthermore, childhood obesity can result in lower-limb problems [3]. Also, obesity in childhood can lead to psychosocial problems such as bullying and decreased health-related quality of life (HRQoL) [4, 5].

Obesity in childhood is associated with higher mortality in middle age due to several causes, for example ischemic heart disease and colon cancer [6-9]. Obese youth are at increased risk of becoming obese adults, this is called tracking [10, 11]. Reduced productivity of these future adults at their work due to health problems is expected [2]. Therefore, the total societal cost burden of obesity is enormous [2].

Treatment of childhood overweight and obesity is necessary. Starting treatment at younger age appears to be associated with a reduction in overweight [12-15]. Research suggests that the age interval from 3 to 7 years is a critical growth period. Early adipositas rebound (the time point when body mass index rises after reaching a nadir) specified to rebound before the age of 5.5 years, predicts obesity later in life [10, 16, 17]. Therefore, early treatment of childhood obesity is important. In this thesis, we focused on the treatment of young obese children (defined as 3 to < 8 years) to reduce their overweight, and its cardio-metabolic and psychosocial consequences.

Definition, diagnosis and prevalence of obesity in young children

Defining and diagnosing obesity in young children

The World Health Organization (WHO) defines obesity as 'a condition of abnormal or excessive fat accumulation in the adipose tissue, to the extent that health may be impaired' [18]. The body mass index (BMI), calculated by Weight(kg)/[Height(m)]^2, is widely used to define obesity [19]. The disadvantage of BMI is that it is an indirect measure of fat mass and does not specify fat and lean mass [20]. Body fatness is also measured by more direct methods, including bioelectrical impedance, dual energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), and densitometry (BodPod). These methods are mostly used in scientific research, more expensive, sometimes not easy to perform in young children (because of fear for the procedure) and are therefore less appropriate for use in clinical practice [21]. Skinfold thickness measurements are often used in clinical practice despite of the poorer accuracy and precision when used for obese children compared to normal-weight children [20]. However, skinfold thickness measurements are reasonably reliable, with a fair correlation with DEXA (r 0.5-0.83 in different studies) and intra- and inter-observer variability are low compared to between-subject variability [20, 22]. Furthermore, waist circumference and mid-upper arm circumference (MUAC) are used for diagnosing overweight or obesity, but these measures do not exclusively measure fat mass [20, 21]. In adults, waist circumference (or waist-hip ratio) was found to be associated with morbidity, also after adjustment for relative weight [20]. In contrary in children, waist circumference was not proven to be superior to BMI. However waist circumference can provide useful additional information, for example when fat mass decreased and fat free mass increased possibly BMI remained stable and waist circumference decreased [21].

In adults, overweight is diagnosed as a BMI ≥ 25 mg/kg/m^2 and obesity as a BMI ≥ 30 mg/kg/m^2 [19]. In children, diagnosing overweight and obesity is more complicated by the fact that height is increasing and body composition is changing [18]. Therefore, specific BMI cut-offs for sex and age-groups are used in children. Two methods have been developed. The first one is based on the use of BMI for age charts (population specific) and the second one is based on the BMI for age international cut-offs. In the BMI for age charts the percentiles can be used as cut-off. The percentiles suggested as cut-off for obesity range from 95% to 99% [21]. The disadvantage of this method is that it is based on population-specific charts, which makes it difficult to compare populations. Therefore, Cole at al. developed BMI cut-offs for age and sex corresponding to adult BMI cut-offs of 25 and 30 kg/m^2 for respectively overweight and obesity [23]. These cut-offs are often referred to as the International Obesity Task Force (IOTF) criteria, are represented in Table 1, and used in this thesis.

Prevalence of obesity in young children

Worldwide, the prevalence of overweight (including obesity) increased from 1980 to 2013 [1]. In the Global North, 23.8% of boys and 22.6% of girls were overweight in 2013, compared to 16.9% of boys and 16.2% of girls in 1980 [1]. In the Global South, 12.9% of boys and 13.4% of girls were overweight in 2013, compared to respectively 8.1% and 8.4% in 1980 [1]. In The Netherlands in 2009, the overweight (including obesity) prevalence in young boys was between 7.8 (age 3) and 14.3% (age 7), and in young girls was between 12.8 (age 3) and 18.8% (age 7) according to the IOTF

Table 1 | IOTF criteria for overweight and obesity, based on the study of Cole et al. [23].

Age (yr)	Overweight		Obesity	
	Males (BMI)	Females (BMI)	Males (BMI)	Females (BMI)
3	17.89	17.56	19.57	19.36
3.5	17.69	17.40	19.39	19.23
4	17.55	17.28	19.29	19.15
4.5	17.47	17.19	19.26	19.12
5	17.42	17.15	19.30	19.17
5.5	17.45	17.20	19.47	19.34
6	17.55	17.34	19.78	19.65
6.5	17.71	17.53	20.23	20.08
7	17.92	17.75	20.63	20.51
7.5	18.16	18.03	21.09	21.01
8	18.44	18.35	21.60	21.57

criteria (Figure 1) [24]. The obesity prevalence in young boys and girls was between 0.8 (age 3) and 2.1% (age 7) and between 1.6 (age 3) and 3.4% (age 7) respectively. An overall increase was seen in the prevalence of overweight and obesity in children from 1980 to 2009. Also in young children this increase is seen, with the highest rise in children aged 7 and 8 years old. For example, the prevalence of obesity in boys and girls doubled in children aged three years. This increase rises with age to a more than fourfold increase in girls and twentyfold increase in boys aged 7 years old [24].

The prevalence of obesity differs between ethnic and socio-economic groups in The Netherlands. The mean BMI of children of Turkish children was the highest, followed by Moroccan, Dutch and Surinamese South Asian children [25]. The mean BMI of children in The Netherlands with low educated parents was clearly higher than in those with higher educated parents [24, 25]. Cultural, biological, environmental, social and economic factors likely cause the difference in prevalence between groups [26].

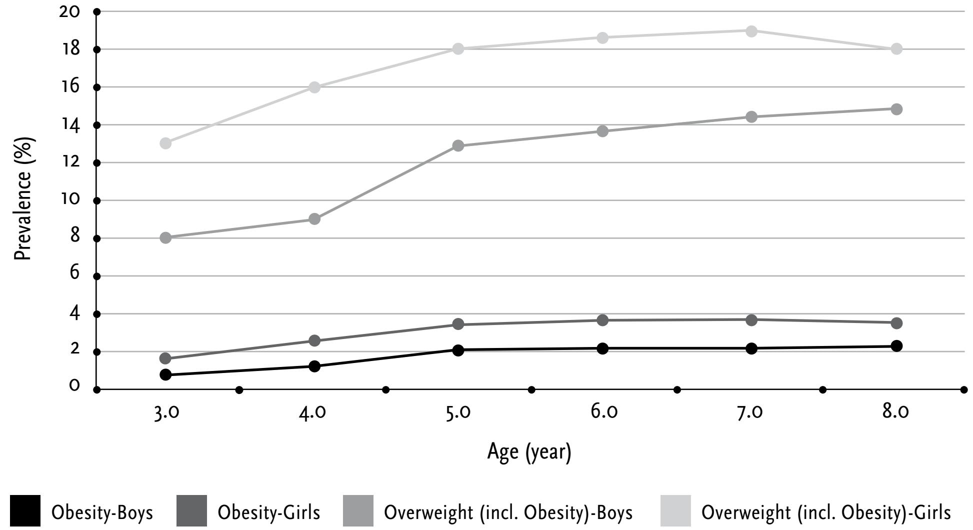

Figure 1 | Prevalence of overweight and obesity in boys and girls in The Netherlands in 2009, data from Schönbeck et al. [24]

Cardiometabolic risk in obese young children

Cardiometabolic risk factors, i.e. risk factors for cardiovascular diseases and type 2 diabetes, as hypertension, dyslipidemia, and insulin resistance are common in obese children [3]. A clustering of dyslipidemia, hypertension, insulin resistance and abdominal obesity is also known as metabolic syndrome and results in atherosclerosis, type 2 diabetes and non-alcoholic fatty liver disease [27]. Not only the total body fat is the source of health problems, but specific fat depots are associated with metabolic syndrome, such as hepatic fat, other visceral fat and intramyocellular lipid [27]. These fat depots secrete pro- and anti-inflammatory cytokines (adipokines) that have been linked to cardiometabolic risk factors [27].
Except from body composition and biochemical profile, also several factors from the child's history as for example dietary pattern, lifestyle factors, birth weight, and family history play a role in the development of cardiometabolic risk (Figure 2). All these factors together influence insulin resistance and inflammation, and thereby metabolic syndrome. Together, this whole picture determines the child's cardiometabolic risk.

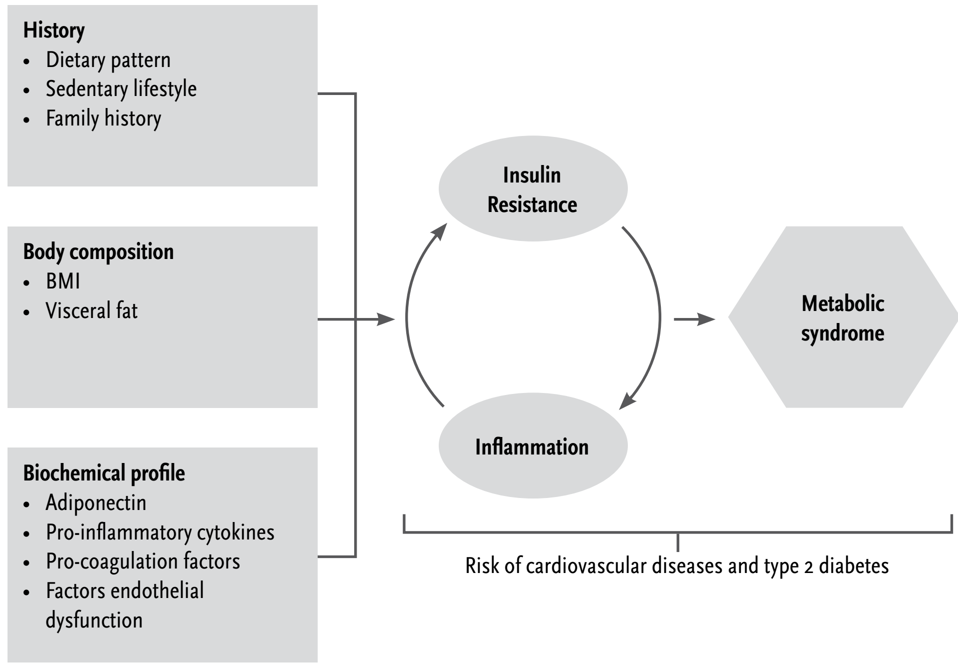

Figure 2 | The development of cardiometabolic risk.

Several environmental and physical factors shown at the left promote development of low-grade inflammation and insulin resistance, which can exacerbate each other. This influences the development of the metabolic syndrome. These factors together can play a role in the child's cardiometabolic risk (i.e. risk or cardiovascular diseases and type 2 diabetes). This figure was adapted from the figure of Weiss [27].

Cardiometabolic risk factors and metabolic syndrome in obese young children

In adults, metabolic syndrome is defined as having 3 out of 5 risk factors, i.e. raised waist circumference, fasting glucose, triglyceride levels, and blood pressure, or reduced HDL cholesterol with absolute cut-off points per risk factor [28]. There are different definitions for metabolic syndrome in children. They all use the components excess of obesity (waist circumference or BMI), blood pressure (systolic and diastolic), blood lipids (triglycerides and HDL cholesterol), and fasting glucose and/or insulin [29-32]. For excess obesity, all these definitions of pediatric metabolic syndrome uses percentile cut-offs (≥ 90^{th} or ≥ 95^{th} percentile), as BMI and waist circumference are age and sex dependent. For blood pressure, all except the definition of the International Diabetes Federation (IDF) [31] use percentile cut-offs as well [29, 30, 32]. The definition of Cook et al. [32], Viner et al. [30], and the definition of the IDF [31] use absolute cut-offs for de components blood lipids, and fasting glucose and/or insulin. However, also these appeared to be age and sex-dependent

[29]. Therefore, Ahrens et al. used percentile cut-offs for all components of metabolic syndrome. They defined metabolic syndrome (monitoring level) as having three or more of the following four risk factors: waist circumference ≥ 90th percentile, systolic or diastolic blood pressure ≥ 90th percentile, triglycerides ≥ 90th percentile or HDL cholesterol ≤10th percentile, and HOMA-insulin resistance or fasting glucose ≥ 90th percentile [29].

In a population-based study in eight European countries among children aged 2-9 years following the definition of Ahrens of metabolic syndrome (monitoring level) 1.5% of the normal weight children had metabolic syndrome, compared to 14.1% of the overweight and 31.5% of the obese children [29]. This shows that a considerable number of obese young children are already at risk for developing cardiovascular diseases. Also, Pedrosa et al. showed that Portuguese treatment seeking 7-9 years old overweight and obese children had a higher prevalence of metabolic syndrome (based on the definition of Cook et al. [32]), higher LDL cholesterol, triglycerides, systolic and diastolic blood pressure and lower HDL cholesterol, compared to normal weight children [33]. An Italian study enrolled young children (aged 2.0-5.8 years) whose BMI changed from normal weight to overweight or obesity in the 12 months before the study. They showed that also in those children metabolic abnormalities were present with at least one metabolic abnormality (hypertension, dyslipidemia, impaired fasting glucose levels, glucose intolerance) in 39.3% of the children [34]. A high proportion of these children (31.1%) had ultrasonography-detected hepatic steatosis (mild or moderate) and were therefore suspected to have non-alcoholic fatty liver disease [34]. This study shows that already at the onset of overweight or obesity these young children an elevated risk for cardiometabolic diseases.

Epicardial fat

Specific fat depots are supposed to be metabolically active and therefore correlated with metabolic syndrome, cardiovascular diseases, type 2 diabetes mellitus, and non-alcoholic fatty liver disease. Epicardial adipose tissue (EAT) is a metabolic active fat depot. Due to its anatomical proximity with the heart it could locally contribute to coronary artery disease [35, 36]. EAT is located between the visceral layer of the pericardium and the outer wall of the myocardium [35]. It shares the same microcirculation as the myocardium and is supplied by branches of the coronary arteries and can therefore reach out to the myocardium through vasocrine and paracrine pathways [37]. It has the same embryonical origin as viceral omental fat and expresses and secretes cytokines, pro- and anti-inflammatory adipokines and vasoactive factors [35, 37]. Epicardial adipose tissue thickness (EATT) measured by echocardiography is supposed to be a novel cardiometabolic risk factor.

In adults, it is found that EATT reflects the amount of visceral fat, is related to metabolic syndrome and predicts the extent and activity of coronary artery disease [38-40]. In adolescents and young adults EATT is increased at higher age [41, 42]. In children and adolescents, EATT was correlated with BMI z-score, and other cardiovascular risk factors as blood pressure, HOMA IR, triglycerides, and high-density lipoprotein cholesterol (HDL cholesterol) [43-45]. Furthermore, EATT was associated with the pro- and anti-inflammatory markers leptin, adiponectin, and hsCRP [46, 47]. Also, it was found to be an independent predictor of carotid intima-media thickness [43, 44, 48]. EATT is mostly studied in adults and adolescents. As far as we know EATT is not studied on young children yet, so the significance of this specific fat depot in young children is not clear.

Biomarkers of cardiometabolic risk

Inflammation appeared to play a pivotal role in obesity-related atherosclerosis [49]. Inflammatory mediators are for example C-reactive protein (CRP) [49]. Other markers, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF) are cytokines that are not only inflammatory mediators, but stimulate the production of various other inflammatory mediators [49]. Adipokines, for example adiponectin and leptin, function as signaling molecules in various processes (e.g. satiety) and are also associated with inflammation [3, 49].

Except from inflammation, also endothelial dysfunction is an important event in the development of atherosclerosis. The upregulation of intercellular cell adhesion molecule-1 (ICAM-I) and vascular cell adhesion molecule-I (VCAM-I) appears to be crucial in the process of endothelial dysfunction, because these molecules mediate the binding and subsequent recruitment of monocytes into arterial media [49]. Also, other biomarkers are known to be linked to endothelial dysfunction, for example selectins (as e-selectin) and monocyte chemoattractant protein-1 (MCP-1) [49]. Furthermore, pro-coagulation factors as plasminogen activator inhibitor-1 (PAI-1) play a role in the development of atherosclerosis [27].

In overweight and obese children aged 3-5 years BMI and waist circumference (WC) were positively correlated with leptin [50]. Also, WC was negatively correlated to adiponectin, but not to BMI [50]. Furthermore, in longitudinal research (from birth to 9 years) is seen that leptin closely reflects child body size [51]. There was a significant (but lower than that of leptin) negative association seen between adiponectin and BMI from the age of 2 onwards [51].

Possibly, some of these markers play a role in weight regulation also, as a higher concentration of leptin of children aged 3 years was associated with greater weight gain and adiposity trough age 7 [52]. HsCRP in children aged 2-9 years was associated with significant increase in BMI z-score and higher risk of incident of overweight and obesity over two year follow-up [53].

Psychosocial wellbeing of obese young children

Chronic diseases of childhood, including obesity, may have implications for the psychosocial well-being of children [54]. Lower psychosocial well-being can affect the psychosocial, physical, and cognitive development of a child. Social problems, such as bullying and peer problems, are frequent in obese young children [4, 55, 56]. Parents have substantial concerns about these problems [57]. Furthermore, higher BMI was found to be associated with lower body esteem in young overweight or obese children [58]. Already at a young age, American children were found to have aversion to fatness and a preference for thinness [59-62]. A longitudinal relationship between BMI and psychosocial problems was found. Higher BMI in children aged 4 to 5 years was positively related to poorer peer relationships and teacher-reported emotional problems, but no relationship was found with other childhood mental health problems (as hyperactivity or conduct problems) in these children at 8 to 9 years of age [63]. Possibly, obesity triggers peer problems, it is also possible that there is a common underlying cause that makes obese children vulnerable to peer problems [55].

HRQoL is a concept that also covers psychosocial aspects relevant to obesity. In the next paragraph the HRQoL concept and the HRQoL of obese young children are described

Health related quality of life

HRQoL is a multidimensional concept and it may be defined as physical, psychosocial aspects of a patient's well-being that are relevant and important to the individual and that are relevant to health and that can be affected by ill health [64]. Questionnaires to measure HRQoL are age-specific because they are adapted to developmental stage of the child [64, 65]. In young children, a proxy (generally one of the parents) is used to complete the questionnaire. In older children, several studies showed that the child's HRQoL reported by the parent differs from the child's own rating [66]. The parent rating of their child's HRQoL adds a different perspective, but may be influenced by their own quality of life [65]. Optimally, both the parent and child rating are used to give a broad view on the HRQoL of the child. However, most questionnaires for self-report can be used from the age of 8 only [64].

Generic and disease-specific HRQoL questionnaires have been developed. HRQoL measured by generic questionnaires gives a broad view on quality of life and can be used to compare populations of children with different health problems [64, 65]. Disease-specific HRQoL questionnaires provide a more detailed measurement of dimensions specific to the health problem and are therefore generally considered to be more sensitive to change in clinical applications [64, 65]. Because no validated

disease-specific HRQoL questionnaire is available for young children in this thesis we use the validated generic questionnaires Child Health Questionnaire-parent form with 50 items (CHQ-PF50) for children aged ≥ 5 years and the 103-item Infant Toddler Quality of Life questionnaire with (ITQoL) in children < 5 years [64, 67, 68]. Most dimensions of HRQoL are affected in overweight and obese children and adolescents [69]. Among general samples of young children measured by the generic HRQoL questionnaires Paediatric Quality of Life Inventory (PedsQL) and Child Health Questionnaire Parent Form with 28 items (CHQ-PF28), lower HRQoL on physical domains was found in those who were overweight or obese compared to normal weight young children [70, 71]. In the psychosocial domain no difference was observed. The HRQoL measured by the PedsQL of treatment seeking obese children aged 2 to 5 showed a lower physical and psychosocial HRQoL compared to those who did not seek treatment [72].

Etiology of childhood obesity

Obesity is a complex disorder affected by many interacting genetic and non-genetic factors [3]. Hormones such as leptin, ghrelin, adiponectin influence appetite satiety and fat distribution, and thus play a role in energy balance [3, 73]. In a small part of the children (< 5%) there is a secondary (including genetic) cause of obesity. Especially, obese children with short stature compared to their parental growth potential, with any significant dysmorphism, mental retardation, or onset of obesity in early infancy have higher risk for a genetic cause of obesity [3, 74]. The children with a secondary cause of obesity fall outside the scope of this research project.

Davison and Birch applied the ecological systems theory to evaluate and integrate research assessing risk factors for (primary) childhood overweight (including obesity). This resulted in an ecological model of predictors of childhood overweight (Figure 3) [75]. The child behaviors dietary intake, sedentary behaviors and physical activity are in the core of this model. Furthermore, the authors describe that overweight has a social nature and stress the importance of the ecological niche in which the child is settled. From this ecological model can be seen that many factors potentially influencing development of childhood obesity relate to parenting styles and family characteristics. The predictors in the model provide important insight in the factors that have to be addressed in treatment of childhood obesity.

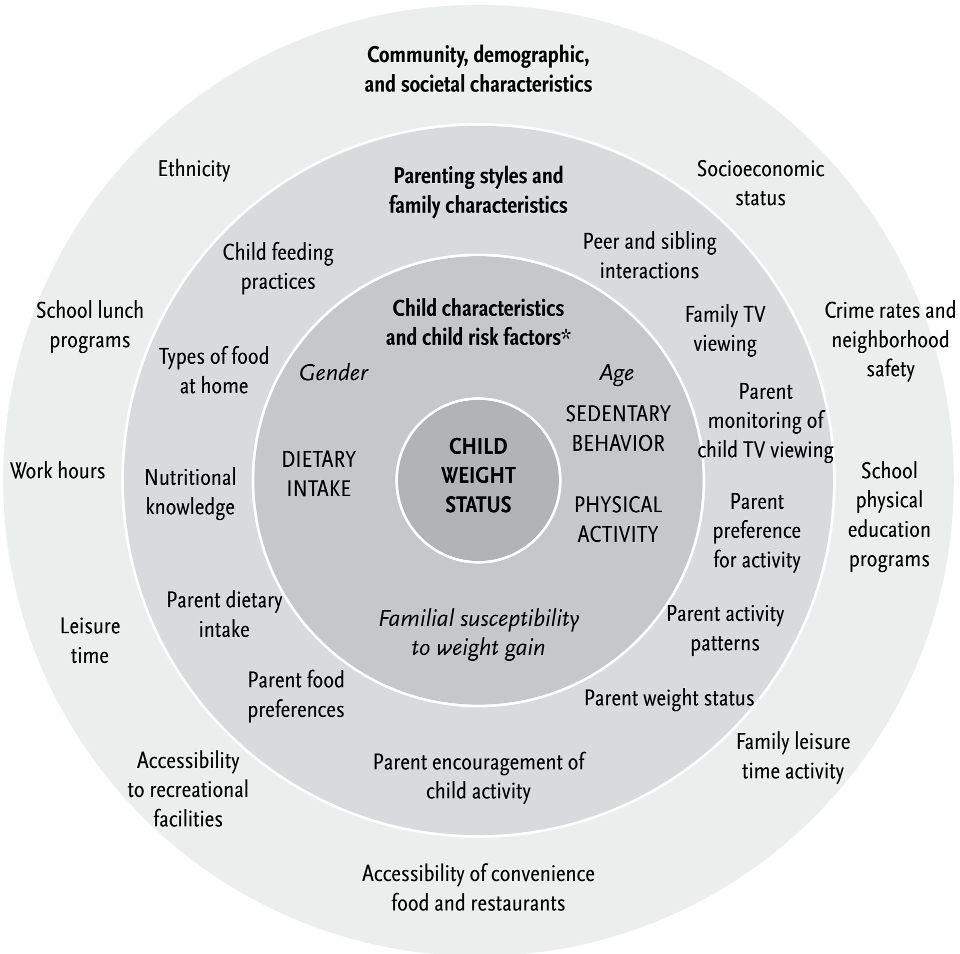

Figure 3 | Ecological model of predictors of childhood overweight.

* Child risk factors (shown in upper case lettering) refer to child behaviors associated with the development of overweight. Characteristics of the child (shown in italic lettering) interact with child risk factors and contextual factors that influence the development of overweight [75].

Treatment of obese young children

In the Cochrane review of Oude Luttikhuis et al. lifestyle change was the predominant recommendation in treatment of obese children [76]. This is consistent with the child behaviors dietary intake, sedentary behavior and physical activity that are in the core of the model of Davison and Birch (figure 3) [75]. Multidisciplinary

treatment, which means the combination of education and behavioral change techniques targeting nutrition and physical activity, appeared to be the most effective [76]. Furthermore, interventions for obese children below the age of 12 year focusing at parents appeared to be more effective than interventions focusing at children alone or parents and children together [77-80].
According to developmental aspects it is probable that behavioral change techniques and goals for children in different age groups need to be tailored to the developmental stages of children. The Dutch guideline for treatment of obesity in children recommends that advises for weight change and diet should be age-specific. However, no recommendations are given for tailoring treatment to the developmental stage of the child [81].
In 2009, there was no evaluated treatment program for obese young children available in The Netherlands. The Department of Pediatrics of the Gelderse Vallei Hospital (ZGV, Ede, The Netherlands) was confronted with a growing number of young obese children. Therefore, this research project was started to develop and evaluate an evidence and practice based treatment program for obese young children.
This research project is performed in the secondary care setting.

Objective, research questions and outline of this thesis

The overall objective of this project is to develop, implement and evaluate a treatment program for obese young children and contribute to effective treatment programs targeting obesity and its comorbidities in young children. Effective programs can potentially lower the high burden of obesity on health and wellbeing of young children in the short and long term.
To accomplish this objective, four research-questions are formulated.

1. What is the effectiveness of treatment programs in overweight and obese young children and what are the general characteristics of effective treatment programs for overweight or obese young children?
2. How can we develop a treatment program for overweight or obese young children using evidence from science and practice?
3. What is the effect of the treatment program *AanTafel!* on body composition, cardiometabolic risk (cardiovascular risk factors and markers of inflammation), psychosocial wellbeing (HRQoL) and behavior (nutritional intake, eating behavior, and physical activity) of overweight or obese young children?
4. Is EATT increased in overweight and obese young children compared to normal weight young children, is it correlated to cardiometabolic risk factors, and does it change during multidisciplinary overweight treatment?

In **chapter 2** a systematic overview is given of the literature about treatment programs for young overweight or obese children. The effectiveness of these treatment programs is summarized by meta-analysis in this chapter and general characteristics of these treatment programs are given. **Chapter 3** aims to give insight in the development process of *AanTafel!*, a treatment program for overweight young children. Evidence on characteristics for effective treatment from literature research and practice is combined with professional judgement to develop this treatment program. The resulting treatment program *AanTafel!* includes the following key characteristics: multicomponent, multidisciplinary, family-based with focus on the parents, tailored to individual children and families, duration of one year, and using a combination of individual and group sessions with low intensity and complementary a web-based learning module. **Chapter 4** addresses the process evaluation and further development of this treatment program by a pilot study, specifically with regards to parental and multidisciplinary involvement. The study in **chapter 5** aims to assess the effectivity of *AanTafel!* on the overweight, cardiometabolic risk profile, HRQoL and eating behavior and physical activity of the children. The study described in **chapter 6** assesses if EATT of overweight and obese children is increased compared to normal weight young children. Furthermore, it was studied if EATT is correlated to cardiometabolic risk in those children and if EATT changes during treatment with *AanTafel!*. In **chapter 7**, the final chapter of this thesis, the main findings of the previous chapters are summarized and discussed in a broader perspective and implications for practice and research are given.

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Chapter 2

Effective interventions in overweight or obese young children: systematic review and meta-analysis

E. van Hoek, E.J.M. Feskens, L.I. Bouwman, A.J. Janse

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ABSTRACT

Introduction
Treatment programs for overweight and obese young children are of variable effectiveness, and the characteristics of effective programs are unknown. In this systematic review with meta-analysis, the effectiveness of treatment programs for these children is summarized.

Methods
PubMed, Embase, Web of Science, and PsycINFO databases were searched up to April 2012. Articles reporting the effect of treatment on the body weight of overweight or obese children with a mean age in the range of aged 3 - < 8 years are included. Studies reporting the change in BMI z-score with standard error were included in a meta-analysis. For this purpose a random effects model was used.

Results
The search identified 11,250 articles, of which 27 were included in this review. Eleven studies, including 20 treatment programs with 1015 participants, were eligible for the meta-analysis. The pooled intervention effect showed high heterogeneity; therefore, subgroup analysis was performed. Subgroup analysis showed that program intensity and used components partly explained the heterogeneity. The subgroup with two studies using multicomponent treatment programs (combining dietary and physical activity education and behavioral therapy) of moderate or high intensity showed the largest pooled change in BMI z-score (-0.46, I^2, 0%).

Conclusion
Although the subgroup multicomponent treatment programs of moderate to high intensity contained only two studies, these treatment programs appeared to be most effective in treating overweight young children.

Introduction

The prevalence of overweight and obesity is on the rise worldwide [1] Obesity in childhood has severe somatic and psychosocial consequences in the short and long term [2-5].
Successful treatment programs change behavior (diet and activity level) and therefore decrease overweight and its consequences [6]. Often, behavioral therapy is included to help participants to initiate and sustain behavioral change [6].
A ≥ 0.5 reduction in body mass index (BMI) z-score is clinically relevant as it is associated with a reduction in cardiovascular (CVR) risk factors and insulin resistance (IR) in children 4-15 years of age [7-9].
Starting treatment at a young age appears to be more successful than treating older children [10-13]. First, parents have more control over their children's daily environment at early age, potentially making lifestyle changes easier. Second, starting treatment at a young age possibly prevents early adiposity rebound, the time point when BMI rises after reaching a nadir, predicting later obesity [14-16]. To change targeted children's lifestyle behavior, optimal strategies must take into account children's developmental stage, because developmental stage influences the child's liking or disliking healthy behavior and understanding of health [17].
Clinical guidelines from the United States, UK, and The Netherlands summarize the recommendations for the treatment of children with obesity, but do not give age-specific recommendations for young children [18-22]. The Cochrane review on interventions for treating obesity in children by Oude Luttikhuis et al. concluded that combined behavioral lifestyle interventions give favorable results, but interventions in young children were not reviewed separately [23]. Two systematic reviews were performed describing interventions to prevent or treat obesity in preschool-age children (2-5 years of age) [24, 25]. Both reviews concluded that it was advisable to address adults (e.g. parents and teachers) rather than children alone, to employ multicomponent interventions focusing on more than one strategy [24, 25]. Given that a meta-analysis was not performed, the overall effectiveness of treatment programs and the characteristics of effective treatment programs for overweight or obese young children are unknown. The aim of this article is therefore to summarize the effectiveness of treatment programs in overweight or obese children at an early age (mean age, 3 - < 8 years) as indicated in the literature up to April 15, 2012.

Methods

Search

The databases PubMed, Embase, Web of Science, and PsycINFO were searched. Database-specific keywords relating to overweight, obesity, children, treatment, and trial were used (Table 1). The search was limited by language (English, Spanish, German, and Dutch). The search included publications up to 15 April, 2012.

Table 1 | Keywords used in databases.

Subject	Keywords
Overweight	Overweight, obesity, obese
Children	Children, child, childhood, schoolchildren
Treatment	Treatment, therapy, treating, intervention, interventions, program*, diet, dieting, diets, slimming, fasting, physical activity, exercise, movement therapy, exercise therapy, motor activity, activity-based, physical education and training, behavioral therap*, behavioural therap*, behaviour modification*, behavior modification*, family therapy
Design	Trial, clinical trial*, controlled trial*, randomized controlled trial, randomized, randomised, randomisation, random allocation, random, randomly, double-blind method, single-blind method, single blinded, double blinded, single masked, double masked, placebo*, retrospective, prospective, baseline, follow-up

* Wildcard symbol for search term truncation. Search is on every word that starts with the letters before the asterisk.

Literature selection

Inclusion criteria were: body weight or another variables that contains body weight as the outcome of treatment (compared to no treatment, usual care, or baseline); population of overweight or obese young children, with a mean or median in the age of 3 - < 8 years; and English, Spanish, German, or Dutch language. If mean or median age was not reported, the article was included if the estimated mean age, based on age range and normal distribution, was in the range of 3 - < 8 years. No inclusion criteria were used regarding duration, aim, or design of the study.

All titles were reviewed. If the title showed that the study was not potentially relevant, the study was excluded; otherwise, abstracts were obtained. The first 10% of abstracts were reviewed by three authors (E.vH., E.F., A.J.), and discrepancies were discussed to arrive at a consensus. Because the level of consensus was high (> 90%), the other abstracts were reviewed by one author (E.vH.). The selected

publications were critically and independently appraised by three authors (E.vH., E.F., A.J.) using a checklist including the above-named inclusion criteria, characteristics of the study, validity, and applicability. Discrepancies were discussed to reach consensus. The references of included articles were checked to prevent articles meeting the inclusion criteria from being missed [26-50].

Data extraction

Data on design, participants, intervention, outcome variables, and results were extracted. An Excel data extraction form was used. Uncertain data were discussed. BMI z-sore is the preferred outcome variable because it accounts for weight, height, and age [51]. Changes in BMI z-score (difference between mean before and after treatment) were extracted from the articles. Height and weight were assessed by objective measures (not self-reported). All groups that underwent a described treatment were seen as a treatment group in this review, regardless of their status as intervention or control group in the trial. If the change in BMI z-score was not reported, it was converted from the data given in the article (BMI z-score before and after treatment) whenever possible. If a BMI z-score was not described, but it was reported that BMI z-scores were calculated at any time in the trial, additional information from the authors was requested. Results without BMI z-scores were excluded from further statistical analyses. Risk of bias in the study was taken into account by registering the presence of control group, randomization procedure, and quality of data analysis.

Corresponding measures of precision (standard deviations [SDs], standard errors [SEs], or 95% confidence interval [CI]) of the means and the difference between the means (change in BMI z-score during treatment) were extracted. If SDs were given rather than SEs, the SE was calculated by dividing the SD by the square root of *n*. In some studies, the SD or SE of the mean change was missing [32, 39, 41, 43, 49]. In these cases, the following formula was used: standard deviation$_{\text{difference}}$= square root ([variance$_{\text{baseline}}$ + variance$_{\text{follow-up}}$] – [2 x correlation$_{\text{baseline, follow-up}}$x standard deviation$_{\text{baseline}}$ x standard deviation$_{\text{follow-up}}$]) [6, 52]. The median correlation between the baseline and post-treatment BMI z-score was calculated from the selected studies [35, 43, 47], and was 0.87; this is comparable to the correlation in other studies [6], and hence this value was used in the formula above.

Data Analysis

Results are reported with a 95% CI. Statistical significance was set at $p < 0.05$. The statistical heterogeneity was calculated using the I^2 statistic, which indicates the percentage of variance that is attributable to heterogeneity [53]. Values less than 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity,

respectively [53]. Because of suspected residual heterogeneity resulting from difference between studies and study populations, meta-analysis was conducted according to a random effects model [54]. If heterogeneity was moderate or high, the causes of the heterogeneity were explored by carrying out subgroup analyses. The following determinants were expected to influence the effect of treatment programs for overweight children: different components in the treatment program and intensity of treatment [6, 23]. Therefore, possible subgroups were determined according to these determinants. Important components in treatment programs are dietary (DE) and physical activity (PA) education and behavioral therapy (BT) [6, 23]. BT was defined as therapy, techniques, or counseling on self-monitoring of diet and PA, cue elimination, stimulus control, goal setting, action planning, modeling, limit setting and other behavioral modification techniques [55]. PE included training or education given. Intensity of treatment (duration over the course of the intervention period) was categorized as very low (< 10 hours), low (10-25 hours), moderate (26-75 hours), or high (> 75 hours), as proposed in the review by Whitlock et al. for the U.S. Preventive Services Task Force [6]. Further, parental participation could influence the effect of treatment [56]. However, most studies involved parents, and therefore the subgroup child-only was too small to investigate the effect of parental participation in this age group. To investigate the change in BMI z-score of non-treated overweight children, the results of control groups with overweight children, without intervention or education reported in the selected articles, was used for a subgroup random effects meta-analysis.
All analyses were carried out using the statistical program R (version 2.15.1; R Core Team, Vienna, Austria) with the metafor package [57, 58]. Funnel plots or Egger's test were not conducted to assess for publication bias, because the data were too heterogeneous to combine or, when pooled, groups included a limited number of studies.

Results

Literature search

The search identified 11,250 articles, of which 2516 were duplicates (Figure 1). After the screening of titles, abstracts, and full-text articles, 50 articles were selected for detailed evaluation and discussion of discrepancies by three authors (E.vH., E.F., A.J.). Twenty-five articles were included and 25 were excluded after evaluation and discussion. Two more articles were found in references and included [59, 60], thus finally 27 articles were included for further characterization (Figure 1) [26-50, 59, 60].

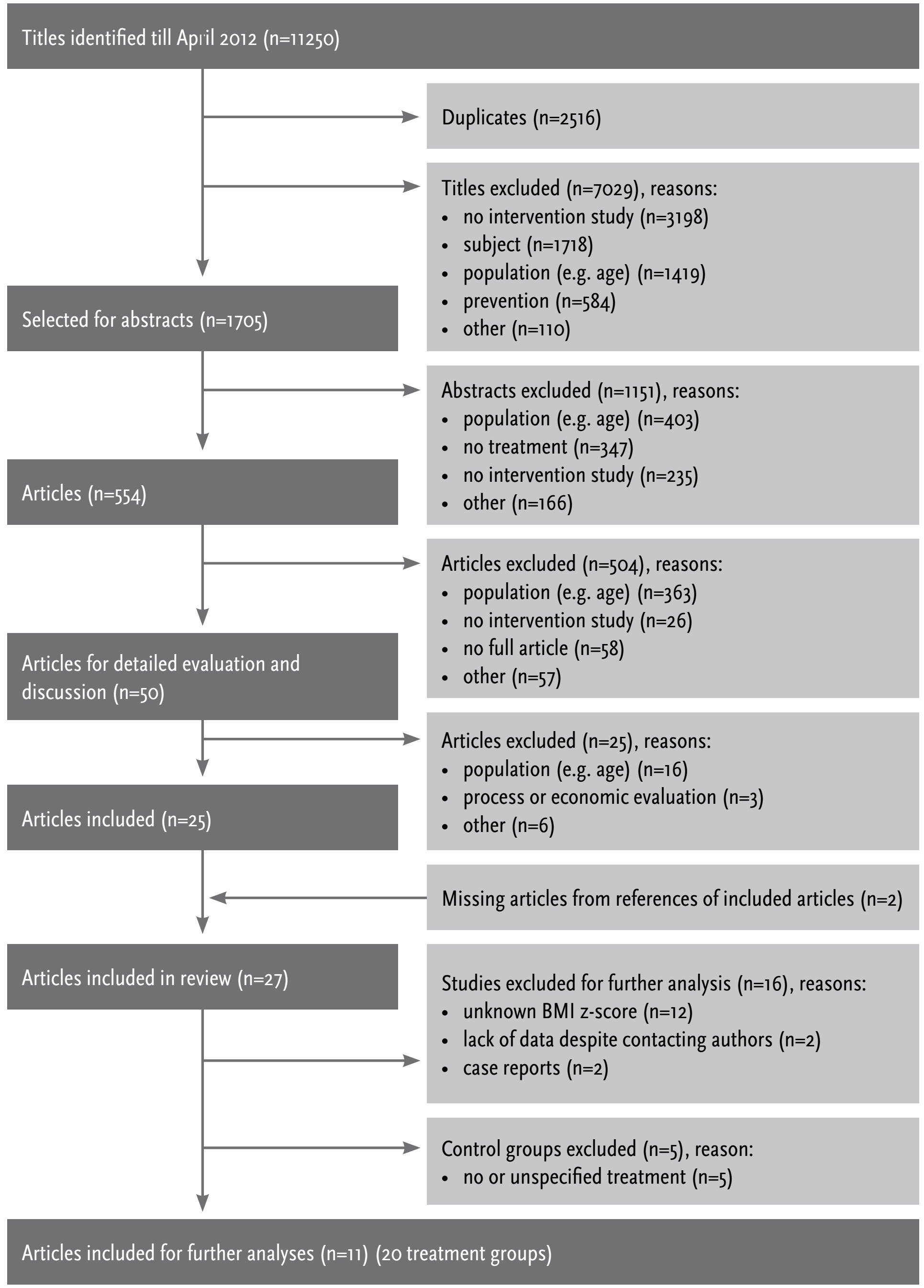

Figure 1 | Flowchart of the search and selection process.

Table 2 | Studies with at least one group treated by a multicomponent treatment program, including dietary (DE) and physical activity (PE) education and behavioral therapy (BT).

First author, publication	Country	Population				Intervention							Result			
		Age range	Gender	Weight status	n	Focus	Components included			Duration	Number of sessions	Setting	Effect		Missings	
							DE	PA	BT				BMI z-score	Other	Imputed	Excluded
RANDOMIZED CONTROLLED TRIAL																
Aragona, 1975 [26]	USA	5-10 y	F	Both parents and physician recommended weight loss	I1:4 I1:1*	P	x	x	x	14 w	15	Rs		Weight and height		
					I2:3	P	x	x		14 w	15	Rs				
					C:5 C:2*	No intervention										
Epstein, 1980 [60]	USA	6-12 y	MF	> 20% above ideal weight (ACHA height-weight tables)	I:6 I:1*	P, Ch	x	x	x	20 w	10 + tele	Rs		Weight and height		
					C:7 C:1*	P, Ch	x	x		20 w	10	Rs				
Epstein, 1985 [30]	USA	5-8 y	F	Obesity (not defined)	I:8	P, Ch	x	x	x	1 y	24	Rs		Percent overweight		
					C:11	P, Ch	x	x		1 y	24	Rs				
McCallum, 2007 [39]	Australia	5-9 y	MF	Overweight according to IOTF, but BMI z-score < 3.0 BMI [61]	I: 73	P, Ch?	x	x	x	12 w	4	PHC	-#			x
					C: 80	No intervention										x
O‘Connor, 2011& [41]	USA	5-8 y	MF	Overweight (≥ 85%), but not morbidly obese (BMI < 99%) [18]	I: 20	P, Ch	x	x	x	6 mo	6 + tele	PHC	-			?
					C: 20	Regular visit to their doctor, not specified							-			?
Raynor, 2012 [43]	USA	4-9 y	MF	≥ 85th p for BMI [61]	1.I1: 35	P	x		x	6 mo	8	Rs	-		x	
					1.I2: 33	P	x		x	6 mo	8	Rs	+/-		x	
					1.C: 33	P	x	x		6 mo	3	Rs	-		x	
					2.I1:26	P	x	x	x	6 mo	8	Rs	+/-		x	
					2.I2: 26	P	x	x	x	6 mo	8	Rs	-		x	
					2.C: 29	P	x	x		6 mo	3	Rs	-		x	
Shelton, 2007[45]	Australia	3-10 y	MF	BMI ≥ 85th p after adjusting for age and gender	I:28	P	x	x	x	5 w	5	Rs		BMI		
					C:15	No intervention										
Stark, 2011[46]	USA	2-5 y	MF	≥ 95th p BMI [61], ≤ 100% above mean BMI	I: 7	P, Ch	x	x	x	6 mo	18	SHC	+		x	
					C: 10	P, Ch	x	x		6 mo	1	SHC	-		x	
Taveras, 2011 [48]	USA	2-6 y	MF	BMI ≥ 95th percentile or BMI 85th-95th percentile and at least 1 parent overweight (BMI ≥ 25)	I: 253 C: 192	Fam	x Usual care, not specified	x	x	12 mo 12 mo	4 + tele	PHC	+/-			x x

Table 2: Continued.

First author, publication	Country	Population				Intervention							Result			
		Age range	Gender	Weight status	n	Focus	Components included			Duration	Number of sessions	Setting	Effect		Missings	
							DE	PA	BT				BMI z-score	Other	Imputed	Excluded
PROSPECTIVE INTERVENTION STUDY WITHOUT CONTROL GROUP																
Gajewska, 2011[31]	Poland	4-10 y	MF	Obese, z-score ≥ 2.0	30	Ch, Fam	x	x	x	3 mo	?	Rs	+			
Kleber, 2009 [35]	Germany	4-8 y	MF	Obese, BMI > 97th p [63]	84	P	x	x	x	1 y	59	SHC	+		x	
Tan-Ting, 2011 [47]	Philippines	5-17 y 5-9 y*	MF	Obese, BMI > 95th p CDC growth chart	44, 9*	P, Ch	x	x	x	3 mo	24	SHC		BMI		
RETROSPECTIVE STUDIES WITHOUT CONTROL GROUP																
Boles, 2010 [27]	USA	2-5 y	MF	BMI > 95p [61], ≤ 100% above median BMI for gender and age	5	P, Ch	x	x	x	6 mo	18	SHC	+/-			
Wile, 1992 [50]	Canada	1-16 y 1-9 y*	MF	Referred for weight control, no cut- off weight status given	96, 14*	P, Ch	x	x	x	?	?	SHC		BMI		
Matos Imbért, 2007 [38]	Dominican Republic	2-18 y 2-8 y*	MF	BMI > 95p	45, 14*	Ch, Fam	x	x	x	2-24 mo	6-28	SHC		Overweight status classified in groups		
STUDY WITHOUT CONTROL GROUP, PRO- OR RETROSPECTIVE NOT REPORTED																
Epstein, 1986 [29]	USA	14-70 mo	MF	Obese: not defined	17	P, Ch	x	x	x	1 y	20	Rs		BMI		
Ray, 1994 [42]	Singapore	3-6 y	MF	Weight for height (CDC-growth chart 1988) > 2SD	1128	Ch, Fam	x	x	x	1 y	4-5	PHC		Overweight status		

-	No effect (upper limit of 95% CI ≥ 0)
+	Positive result (upper limit of 95% CI<0) and mean change of BMI z-score of ≥ -0.2
+/-	Positive result (upper limit of 95% CI<0) and mean change of BMI z-score of 0 to -0.2
Bold	Included in meta-analysis
*	Characteristics of population included in review
**	Waiting list control group reported, but without clear description
#	9 months after start of program
##	6 months after start of program (results provided after contacting authors)
&	Data online available 2011, printed version 2013
y	Years
mo	Months
F	Female
M	Male
ACHA	American Child Health Association
p	Percentile
as	Appetite suppressant (drug)
BT	Behavioral therapy
C	Control group
Ch	Child
Fa	Father
Fam	Family
I	Intervention group
IOTF	International Obesity Task Force
p	Percentile
SDs	Standard deviations
P	Parents
tele	Extra contact by telephone
PHC	Primary healthcare
Rs	Research
Sc	Schools
SHC	Secondary health care

Table 3 | Treatment programs with combined dietary (DE) and physical activity (PA) education.

First author, publication	Country	Population				Intervention							Effect			
		Age range	Gender	Weight status	n	Primary focus	Components included			Duration	Number of sessions	Setting			Missings	
							DE	PA	BT				BMI z-score	Other	Imputed	Excluded
RANDOMIZED CONTROLLED TRIAL																
Kelishadi, 2009[34]	Iran	? mean 5.6y (sd 0.5)	?	BMI ≥ age and sex-specific 95p [61]	I: 40	Ch, Fam	x	x		6 mo	6	Rs	+		?	
					2: 40	Ch, Fam	x	x		6 mo	6	Rs	+		?	
					3: 40	Ch, Fam	x	x		6 mo	6	Rs	+		?	
Schwingshandl, 1999[44]	Austria	6-19 y 6.4, 7.8 y*	MF, F*	Obese (no definition)	I: 14, 2*	Ch	x	x		12 w	28	Rs	+			
					C: 16	Ch	x			12 w	4	Rs				
PROSPECTIVE INTERVENTION STUDY WITHOUT CONTROL GROUP																
Moraga, 2003[40]	Chile	? mean 9.6 y (sd 3.3). < 5 y, 5-10 y*	MF	Obese (no definition)	88 ?*	Fa, Ch	x	x		6-8 mo	8-10	SHC		Percentage weight change		
RETROSPECTIVE STUDIES WITHOUT CONTROL GROUP																
Davis, 1994[28]	USA	1-10 y	MF	> 120% of ideal body weight for height age	93	Ch?	x	x		3-58 w	variable	SHC		Percentage ideal body weight for height age		

- No effect (upper limit of 95% CI ≥ 0)
+ Positive result (upper limit of 95% CI<0) and mean change of BMI z-score of ≥ -0.2
+/- Positive result (upper limit of 95% CI<0) and mean change of BMI z-score of 0 to -0.2
Bold Included in meta-analysis
* Characteristics of population included in review
y years
SD Standard deviation
M Male
F Female
p Percentile
BT Behavioral therapy
C Control group
Ch Child
Fa Father
Fam Family
I Intervention group
mo Months
w Weeks
Rs Research
SHC Secondary health care

Table 4 | Treatment programs including physical activity (PA) or dietary education (DE) only.

First author, publication	Country	Population				Intervention							Effect			
		Age range	Gender	Weight status	n	Focus	Components included			Duration	Number of sessions	Setting			Missings	
							DE	PA	BT				BMI z-score	Other	Imputed	Excluded
RANDOMIZED CONTROLLED TRIAL																
Kelishadi, 2008 [33]	Iran	7-9 y	?	BMI ≥ 95th p for age and gender [61]	I: 45	Ch		x		6 mo	56	Rs	+			x
					C: 47	Mot, Ch	x			6 mo	6	Rs	+			x
PROSPECTIVE INTERVENTION STUDY WITH CONTROL GROUP																
Ildiko, 2007 [32]	Hungary	7 y	M	Overweight or obesity, cut-off points of BMI [62]	I: 31	Ch		x		9 mo	105	Sc	-			xxx ?
					C: 43			No intervention								?
Lazaar, 2007 [36]	France	6-10 y	MF	Obese children: BMI > 97th p [64]	I: 59	Ch		x		6 mo	52?	Sc	+/-			
					C: 41			No intervention								
PROSPECTIVE INTERVENTION STUDY WITHOUT CONTROL GROUP																
Maier, 2011 [37]	Germany	5-8 y	MF	Overweight or obesity [62]	11	P, Ch	x			12 w	4	Rs	+			x
STUDY WITHOUT CONTROL GROUP, PRO- OR RETROSPECTIVE (NOT REPORTED)																
Alley, 1968 [59]	USA	6-17 y 6, 7 y*	MF	Obesity (no definition)	50 4*	?	x + as			1-5 y	?	SHC		BMI change		

- No effect (upper limit of 95% CI ≥ 0)
+ Positive result (upper limit of 95% CI < 0) and mean change of BMI z-score of ≥ -0.2
+/- Positive result (upper limit of 95% CI < 0) and mean change of BMI z-score of 0 to -0.2
Bold Included in meta-analysis
* Characteristics of population included in review.
y Years
M Male
F Female
p Percentile
as Appetite suppressant (drug)
BT Behavioral therapy
C Control group
Ch Child
I Intervention group
Mot Mother
P Parents
Rs Research
Sc Schools
SHC Secondary health care

Table 5 | Results of random effects analysis of subgroups by type and intensity of treatment program.

Subgroup	Difference in BMI z-score	95% Confidence Interval	I^2 (%)
Multicomponent: very low intensity [39, 41, 43, 48, 49]	-0.08	-0.13, -0.03	79
Multicomponent: moderate or high intensity [35, 46]	-0.46	-0.53, -0.39	0
Nutritional education combined with either behavioral therapy or physical activity education: very low intensity [34, 43, 46]	-0.31	-0.51, 0.02	100
- After excluding outlier [34]	-0.05	-0.14, 0.05	11
Nutritional education: very low intensity [33, 37]	-0.46	-0.94, 0.02	100
Physical activity education: high intensity [32, 33]	-0.31	-0.88, 0.27	99

I^2 indicates the percentage of total variation across studies due to heterogeneity

Characteristics of the selected studies

The 27 selected studies were classified according to the components included in the evaluated treatment program of the intervention group (Tables 2-4). Eighteen studies reported on multicomponent treatment programs, combining DE and PE and BT (Table 2) [26, 27, 29-31, 35, 38, 39, 41-43, 45-50, 60]. Four studies evaluated combined DE and PE (Table 3) [28, 34, 40, 44]. Five studies evaluated treatment programs consisting of PE or DE (Table 4) [32, 33, 36, 37, 59]. The characteristics differed highly between studies (Tables 2-4). Unclear or missing data in some publications were age range (n=2) [34, 40], gender (n=2) [33, 34], weight status of the study population (n=6) [26, 29, 30, 40, 44, 50], primary focus (n=3) [28, 39, 49], duration (n=1) [50], and number of sessions (n=4) [31, 36, 50, 59] of the intervention (Tables 2-4).

Meta-analysis

From the selected 27 studies, 16 were excluded from further analyses for several reasons [26-31, 36, 38, 40, 42, 44, 45, 47, 50, 59, 60], resulting in 11 studies (Figure 1) [32-35, 37, 39, 41, 43, 46, 48, 49]. In addition, the control groups, but not the intervention groups, of five studies were excluded from the meta-analysis because no treatment was given or the treatment was unspecified [32, 39, 41, 48, 49].
Meta-analysis was performed with data from these 11 studies including 20 treatment groups and consisting of in total 1015 participants [32-35, 37, 39, 41, 43, 46, 48, 49]. The pooled difference in BMI z-score derived from the random effects model showed a significant improvement in BMI z-score (-0.25, 95% CI -0.36 to -0.14, Figure 2) with high heterogeneity (I^2=100%). The two studies describing case-reports, which were excluded from the meta-analysis, also reported a decrease in BMI z-score during treatment [27, 44].
Six treatment groups (derived from five studies) followed a 'multicomponent very low intensity treatment' program, and random effects analysis showed a small effect (-0.08, 95% CI -0.13 to -0.03) with high heterogeneity (I^2=79%, Table 5) [39, 41, 43, 48, 49]. However, three out of the six treatment groups showed no significant effect [39, 41, 43]. Two groups received 'multicomponent moderate or high intensity treatment' with significant improvement in BMI z-score (-0.46, 95% CI -0.53 to -0.39) and low heterogeneity (I^2=0%, Table 5) [35, 46].
'Nutritional education combined with either behavioral therapy or physical activity education very low intensity treatment' was given to eight treatment groups derived from three studies (Table 5) [34, 43, 46]. The random effects model showed a non-significant effect (-0.31, 95% CI -0.51 to 0.02) with high heterogeneity (I^2=100%). Compared to the other studies, the study of Kelishadi and colleaques is an outlier, with a high reduction in BMI z-scores [34]. The very small 95% CIs were prominent in all three treatment groups (Figure 2) [34]. Despite contacting the author no explanation was available. When these groups were excluded, the effect was smaller, -0.05 (95% CI -0.14 to 0.05), and heterogeneity reduced to 11% (Table 5).
In the remaining categories, 'nutritional education very low intensity' and 'physical education high intensity,' the decrease in BMI z-score in the study of Kelishadi and colleaques was also higher [33] and with very small 95% CI in comparison to the other studies in these categories [32, 37]. In both subgroups, the heterogeneity was high, and the pooled random effects model showed no significant effect (Table 5).
In an additional analysis the three control groups without any treatment or education, which were excluded from the main meta-analysis, were pooled. These showed no change in BMI z-score (-0.01, 95% CI -0.12 to 0.15) [32, 39, 49].

Discussion

This systematic review with meta-analysis shows that treatment programs targeting lifestyle using DE, PE and/or BT, have an overall, positive effect on BMI z-scores of young children. The reviewed treatment programs differed in components and intensity and, partly as a result of this, showed high heterogeneity.
For the subsequent subgroup analysis, pre-defined subgroup analyses were used, which prevents data dredging [54]. It was found that the programs in the category

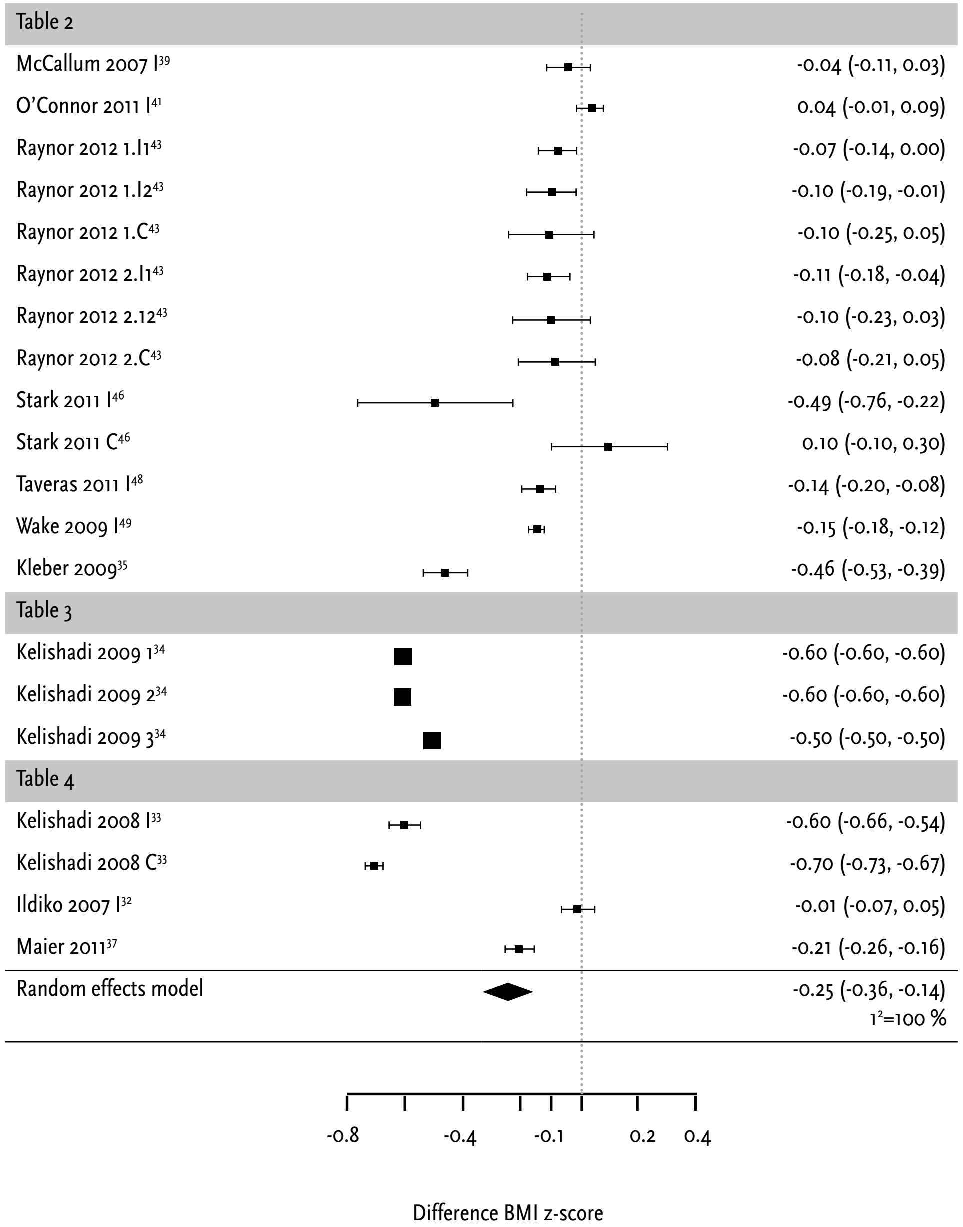

Figure 2 | Forest plot showing change in BMI z-score from start to end of treatment.

Horizontal bars represent 95% confidence intervals. I^2= the percentage of total variation across studies resulting from heterogeneity.

'multicomponent treatment of moderate to high intensity' led to the largest reduction in overweight with 0% heterogeneity. A reduction of this magnitude (i.e. 0.5 BMI z-score) was associated with decreased CVR factors and IR in children ages 4-12, and is likely to be clinically relevant [7-9]. However, this category included only two studies, and therefore the results should be interpreted with caution.

To take children's age into account (change in) BMI z-score was used as the outcome in the meta-analysis. Twelve studies, however, reported no data on change in BMI z-score, and these were excluded from the meta-analysis. Some of these studies did report on BMI, and most of these investigated multicomponent treatment programs of very low to moderate intensity (Table 2) [26, 29, 45, 47]. A BMI decrease of approximately 1-4 kg/m² during treatment was noted, supporting the assumption is that limiting the meta-analysis to BMI z-score as the outcome variable did not bias the results. Future studies evaluating treatment programs for overweight children should report at least BMI z-score with SD as the outcome measure to make it possible to compare all programs.
The observed heterogeneity was partly explained by intensity and components used in treatment. In the sensitivity analysis, two studies by Kelishadi et al. were excluded, which lowered the heterogeneity in one subgroup and resulted in an inadequate number of studies for meta-analysis in two other subgroups. After these analyses, the heterogeneity in the remaining subgroups was 0%, 11%, and 79%. Because of the limited number of included studies (n=11), it was not possible to investigate the heterogeneity in more detail. Other characteristics of the intervention programs, such as setting, and experience of caregivers, may additionally have induced heterogeneity. In addition, characteristics of the study population, such as age range, socioeconomic status, ethnicity, and weight status may have played a role.
Only a limited number of randomized controlled trials (RCTs) were found on lifestyle treatment of young overweight children. Control groups differed from no treatment to treatment with different components at a very low intensity. Accordingly, it was difficult to compare the difference in BMI z-score between intervention and control groups of different RCTs. For the meta-analysis, it was therefore decided to compare the effects of each group that underwent a well-specified treatment, even if these groups were used as a control intervention in a trial. This avoids loss of information about the groups that underwent treatment but were used as a control group. The subgroup ´multicomponent very low intensity´ was the only subgroup which contained several RCTs [39, 41, 43, 48, 49]. These RCTs were additionally analyzed, pooling the changes compared to changes in the control group (random effects model) and this did not change the conclusions (-0.04; 95%CI -0.08 to -0.01; I^2=0%).

Studies with a non-randomized control group or without a control group were also included. Therefore, this study can also be seen as a meta-analysis of observational data. Analysis of observational data has a role in medical effectiveness research [65]. In the included studies, selection bias and secular changes could have affected the results. Random effects analysis of the control groups without any treatment or education showed no change in BMI z-score (-0.01, 95%CI -0.12 to 0.15) [32, 39, 49]. Therefore, it can be considered that a decrease in BMI z-score, particularly if this decrease is higher than the lower confidence limit on the non-treated groups (-0.12), results from a true treatment effect and not from secular changes. Also, it can be argued that non-randomized studies are more likely to be representative of typical clinical practice than RCTs [66], and this also prompted us to include non-randomized studies.

In most trials, an intention-to-treat analysis was done, but in three trials, this was not clear [32-34]. Most studies excluded missing measurements from the analyses. Only in three studies was a type of imputation of the missing final BMI z-score data used (Tables 2-4) [35, 43, 46]. The inclusion and exclusion criteria (and the used definition of overweight/obesity) and recruiting strategies differed between studies, hence between intervention groups as reported in Tables 2-4. Together with the differences in handling missing measurements and dropouts, this may have introduced selection bias. However, these differences were present in each subgroup and hence cannot explain the differences in observed effect. The length of intervention, and therefore the length of follow-up, differed between the studies. For the studies in the meta-analysis, the length of intervention varied between 12 weeks and 1 year. This was not equally distributed between the subgroups and could therefore have led to a detection bias in outcome. It can be hypothesized that a longer duration of intervention and follow-up (with the same hours of contact with therapists) would lead to a smaller BMI reduction. In the subgroup 'multicomponent treatment of moderate to high intensity', the duration of intervention was, on average, the longest, and therefore the effect may have been underestimated, rather than overestimated. Performance bias, resulting from a concurrent intervention or to low fidelity to the intervention, for example, could not be ruled out because this was not reported in the included studies. The intervention setting may affect the generalizability of the study findings. Both studies in the subgroup 'multicomponent treatment of moderate to high intensity' were performed in secondary healthcare [35, 46]. Further, aspects such as collaboration between healthcare professionals, patient motivation, and access to healthcare may vary between countries and regions. Most studies included in the meta-analysis were performed with children of a broad age range. Some studies found were performed exclusively with

children of preschool or school age, but these studies included different strategies (intensity and components of treatment) [39, 41, 46, 48]. If these age groups were compared in the analysis, the used strategies would act as a confounder.

Based on this review, the treatment of choice for overweight or obese young children is a multicomponent treatment of moderate to high intensity. In both treatment programs in the subgroup 'multicomponent treatment of moderate to high intensity', parental participation was high, and parents were seen without the presence of their child [35, 46]. However, in most other included studies, parents were also involved as recommended in the guidelines, and therefore it was not possible to further investigate the effect of this strategy. This study focused on BMI, but changes in somatic parameters, such as CVR factors and psychococial parameters, such as health related quality of life (HRQoL), are important, given that psychosocial effects especially may not always correspond wiht the change in body weight. In both studies included in the subgroup ´multidisciplinary treatment of moderate to high intensity´, somatic or psychosocial parameters were also evaluated [35, 46]. In the study of Stark et al. no changes in overall HRQoL were observed [46]. However, physical functioning was significantly improved at the end of treatment, in comparison to the control group [46]. In the study of Kleber et al. a significant improvement of blood pressure, IR, triglyceride levels, high-density lipoprotein cholesterol, and intima-media thickness of the carotid artery was observed [35]. Both treatment programs also described long-term results (from 6 months to 4 years after treatment), and these results were also positive [35, 46].

To evaluate how treatment programs work, additional information on change in knowledge, thinking patterns, and behavior (dietary intake and PA patterns) should be obtained. This was not completely available for the two clinically effective programs. The study of Stark et al. assessed the effect on thinking patterns and lifestyle behavior [46]. Changes in caloric intake and parental motivation, but not in PA, were observed. For the study of Kleber et al., these data were not available [35].

In addition, the exact content and theory base of many treatment programs included in this review were not sufficiently or clearly reported, as noted before [67]. For future studies, it is important to report the content and theory base of treatment programs more completely, given that this will enhance the transferability of successful programs to other settings and other locations. Further, reporting on the study population was not sufficient in various studies, which is also important for the transferability of the intervention. It is it is also important to report on smaller subgroups of age, to increase the knowledge on age-appropriate treatment.

Conclusion

This systematic review with meta-analysis found a positive effect on the BMI z-score of overweight in young (mean age, 3 to < 8-year-old years) children in treatment programs targeting lifestyle. Although the subgroup of two studies using 'multi-component treatment programs of moderate to high intensity' contained only two studies, these treatment programs appeared to be most effective in treating overweight young children. These programs contained ≥ 26 hours of treatment with a combination of DE and PE and BT.
Because of the low number of studies performed, more research is needed on treatment programs for overweight or obese young children, especially multicomponent treatment programs of moderate to high intensity. Ideally, the studies should report content and theory of the treatment program, the effect on somatic and psychosocial parameters, the effect on knowledge and behavior, long-term effects, and, finally, how the treatment program works in a real-life setting.

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Chapter 3

Development of a Dutch intervention for obese young children

E. van Hoek, L.I. Bouwman, M.A. Koelen, M.A.J. Lutt, E.J.M. Feskens, A.J. Janse

Submitted

ABSTRACT

The objective of this article is to provide insight in the five-steps development process of the best evidence, best practice treatment program for obese young children *AanTafel!*. A set of requirements for program development was developed to guide the data inquiry: the use of theory, influencing factors, tailoring, multi-disciplinarity, duration/frequency and evaluation and monitoring. Step I retrieved evidence from clinical guidelines, followed by a systematic review with meta-analysis (Step II) and an extended literature review (Step III). Evidence was consistent with regards to a parent-focus, targeting family-level, including diet, physical activity and behavior change techniques and tailoring to age. However, no evidence or inconsistent evidence emerged on the theory-basis, group versus individual sessions, face-to-face contact versus ICT-mediated contact, which disciplines to involve and how and program duration and –intensity. Hence, practice-based insights from parental interviews (Step IV) and involved therapists were added and subsequently integrated to the treatment program *AanTafel!* (Step V). 'Aan Tafel!' is a multicomponent, multidisciplinary, family-based, parent focused, age-specific, tailored to individual children and families with a duration of one year duration and using a combination of individual and group sessions and a web-based learning module. Changes in scientific working principles with regard to data collection, reporting and translation to guidelines are required. Practice and science may benefit from close collaboration in designing, implementing and evaluating interventions.

Introduction

In 2009, the Department of Pediatrics of the Gelderse Vallei Hospital (ZGV, Ede, The Netherlands) was confronted with a growing number of young obese children. ZGV provides an intervention for obese children aged 8-12 years. However, no intervention was available for young children aged 3-8 years. Therefore, the ZGV professionals involved in obesity treatment decided to develop an intervention, resulting in *AanTafel!* (Dutch for 'to the table', synonymous with sharing a meal).

This intervention was piloted in 2010 and up till now 5 groups with 34 children with their parents have participated. All participating children were referred for treatment by their general practitioner, youth health care physician, or pediatrician. Preliminary results show a clinically relevant decrease of BMI z-score of 0.5 on short and long term with follow-up two years after intervention.

The prevalence of childhood obesity is increasing worldwide [1]. Obesity in children has severe somatic effects, such as hyperlipidemia, hypertension, insulin resistance, diabetes mellitus, and liver disease even at a young age [2-5]. This increases the risk of cardiovascular diseases later in life and several studies found a higher mortality in those who had been obese in childhood [4, 6-8]. In addition to the somatic effects, the psychosocial effects of obesity in childhood are serious. Obese children are suffering more frequently of negative discrimination, social stigmata, bullying, depression, a lower self-image, and a lower Health Related Quality of Life (HRQoL) compared to normal weight children [3, 9-11].

Research indicates that intervening at a young age is correlated with a reduction of BMI [12-14] and may delay adiposity rebound, the time point when body mass index rises after reaching its lowest point, preventing later obesity [15, 16].

During the development process of *AanTafel!*, an extensive literature search was performed. A gap was found in evidence required for the development of the treatment program. The science-practice gap is known in literature and is possibly partly due to the rigid protocols used to ensure internal validity in randomized controlled trials (RCT's). Review studies and the development of clinical guidelines result in evidence which is perceived as less relevant and applicable to the real-life context of program developers [17].

This article describes the process of the development of *AanTafel!* through data inquiry and data integration. During this process we derived scientific evidence from the literature and filled gaps with insights from the target group and with professional expertise and -judgment. By providing insight in this process, we specify the request for more practice-based evidence in the area of childhood obesity and ultimately, aim to contribute to the development of evidence-based treatment programs.

The Development Process

The authors compiled a set of requirements to guide the inquiry of evidence from the scientific literature. The requirements are based on the general recommendations on using theory, monitoring and evaluation and a clear understanding of the targeted behaviors and the context in which they occur, as emphasized in the literature on health program development [18]. The international recommendations were used to specify for childhood obesity treatment (tailoring to developmental stage, duration and intensity of treatment) [19]. The set entails the following six requirements:

1. *Use of relevant theoretical models*
   Programs have to be based on appropriate theory and evidence (Green and Kreuter, 2005, p. 197);
2. *Use of multi-level factors*
   Various factors at multiple levels influence the development of childhood obesity [20]. The reciprocal interaction between these factors and, hence between levels, demand multi-component efforts in everyday-settings in which children grow up, learn and play, as well as efforts at community and policy level (Green and Kreuter, 2005, p. 2);
3. *Intervention tailored to the specific needs and circumstances of the target group*
   Targeting the program to take into account age-related concerns, culture, circumstances and needs (Green and Kreuter, 2005, p. 6). Tailoring to the age of the child is important because of age-specific physical and psycho-social development (WHO 2007);
4. *Collaboration and multi-disciplinary responsibility*
   Collaboration and participation of all actors concerned and encouragement of shared responsibility at all levels (Green and Kreuter, 2005, p. 85; WHO 2000);
5. *Sufficient duration and intensity*
   Obesity should be treated as a chronic disease which requires long-term follow-up and management. Interventions must recognize this need and provide support for life-long lifestyle changes needed for successful obesity management (WHO, 2000, 2007).
6. *Monitoring and program evaluation*
   Program developers must evaluate all interventions to ensure reach, coverage, quality, impact and improvement (Green and Kreuter, 2005, p. 243).

The development process involved five steps

In step I, II and III, the scientific literature was reviewed based on the total set of requirements:

- *Step I*
  A review of clinical guidelines and reports on childhood obesity interventions;
- *Step II*
  A systematic review with meta-analysis of effective childhood obesity interventions for children 3-8 years of age [21];
- *Step III*
  Review of evidence on effective childhood obesity interventions and the use of Internet without age-specificity;

This inquiry is supplemented with practice-based information in step IV and V:

- *Step IV*
  Semi-structured interviews with parents on the waiting list for treatment of their obese child;
- *Step V*
  The expertise and experience of the involved therapists was tapped into to integrate the findings, fill gaps in evidence and compile the *AanTafel!* program.

Results: Step I to V

The scientific evidence and practice-based insights with regards to the requirements for theory, influencing factors, tailoring, multi-disciplinarity, duration/frequency and evaluation are described for each step (for an overview see Table 1).

Step I: Review of clinical guidelines and reports

The Dutch [22, 23], the British [24] and the USA guidelines [25, 26], and the WHO reports at European [19] and global level [27] were reviewed.

Theory
No recommendations were found with regard to using theory or the theories used to set those recommendations.

Influencing factors
All documents emphasize the need to intervene at family-level and recommend the involvement of parents [19, 22-27]. However, this is done without specific reference to the preferred setting for the provision of such intervention. Group intervention, which partly mimics influence of peers, is advised for pre-school children in the European Region WHO report [19], without further specification. According to the USA guideline, group intervention has therapeutic benefit and may be more cost-ef-

Table 1 | Overview of the data inquiry and integration steps.

	Data inquiry				Data integration to *AanTafel!*
Retrieved scientific (step I-III) and practice (step IV-V) based insights	**Step I** **Clinical guidelines and WHO reports**	**Step II** **Systematic review**	**Step III** **Scientific literature not age-specific**	**Step IV** **Interviews with parents**	**Step V** **Professional judgement**
Theory	No evidence	Not available due to limited number of included studies	No evidence	Not applicable	No specific theory
Influencing factors	Consistent: family level; parents involved; group-sessions; diet and physical activity Inconsistent: behavior change techniques	Consistent: multi-component including behavior change techniques for diet and physical activity	Consistent: family level; at least one parent involved. Multi-component: diet, physical activity, behavior modification techniques Inconclusive: sleeping behavior Inconsistent: group or individual sessions	Diet and physical activity	Family level Parent focused: participation of at least one parent Group and individual sessions Behavior modification techniques on parenting, diet, physical activity and sleeping pattern
Tailoring	Consistent: age-specific weight goals and dietary intake	Not available due to limited number of included studies	No evidence	Child and family (housing, weight of parents, work-, eat and physical activity patterns)	Age: physical-motoric, social-emotional, cognitive development stage of the child Family setting and preferences
Multi-disciplinarity	Consistent: multidisciplinary	Not available due to limited number of included studies	Consistent: multidisciplinary Inconsistent: which disciplines to involve	Not applicable	Multidisciplinary: paediatrician, child psychologist, paediatric dietician, child-physiotherapist Multidisciplinary presence at sessions Regular team meetings
Duration/intensity	Inconsistent: range from weekly to once/3 months to 1 year with long-term follow-up	Consistent: moderate to high intensity	Inconsistent: frequency of contact; substitution face-to-face with Internet mediated contact	High access to and likeability of Internet-mediated contact	One year: 4 months high intensity (8 sessions) and 8 months low intensity (6 sessions) 20 contact hours; 14 sessions (12 group, 2 individual; 9 parents only) Web-based learning module (13 chapters)
Evaluation	No evidence	Not available due to limited number of included studies	Consistent: weight, somatic, psychosocial and health behavior indicators	Weight, somatic, psychosocial and behavioral indicators	Reach Acceptability MBI-z score, cardiovascular risk-profile, HRQoL, dietary intake, physical activity level

fective [25]. Consistent emphasis is put on using a multi-component approach including diet and physical activity and most guidelines also recommend behavioral modification techniques for some or all families [19, 22-27]. *Tailoring*: Age-specific recommendations are found for setting weight goals and dietary changes. Regarding weight goals, the USA guidelines recommend very gradual weight loss for children under five years of age [26]. For cognitive or physical development stages no recommendations were found [19, 22-27].

Multi-disciplinarity
The involvement of a multidisciplinary team (dietician, physiotherapist and expert for psychological help and parenting skills) is recommended during the intensive stage of the intervention [25], or in general [23]. The composition of the multidisciplinary team, however, is not specified in all documents.

Duration/frequency
The guidelines provide different recommendations on duration and frequency of intervention, ranging from weekly to once per 3 months and from 3 months to 1 year with long-term follow-up to maintain healthy behavior [22-25]. *Evaluation*: No recommendation for monitoring and evaluation of programs was included.

Step II: Systematic review obesity intervention 3-8 years old

Step I did not provide evidence with regards to the use of theory, tailoring to cognitive of physical development stages and monitoring and program evaluation. The evidence on multi-disciplinary collaboration and duration and intensity was inconsistent. Therefore, a systematic review with meta-analysis of effective childhood obesity interventions for children 3-8 years of age was performed by van Hoek et al. [21]. A total of 27 studies were included in this review, of which 11 were eligible for meta-analysis. Because of high heterogeneity a subgroup analysis was performed.

Influencing factors and duration/intensity
The subgroup multicomponent interventions (including behavioral change techniques in relation to diet and physical activity) of moderate to high intensity (>26 hours face-to-face contact) showed the largest change in BMI z-score which was clinically relevant [21]. However, no evidence was found regarding the optimal duration of the intervention.

Theory, tailoring, multi-disciplinarity
Further analysis regarding theory, group or individual sessions, tailoring to age, and multidisciplinary team composition was not possible due to limited numbers of papers and limited description of interventions. The subgroup with the largest change in BMI z-score included only two interventions [28, 29]. Both studies were group interventions, and were tailored to age by focusing on parents rather than on children and on targeting behaviors unique for the preschool years: e.g. food neophobia and tantruming for food [28, 29].

Step III: Review of obesity interventions without age-specificity.

Step II did not provide additional evidence on theory, tailoring to cognitive of physical development stages, multi-disciplinary collaboration, duration and monitoring. Therefore, scientific literature was reviewed with use of an extended age-range. Specific attention was paid to the use of Internet-mediated communication for reasons of potential lowering the frequency of costly face-to-face contact and its user-friendly character with regard to flexibility in location and time.

Theory
No evidence was found for the use of specific theory in an obesity intervention.

Influencing factors
The Cochrane review of childhood obesity interventions of Oude Luttikhuis et al. [30] recommends targeting the family-level, with at least one parent involved. The involvement of parents contributes to a decrease in their child's overweight, particularly for children younger than 12 years [31-33]. RCT's are inconclusive regarding the use of group or individual intervention [34-36]. Combined behavioral lifestyle interventions can result in a clinically relevant reduction of overweight [30]. In addition to the components of diet and physical activity, a link between sleep and overweight is reported [37].

Tailoring
In relation to obesity intervention, tailoring to cognitive and psycho-social developmental stages is not specifically mentioned.

Multi-disciplinarity
In the literature, no consistent evidence was found on which disciplines should be involved.

Duration/frequency
Also no consistency was found on the optimal frequency of contact [26] and on whether and how to substitute face-to-face contact with Internet-mediated contact. Besides potential cost-reduction, the use of Internet may reduce participation barri-

ers such as travel time, transportation difficulties and work-related issues, and enhance adherence by allowing for a self-chosen time and location for the participants [38, 39]. Smith et al. [40] reviewed the impact of health information technology (IT) targeted on parents or children on patient outcomes and care processes in obesity clinic-based intervention in children 2 to 18 years of age. They conclude that IT may improve access to interventions but that its impact on weight loss and behavior change is understudied and findings are inconsistent. Other reviews also conclude that Internet-mediated strategies could be a valuable addition to other strategies, however, requirements for successful use in childhood obesity interventions are still unknown [41-43].

Evaluation

Regarding evaluation, the intervention aims to improve health and well-being of the obese child, and hence the effect at 1) overweight, 2) somatic parameters, 3) psychosocial parameters, and 4) health behavior should be evaluated [17, 44, 45].

Step IV: Interviews with parents

In addition to the scientific evidence, insights were derived from interviews with parents of the waiting list for treatment of their overweight child. The children were referred for obesity treatment by their general practitioner, youth health care physician, or pediatrician. Twelve randomly selected parents were asked to participate in the semi-structured telephone interviews. Eleven parents (10 mothers, 1 father) consented and one parent could not be reached.

The interviews focused on the expectations and preferences with regards to the design and content of the intervention and the use of Internet-mediated elements. The interviews were audio-taped and fully transcribed. The text was analyzed using content-analysis which involved a process of selecting and coding text fragments [46] based on the requirements relevant to this step: Influencing factors, tailoring, duration/intensity and evaluation.

Influencing factors

Parents indicate strategies to change their child's diet and physical activity as essential components. With regard to diet, they prefer to learn how to apply dietary recommendations in the home situation and parents prefer to learn how to support their child rather than gain basic knowledge on a healthy diet. Parents prefer support for stimulating their child to be physically active, some regard this as more important than dietary support. Some parents request behavioral change techniques. One parent mentioned that she already went to a dietician with her child, but that this did not offer her anything useful. Some parents did not mention specific elements, but emphasized that elements in which their child participates should be fun, learning by playing.

Tailoring

In the literature, tailoring to cognitive and psycho-social developmental stages is not specifically mentioned. In contrast, the so called 'developmental and parenting tasks' are commonly known principles in child development [47]. It emphasizes the themes in childhood and tailoring parenting skills to the developmental stage of the child. In relation to obesity it follows that different learning processes should require consideration per developmental stage. From the age of three, children first learn by modelling, they become more sociable and learn parents' values. Afterwards (school age), they learn about social relationships with other children and they develop a feeling of self-worth. They develop autonomy gradually. In relation to eating, age influences the child's understanding of health and the (dis)liking of healthy eating behaviors such as eating fruit and vegetables [48]. These findings point at differences in learning processes which require consideration in an intervention. Parents prefer an approach tailored to the characteristics of their child and family, such as housing conditions, weight status of the parents, working schedules and the family's eating and physical activity patterns. The approach should be positive, highlighting their child is OK and not (only) 'too fat'. One parent emphasized that this is especially relevant because of her child's young age (four years).

Duration/intensity

All parents had access to Internet. All, except one parent, said they like the use of Internet in the intervention because it is time-saving (saving travel time, faster working compared to paper), 'normal' (everything nowadays is on the Internet), own choice of moment. However, one parent also mentioned that it should be combined with face-to-face contact because she needs external pressure to actually use the Internet.

Evaluation

Parents expressed concerns about the overweight itself (should decrease) as well as the somatic (e.g. diabetes), psychosocial (e.g. teasing), and behavioral consequences. Some parents emphasized that they want their child to be healthy and able to be as physically active as any other child.

Step V: Integration based on professional judgement

The last step entailed the integration of findings from step I to IV to compile the treatment program *AanTafel!*. Data integration was performed by the involved team of therapists: a pediatrician, child psychologist, pediatric dietician and a child physiotherapist. All team members are experienced in the diagnosis and treatment of overweight children in the secondary care setting. For each requirement, the best available evidence was combined with the rich knowledge and expertise available within the team about obesity treatment for other age groups (Hospital Gelderse Vallei provides an obesity treatment program for 8-12 year old children) and the local setting. In addition, the team consulted their network of researchers from Wageningen University (WU) with expertise in nutrition, physical activity, health behavior change, and health promotion. The co-operation between the WU and the ZGV takes place within the Nutrition Alliance Gelderse Vallei to obtain a better connection between research and practice. No systematic procedure was followed during this step. This is characteristic to practice, where decisions arise from a flow of daily actions (regular and ad-hoc meetings) rather than from a pre-defined procedure, also budget constraints played a role in weighing the findings.

Theory
No specific theory but rather a mixture of theoretical insights from the team members and consulted scientists has been applied.

Influencing factors
AanTafel! is a parent-focused intervention and targets the family-level. At least one parent has to be involved. It is a multicomponent program and includes behavioral change techniques with regards to dietary intake and physical activity and for a small part sleeping pattern (see also Table 2). Group sessions (n=12) to provide peer-support and individual sessions (n=2) for family and child tailoring are combined to reduce costs.

Tailoring
The team included tailoring to the motoric, social-emotional and cognitive development stage of the child, despite of the lack of retrieved evidence. In contrast to the literature on obesity, the so called 'developmental and parenting tasks' are commonly known principles in child development [47]. It emphasizes the themes in childhood and tailoring parenting skills to the developmental stage of the child. In relation to obesity it follows that different learning processes should require consideration per developmental stage. From the age of three, children first learn by modelling, they become more sociable and learn parents' values. Afterwards (school age), they learn about social relationships with other children and they develop a feeling of self-worth. They develop autonomy gradually. In relation to eating, age influences the child's understanding of health and the (dis)liking of healthy eating behaviors such as eating fruit and vegetables [48]. These findings point at differences in learning processes which require consideration in an intervention. Therefore, *AanTafel!* differs from the obesity intervention for 8-12 years old, the

Table 2 | Key themes in *AanTafel!*.

Theme	*AanTafel!*
Behavioral change techniques and parenting	Self-monitoring (parents awareness of current lifestyle) Group discussion of current lifestyle Individual goal setting * Discussion of plan goal getting and problems facing Parent as role model Parenting skills Praising and rewarding Build self-esteem of the child
Dietary patterns	Dietarian goals based on dietary record (self-monitoring and evaluation) Education based on healthy eating advice Target is small reduction in energy intake Healthy food choices (for example instruction by supermarket visit) Healthy (low fat and calorie) snacking Limit sweetened beverage Eat breakfast Eat at the table as a family
Physical activity patterns	Physical activity goals based on physical activity diary (self-monitoring) Target: increase physical activity (≥ 1 hour/day at least moderate intensive), reduce sedentary behavior Increase exercise in daily life (walking/cycling) Encourage general activity and active play Encourage to participate in sports or other active recreation Four meetings in which parents and children are physically active together to stimulate parents to be active with their child and learn what kind of activity their child likes Learn active games: inside home with in every household present materials
Sleep Patterns	Information on normal sleep patterns Assignment to monitor the sleep pattern of their child If there are clues for sleep disturbances, these will be further evaluated and therapy will be offered

* The therapists support the parents to formulate goals which are effective for weight control, realistic and fit the individual families.

main difference is that this program for older children is not only parent, but also child focused.

Central to *AanTafel!* is the tailoring to age and family situation. For instance, parents learn age-appropriate parenting skills in relation to diet (e.g. praise/reward tailored to social-emotional development), physical activity (e.g. activities tailored to motoric development) and sleep. Goal-setting per family is used to further tailor the intervention to each family. Part of the group sessions (9 out of 14) is for parents only. The children actively participate in the physical activity group sessions and the individual sessions. Behavioral change techniques and parenting techniques are offered, such as goal-setting and modelling (Table 2).

Multi-disciplinarity

No evidence was found on which disciplines to involve. In line with the existing childhood obesity treatment program at the hospital, the multidisciplinary team consists of a pediatrician, child psychologist, paediatric dietician and child-physiotherapist. This combination of expertise covers the factors influencing childhood obesity that are indicated in the previous steps. No evidence was found on how to involve the disciplines. The team matched their presence with the factors addressed in the sessions, resulting in partly multidisciplinary sessions. Regular team meetings intent to safeguard the exchange of information about participants between sessions.

Duration/intensity

The literature did not provide conclusive evidence with regards to duration. Based on previous experience with treatment programs, *AanTafel!* has a total duration of one year, starting with 4 high-intensity months (8 sessions), followed by 8 low-intensity months (6 sessions). The first part aims to increase awareness and to set goals for diet and physical activity; the second part aims to prevent slip-back and to sustain the learnt behavior in the family setting. The program entails a total of 20 contact hours divided in 14 sessions of which 12 group- (1.5 hrs.) and 2 individual sessions (1 hr.). The web-based learning module provides 13 chapters with information, short movie clips and homework assignments, which participants have to complete before each next session. The team decided to include this module to reduce the number of high-cost individual sessions without reducing the amount of tailored feedback.

Evaluation

Although the previous steps did not report on process evaluation, indicators to assess reach (attendance, drop-out, log-ins and completed assignments of web-based learning modules) and acceptability (interviews with parents and therapists) are included in the program to provide insights for future improvement. In line with the evidence, outcome indicators include BMI-z score, cardiovascular risk-profile, HRQoL-score, nutritional intake and level of physical activity.

Discussion and Conclusion

Discussion

In this study, evidence lacked, was not specific or inconsistent with regards to the requirements of the use of theory, involvement and collaboration between therapists from multiple disciplines, duration, intensity and monitoring and evaluation of interventions. In the area of childhood and adolescent obesity intervention, the USA Expert Committee on obesity also concluded in their most recent (2007) report that since their previous 1998 review, gaps in evidence-based recommendations remain [25]. Hence, the committee developed their recommendations on available evidence as well as on expert opinion [25]. The preferences of parents are important to gain insight in the best strategy to involve them and to be able to optimally tailor to the target group. Therefore we performed interviews with parents of obese young children. The most important findings are that parents preferred to address the problem at a family level, receive learning strategies for changing their child's diet and physical activity, and that an intervention is tailored to their child and family. Furthermore, the target group was positive on the use of Internet-mediated elements. The information from step I-IV was integrated into the program by professionals of different disciplines. As described above, the recommendations derived from science did not totally fill the needs in practice. Similar to findings in literature, no explicit theory was used to develop *AanTafel!*. However, the multi-disciplinary team used their background of theoretical models, resulting in the multidisciplinary approach, behavioral change techniques as role modelling, and tailoring to the family and child development stages. In the process of integrating evidence, practical issues and circumstances also play a role, such as in our case the budget limitations. Budget limitations are common in most settings and force decisions to reduce the intensity of interventions.

The effective programs were moderate to high intensive (face-to face contact of at least 26 hours) [21], but *AanTafel!* includes only 20 hours of face-to-face contact in one year. The evaluation of the web-based learning module has to show if it is an effective substitute, keeping in mind the lower costs of ICT mediated tools as well. The 'science-practice gap' is a well-known issue in health program planning. It may be partly the result of disagreement between producers (scientists) and users (practitioners) of evidence, specifically on what is relevant evidence and how to obtain it [49]. To allow health professionals to work more evidence-based, more practice-based research is required. There is a need for more extensive reports on the theoretical base, structure and content of interventions targeting obese children. It is also of high importance to report on the external validity, such as recruitment and selection procedures of participants, intervention staff, delivery settings, and the degree to which the intervention is modified [17]. Furthermore, in publications on the evaluation of interventions the effect on overweight is provided, but information on the structure and content of the intervention and effect on other physical and psychological parameters is frequently missing [21]. A process evaluation as well as an outcome evaluation is important and are planned for *AanTafel!*. Results of such evaluations have to be published to allow for a comparison of different interventions [45].

RCT's are often mentioned as gold standard to examine what (components of) interventions are effective. However, results of interventions in RCTs differ from clinical practice outside the RCT due to lack of documentation and high drop-out rate [44, 50]. Possibly, this can be explained by the difference in setting and population [17, 50]. In our opinion, not only RCT's but also practice based research helps to unravel the factors for success in behavioral change.

Remarkable 10 of the 11 interviewed parents were mothers. Because it is known that mothers and fathers have different parental influences on their children's weight status and lifestyle behavior [51], this can be seen as a limitation of this study. Perhaps, mothers were more at home, and therefore better to reach. Another limitation of this study is that the process of professional judgement is based on the individual experience and knowledge of the professional and is therefore not an objective process. However, as described above this an important step for integrating the findings and makes use of information that professionals have collected by their own experience, but also by the experiences of other professionals in their networks [52].

In this paper we provide information on the basis and content of our program for other health practitioners who want to develop or improve an intervention for obese young children. In case of lack of specificity of guidelines, deriving different types of evidence is needed to develop a new best evidence intervention. For obese young children in a secondary care setting, the result of this process is an intervention with the following key characteristics: multicomponent, multidisciplinary, family-based with focus on the parents, age-specific, tailored to individual children and families, duration one year and using a combination of individual and group sessions with a web-based learning module. Because of the importance of tailoring the intervention to different target groups, this advice cannot be transferred to other target groups, for example other age groups or non-obese children (i.e. prevention of overweight); for other target groups the process of deriving and integrating evidence has to be repeated.

Conclusion

We have integrated evidence from science and practice for the development of an intervention for obese young children. Requirements for effective interventions were set. The clinical guidelines provided not enough specific information on the requirements, and on several requirements the information from different guidelines was conflicting, missing or vague. The method of integrating evidence from clinical guidelines, additional literature review, target group interviews, and professional input was a helpful method to fill in the requirements. The obtained information was integrated in the final step of the development process. The characteristics of the resulting intervention are described in this article. With Internet-mediated elements we hope to maintain effectiveness, despite intensity lower than advised in literature. A process evaluation and outcome evaluation is essential to provide more information on key characteristics for effective intervention, and has been planned. We recommend changes in scientific working principles on program development. First, with regards to the inclusion of target-group and therapists perspectives, essential in practice to align with context-specific circumstances at the family homes as well as the secondary care setting. Secondly, data reporting and thus, clinical guidelines should be more sensitive to the specificity required in practice with regards to how to involve both the target group and therapists, how to combine different strategies such as face-to-face and ICT mediated contact, group and individual sessions and the optimal duration and intensity of contact.

Practice Implications

In practice, the process of integrating evidence from science and practice is a useful method to overcome the gaps in clinical guidelines. Practice and science may benefit from close collaboration. If practitioners voice their concerns, scientists may become more sensitive to report not only outcomes, but also the theory base, structure and content of the intervention and help make the evidence more relevant and applicable to practice.

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Chapter 4

Process evaluation of a family-tailored, multi-method childhood obesity treatment program in a secondary care setting

E. van Hoek, A.J. Janse, L.I. Bouwman, E.J.M. Feskens

Submitted

ABSTRACT

Introduction

Despite the rise in obesity among children, treatment programs for children aged 3-8 years are rare. We developed a program based on the available evidence and secondary care guidelines. Two gaps in evidence emerged. Firstly, parents should be involved, yet it is unclear how to involve them. Secondly, treatment requires multi-disciplinarity, yet no guidelines exist on which therapists and how to involve them. The gaps were filled based on consultations with the target group and experts. The multi-component, multidisciplinary, family-tailored treatment program *AanTafel!* has a duration of one year with 14 sessions and a 13-chapter web-based module. This paper reports on the process evaluation of the pilot and aims to contribute to the development of evidence-based childhood obesity treatment, specifically with regards to parental and multidisciplinary involvement.

Methods

The pilot included seven obese children and their parents and showed a clinical relevant 0.5 decrease in BMI z-score directly and two years after the program. Parental participation was assessed based on drop-out, attendance rates, log-ins and completed assignments of the web-based module. Perceived acceptability was measured by interviews with parents at 4 and 12 months and questionnaires with involved therapists at 4 months. Questions regarded the programs' content and structure characteristics: multi-component, multidisciplinary, family/parent-focus, intensity, duration and group/individual/web-based session combination.

Results

The drop-out rate was 14% (one child) and the median attendance rate was 86%. On average, parents logged-in 18 times and completed 75% of the web-based module assignments. Both parents and therapists rated the program as acceptable, favored elements with high parental involvement (e.g. self-monitoring) and suggested further family-tailoring. Parents appreciated parental peer support and suggested to increase interactive elements in the web-based module. They appreciated the multi-disciplinary presence yet therapists suggest a reduction in order to reduce costs.

Conclusions

Parents and therapists positively evaluated the programs' content and structure. Parental peer support, individual family tailoring and highly participative elements are evaluated as important strategies for parental involvement. High involvement of multiple disciplines is viewed as positive but has to be reconsidered to reduce costs. Interaction between therapists should be frequent to stay up-to-date with participants' progress.

Introduction

The global prevalence of childhood obesity worldwide is high and still increasing [1]. Childhood obesity negatively impacts psychosocial and physical health in the short and the long term and demands for effective treatment [2-4]. Obesity starting in the age-interval of 5 and 7 years increases the risk of persistent obesity, and starting obesity treatment at young age is a good predictor of successful overweight reduction [5-7](Reinehr et al., 2010, Sabin et al., 2007). It is important to tailor treatment to the developmental stage of the child and to the family situation. The pediatricians of our regional hospital saw a growing number of young obese children. Because no treatment program was available for young obese children in The Netherlands, we developed *AanTafel!*, a family-tailored treatment program for 3-8 year old children with obesity [personal communication van Hoek et al.]. The program is based on extensive review of evidence from clinical guidelines and scientific literature [8][personal communication van Hoek et al.].

Gaps in evidence emerged with regard to firstly, parental involvement and secondly, multi-disciplinary involvement. Evidence is consistent on the need to involve parents in treatment. However, no evidence was available about optimal strategies to involve them. Evidence was inconclusive regarding the balance between group and individual sessions. Also, no evidence is available about whether and how to substitute face-to-face contact with ICT-mediated contact.

Parental involvement in treatment programs should meet the expectations and preferences of parents themselves. In the literature, very view studies report on their opinion. Lachal et al. reviewed 45 studies on perceptions of (parents of) obese children and adolescents and health professionals towards treatment [9]. They found a lack of studies on the perception of (parents of) obese young children in secondary care [9]. Parents agree on the fact that they have a role in treatment, but strategies to involve them are not discussed in this review [9].

The second gap in evidence regarded the translation of the need for a multidisciplinary approach to the design of the program. Evidence is conclusive about the need to address diet and physical activity and most literature recommends to include behavioral change techniques [personal communication van Hoek et al.]. However, no evidence is available about which therapists to involve, how to involve them and how they should collaborate [personal communication van Hoek et al.].

These two gaps in evidence were dealt with by consulting the target group and experts in nutrition, physical activity, health behavior change and health promotion [personal communication van Hoek et al.]. The resulting treatment program is called *AanTafel!*, which is Dutch for 'To the Table!' and is used as a synonym for sharing a meal together. The pilot-version of *AanTafel!* is primarily parent-focused

with most sessions and a web-based learning module for parents only. This treatment program is multidisciplinary with two or more disciplines involved in 13 of 14 individual and group sessions. A decrease in BMI z-score was observed in the children participating in this pilot study.
This paper reports on the process evaluation of the pilot and aims to contribute to the development of evidence-based childhood obesity treatment, specifically with regards to parental and multidisciplinary involvement. The results will be used to further develop the next version of *AanTafel!*.

Methods

Subjects and setting

Patients were enrolled in a regional hospital (Gelderse Vallei Hospital, Ede, Netherlands) in March 2010. Eligibility criteria were children with obesity according to the international criteria of Cole [10], age 3 to 8 years old, parent(s) Dutch speaking (or bring along a translator), no known endocrine or chromosomal cause of obesity, no psychological or social problems of the parents interfering with treatment.
Seven obese children (three boys, four girls) with a median age of 5.6 years (interquartile range (IQR) 4.8-6.7 years) with their parent(s) started treatment. The median BMI z-score of the children at start of treatment was +3.3 (IQR 3.1-5.2), which indicates severe obesity. The median decrease of BMI z-score after treatment was -0.4 (IQR -0.6 to -0.1, intention to treat analysis (ITT)). The median change in BMI z-score of the children who finished treatment was -0.5 (IQR -0.6 to -0.1). During 24 months follow up this result was sustained (ITT).
Written informed consent was obtained from all parents who participated in the treatment program. The ethics committee of the hospital approved the study protocol.

The treatment program

AanTafel! is focused primarily on the parents and tailored to family lifestyle. The treatment program consisted of 20 contact hours over a period of one year, divided over eight group sessions with parents, four physical activity sessions with parents and children, and two individual sessions with parent(s) and child. Eight sessions took place in the first four months (intensive phase) and six sessions in the second 8 months (less-intensive phase). After each session, the corresponding chapter in their personal (log-in code per family) web-based learning module became accessible for the parents. At the end of the program all 13 chapters were accessible. Each chapter provides information (key-information and background information), assignments (including dietary and physical activity records), short movie clips, and the possibility to send the therapists a message. Separate emails (not within the web-based learning module) were sent to remind parents to visit the session and to use the web-based learning module. Therapists could directly evaluate and discuss the completed assignments with parents during the subsequent session.
The program has a multicomponent nature, including behavior modification techniques to change dietary intake and physical activity levels. The multidisciplinary team consists of a pediatrician, child psychologist, pediatric dietician and child physiotherapist. In 13 out of the 14 sessions, two or more therapists were involved. Regular interdisciplinary meetings took place to discuss progress of the families.

Process and outcome measures

The process evaluation consisted of the parental participation rate and perceived acceptability of parents and therapists. The parental participation was measured by drop-out rate, attendance rate, number of log-ins, and completed assignments in the web-based learning module. The perceived acceptability was measured based on semi-structured in-depth telephone interviews with the parents at 4 and 12 months after starting treatment. At 4 months, at least one parent(s) of all seven children were interviewed. At 12 months the parent(s) of six children were interviewed. One parent (not drop-out) refused to participate in the interview at 12 months due to concurrent psychosocial problems in her family. The interview topics were based on the key content and structure characteristics of *AanTafel!* listed in Table 1. The interviews were conducted by two persons (unknown to the parents) instructed to conduct interviews [11]. Interviews were audiotaped and transcribed verbatim. The text was analyzed using textual content analysis. This involved a process of selecting and coding text fragments according to the key characteristics of the program [12]. The perception of all four involved therapists regarding the key characteristics were measured by a questionnaire 4 months after starting treatment, listed in Table 1.

Results

Participation rate

The drop-out rate was 14%. One child dropped out during the less intensive phase of treatment due to illness of the participating parent. The median attendance rate of sessions during the total treatment period was 86% (IQR 71-100, including drop-out). All parents had Internet access at home. The median number of log-ins per person during the program was 18 (IQR 10-29, including drop-out). A median of 75% of the assignments in the web-based learning module (IQR 42-91%, including drop-out) were completed.

Table 1 | Topics of interviews and questionnaires.

Topics based on key characteristics programme	Interview parents (4 months)	Interview parents (12 months)	Questionnaire therapists (4 months)
Content			
Multicomponent	Usefulness of components Relevant, missing or redundant information	Usefulness of compo-nents Relevant, missing or redundant information	Multicomponent approach Relevant, missing or redundant information
Structure			
Multidisciplinary	Interaction with therapists Use of different disciplines		Multidisciplinary ap-proach and cooperation
Family-based, parent-focused	Child and family, social environment	Child and family	Child and family, social environment
Intensity, duration	Intensity and duration	Intensity and duration	Intensity and duration
Combined group and individual sessions	Group versus individual		
Web-based	Digital workbook: film-fragments, texts and assignments	Digital workbook: film-fragments, texts and assignments Reminder emails Possible improvements	Digital workbook: structure, film, texts, assignments. Missing or redundant information or assignments Possible improvements

Acceptability: perceptions of parents

Because of overlap in results, the two interview sessions were analyzed and shown integrated (Table 2).

Multicomponent and Multidisciplinary

All parents perceived the multicomponent composition and multidisciplinary approach positive. Some parents mentioned previous visits to a dietician, but had missed in those visits the overall view on their child's lifestyle and well-being. One parent suggested adding a social worker to the therapists' team. Overall, the sessions which aimed to inform parents about a subject (e.g. nutritional information

labels) and required low levels of parental participation were rated lower compared to sessions with high levels of participation (e.g. self-monitoring of diet, visit to the supermarket). A minority of parents were worried about their child's eating behavior (e.g. fixation to food). Parents perceived that eating in social and cultural settings (e.g. visit to extended family or Ramadan) requires more attention in treatment. One parent perceived that although she knows what is healthy, she is unable to change towards a healthier lifestyle.

Family based, parent-focused

All parents were positive about the fact that they themselves are the main focus of intervention. They express the need to discuss lifestyle-issues without the presence of their child. However, one mother favored the presence of her child in individual sessions, so that her child is also involved in the behavioral change techniques. Parents suggested several improvements regarding additional tailoring to their private situation (e.g. pay attention to parental overweight, help with struggle to deal with the combination of an obese and an underweight child, and add home visits).

Intensity and duration

Parents had a favorable opinion about the high intensity of the treatment's first four months and the low intensity of the second part (8 months). The second part was easier to combine with a busy family life. According to one parent, the intensity in the second part of treatment was too low to achieve a large effect. For some of the parents the sessions in the less intensive period were a good reminder to maintain a healthier lifestyle.

Combined group and individual sessions

All parents appreciated the contact with other parents during the group sessions. In the first interview sessions, less than half of the parents told that they hoped for more advice from the other parents. Some parents told that the physical activity sessions helped to create an open ambiance in the following sessions. In the second interview session, one parent said that the ambiance became more open during treatment. Less than half of the parents needed more individual attention and suggested at least one extra individual session.

Web-based

All parents were positive about the web-based characteristic of the learning module. Two parents did not often use this module, one due to technical problems and one due to a lack of computer skills. They did not prefer to do use a paper version instead. Parents suggested several improvements regarding the learning module;

adding the option to change the password, an easier way to complete the assessments, options to interact with the other parents and receive messages from the therapists. Half of the parents perceived the separate reminder-emails to use the web-based learning module as helpful, and one parent did not need those reminders. For less than half of parents the next planned session was a reminder to use the web-based learning module.

Acceptability: perceptions of therapists

The therapists were overall positive about the treatment program, including the web-based learning module (Table 2).

Multicomponent

Therapists perceived goal setting and discussions on how to reach these goals as essential parts of the treatment program. The discussion on the dietary record and the physical activity pattern should be more tailored to the families with more structured feedback and more time scheduled for discussion. This requires the calculation of the nutritional content of the dietary record per child.

Multidisciplinary

The therapists were satisfied with the cooperation and suggested no additional disciplines. The multidisciplinary sessions were helpful, but to decrease costs and time they perceived it important to discuss which contribution is crucial in which session and attempt to lessen multidisciplinary presence. The therapists suggest contact between disciplines after each session to inform non-present therapists on the progress of each family.

Family-based, parent focused

The involvement of the whole family is perceived as important to achieve a positive effect. According to the therapists, parents can benefit from additional support from their direct social environment. They suggested to invite for instance grandparents to sessions and discuss with parents more extensively how they can mobilize their social environment to support them in changing to a healthier lifestyle.

Intensity, duration, combined group and individual sessions

The professionals suggested to increase the intensity at the beginning of the program, and to schedule more individual time and attention to set family goals more quickly and design a plan on how to reach these goals.

Table 2 | Results interviews parents and questionnaire therapists.

Topics	Interviews parents	Questionnaire therapists
Multicomponent	Overall positively perceive	
	Useful • Self-monitoring and evaluation components • Supermarket visit • Assignment and discussion healthy snacking • Workshop 'Being physically active within every household available materials' More attention needed • Eating behavior • Healthy food and cooking • Problems in social settings • How to change lifestyle Missing • Change in lifestyle during Ramadan	Useful • Discussion about goal setting • Discussions about how to reach goals Suggested improvements • More structured and concrete discussion on dietary record and PA
Multidisciplinary	Overall positively perceived	Satisfied with cooperation, no additional disciplines needed
	Suggestion improvements • Home visits • Social worker	Suggested improvements • Discuss who is essential in which session
Family-based, parent-focused	Parent-focused is positively perceived	Involvement of whole family is important for positive effect
	Useful • Sessions without child present • Presence of child in individual sessions More attention needed • Deal with different needs of children in family • Parental overweight	Suggested improvements • Increase involvement of important persons in the social environment • Encourage parents to invite e.g. grandparents to session(s) • Discuss with parents how to involve those persons
Intensity, duration	Overall the intensity is positively perceived	
	Useful • Sessions as reminder for healthy lifestyle • Suggested improvements: • Increase intensity in 2nd part (2nd interview)	Suggested improvements • In the beginning of the programme more time and attention to set goals faster and make concrete plans how to reach goals

Topics	Interviews parents	Questionnaire therapists
Combined group and individual sessions	Contact with other parents highly appreciated	
	Useful • PA sessions for open ambiance • Suggested improvements • At least 1 extra individual session	Suggested improvements • In the beginning of the programme more time and attention to individual families
Web-based learning module	Web-based characteristic of module was positively perceived	Is overall rated positive
	Useful • Reminder-emails • Coming session as reminder to use module • Overall, assignments on knowledge were rated less valuable Suggested improvements • Add possibility to change password • Easier ways to fill in the assignments • Add possibility to interact with other parents • Add possibility to receive reactions from therapists	Useful • Structure and look and feel of module • Key information in small texts Suggested improvements • Parental instruction on dietary record • Add film fragment with one of the participating parents • Complete background information • Add e-mail module within learning module • Add possibility of automatic feedback on dietary record • Remove redundant (nutritional logos) and less extensively filled in (self-confidence, keep group discussion) assignments

PA Physical activity

Web-based

Overall the therapists were positive about the comprehensible structure and suitable look and feel of the web-based learning module. They perceived that a more clear instruction on the goals of the dietary record is needed. Suggested improvements to the web-based learning module were to add a film fragment, extra background information, add an e-mail module, add automatic feedback on the dietary record, remove redundant and less extensively filled in assignments (Table 2).

Discussion

The parents and therapists perceived the program as highly acceptable. They held favorable views towards the family based approach with focus on parents. Parents and therapists preferred the topics with that were directly applicable to the family.

Parents appreciated the peer support of other parents, while further tailoring of treatment to the individual families can be helpful in further changing their lifestyle. Parents and therapists perceived the need to tailor the treatment to the social and cultural environment of the family.

The evaluation of the web-based learning module suggests that adding possible interaction between parents and therapists within this web-based learning module could increase parental involvement. According to parents and therapists the multidisciplinary approach with multidisciplinary presence in most sessions was highly appreciated. But the therapists suggested that the multidisciplinary presence can be decreased to save costs and time, and non-present therapists should be informed on the progress of the parents after each session. Despite the low number of patients in this study, the treatment program *AanTafel!* seemed to be effective at short and long term, this indicates the potential impact of the program and the relevance of our findings for the further design of effective childhood obesity treatment.

As far as we know, this is the first study that reports on perception of both parents of obese young children and their therapists on their involvement in a treatment program. The perceived need of parents for social support from other parents with an overweight child is also found in other studies [13]. Besides the social aspect, tailoring of treatment to the individual families is also perceived as a key to success. Parents and therapists in our study agreed on the need for one extra individual session in the beginning of the treatment to set family goals and design a plan on how to reach these goals. This is changed accordingly in the next version of *AanTafel!*.

Internet access is high in North America and Europe and the Internet is increasingly used to deliver treatment [14-16]. The use of Internet provides flexibility in location and time for the users; also it has the potential to increase the access of individuals to treatment [14-16]. Studies using Internet to promote health in other target groups conclude that Internet hold promise as a complement to treatments and that the effectiveness of Internet-based interventions is associated with use of additional methods of interacting with participants [14-16]. Our findings support this for (parents of) obese young children. Parents and therapists held favorable views towards the web-based learning module, however there was a wish for increasing its interactive features. After treatment, the BMI z-score showed a median decrease of -0.5 in children who finished treatment, which is similar to other successful treatment programs [17, 18]. These treatment programs include more face-to-face contact compared to *AanTafel!*. Additional contact through the Internet may substitute face-to-face contact with similar effect, but further research is required. In those other treatment programs the drop-out rate varies from 10-25%, but the participation rate is not reported [17, 18].

At the end of treatment some parents still struggled with changing their lifestyle, dealing with the eating behavior of their child, and eating in social and cultural settings. The gap between good intentions and the inability to pursue these intentions in everyday-life has been described before [19]. These issues are described as belonging to the maintenance stage of the stages of change model of Prochaska et al. [20]. Individually induced social change is needed, and parents have to be equipped with the social tools to organize the new situations needed to improve lifestyle [19]. A qualitative study in parents of overweight children in a wider age range (5-11 years) who participated in treatment showed that parents often feel that other members of the close and extended family undermine efforts to change lifestyle [21]. The need for engaging the whole nucleus and possibly extended family in treatment to improve success of treatment is suggested [21]. The professionals in our study also were aware of the problems in social settings and suggested to activate the extended family to help parents in changing their lifestyle by discussing this more extensively with parents and invite extended family (for example grandparents) to the session. This will be added to the next version of *AanTafel!*.

The strength of this study is the combination of quantitative and qualitative indicators to operationalize the concepts of parental involvement and multi-disciplinary involvement Qualitative studies methods are appropriate for health research that investigates human behavior [11]. As discussed by Draper and Swift, interviews or questionnaires are the recommended method to find out what people do in private and to find out what they think, feel and believe [11]. The interviews were held by telephone. This method required only a small time investment of the parents who were already expected to invest substantial time in the program. The parents knew that the information would be shared with the therapists. This could have affected their openness, despite the reassurance that the interview would not affect the treatment of their child and that the results are anonymized before analysis. To enable the parents to be open and critical during the interviews we choose people unknown to the participants to perform the interviews.
The method of studying the perspectives of the therapists by questionnaires is a limitation of this study because therapists did report what their opinion was but not why. Two of the researchers (EvH and AJJ) are therapists and this could have affected the results. At one side these therapist were already immersed in the field and have insights into patient issues and the treatment process, but at the other side this could have added subjectivity [11]. Therefore we (therapists and non-therapists) discussed the results together before conclusions were drawn to avoid misinterpretation.

The selected sample of parents of young obese children and therapists in a specific treatment program makes the results not generalizable to other target groups (i.e. empirically generalizable). Instead, this research is theoretically generalizable, because it gives insight in appropriate strategies to involve parents and implement multidisciplinary approach.

Conclusions

Studies about the views of participants of each target group and their therapists are needed to uncover components of success and failure in childhood obesity treatment, because of the importance of tailoring treatment to the specific target group. In this process evaluation of the treatment program *AanTafel!* we focused on strategies to involve parents and to apply a multidisciplinary approach in treatment of obese young children. In involving parents to the treatment of their child our study results point at the importance of parental peer support, tailoring to individual families and including topics in treatment that require high parental participation and therefore are practically applicable. In applying a multidisciplinary approach, we would recommend multidisciplinary presence in part of the sessions. Because of cost and time constrains not all disciplines have to be present in all sessions, provided that non-present therapists stay informed on the progress of the parents. A web-based learning module is useful to provide information and assignments to parents, with the benefit for therapists to easily monitor the progress of families. Increased interactivity in the web-based learning module can probably further increase parental involvement.

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Chapter 5

A novel multidisciplinary treatment program with web-based learning module for young obese children

E. van Hoek, E.J.M. Feskens, L.I. Bouwman, W.H. Verburgt, W. de Jager, H.S. Schipper, T.G.M. Vrijkotte, A.J. Janse

Submitted

ABSTRACT

Introduction

Obesity in childhood causes an increased risk of physical and psychosocial problems, as metabolic syndrome and a lower health related quality of life (HRQoL). The critical growth period from 3 to 7 years provides a window of opportunity for interventions. Multicomponent treatment with moderate or high intensity for young (3 to <8 years old) children results in promising effects, but the effect of low intensity treatment is less often studied. The multicomponent low intensity treatment program *AanTafel!* has a duration of one year, is focused on the parents of obese young children, and is complemented by a web-based learning module. The goal of this study was to assess the effect of *AanTafel!*.

Methods

A pre-post-design in clinical practice. Included were children with overweight or obesity, age 3 to <8 years old, with a caregiver willing to attend the sessions and able to speak Dutch. Forty patients (13 boys with median BMI z-score of 4.2 and 27 girls with mean BMI z-score of 3.3) started *AanTafel!*. The main outcome measure was BMI z-score at baseline, after 4 months, and at the end of one-year-treatment. In the first 23 patients that finished treatment, BMI z-score was also measured 3 years after baseline. The components of metabolic syndrome (waist circumference, blood pressure, serum lipids and glucose), several biomarkers of cardiometabolic risk, and HRQoL were measured as well.

Results

Eighty percent (n=32) of children finished treatment. They showed a decrease of BMI z-score of 0.45 from baseline to end of treatment, and this reduction in BMI z-score sustained in long term (3 years) in the 1st cohort of children. At baseline, 16.7% of the children had all four components of metabolic syndrome. This decreased to 0% at the end of treatment. HDL cholesterol significantly increased. Concentrations of the markers IL18, e-selectin, and sICAM significantly decreased from baseline to the end of treatment, indicating a reduction in inflammation. HRQoL showed a non-significant increase in most domains, and a clinically relevant increase in the physical summary score.

Conclusion

AanTafel!, a multicomponent and multidisciplinary treatment program of low intensity with complementary a web-based learning module is effective in improving health and well-being of obese young children. The reduction of overweight is clinically relevant and sustained at long term.

Introduction

Childhood obesity has serious physical consequences including an increased risk of cardiovascular disease, diabetes mellitus, fatty liver disease, and all-cause mortality later in life [1]. In addition, severely obese children have lower health-related quality of life (HRQoL) than normal-weight children, and comparable to children with cancer [2]. Obesity-associated health risks seem to affect overweight children as well. Even among preschoolers with overweight or obesity, cardiometabolic risk factors are common and HRQoL is impaired [3, 4]. Previous research suggests that the age interval from 3 to 7 years is a critical growth period with increased risk of persistent obesity [5, 6].
Importantly, this period provides a window of opportunity for interventions. Several studies showed that obesity treatment of young children is more effective than treatment of older children [7-9]. However, evidence regarding the effectivity of treatment of obese children below the age of eight is limited.
Recently, we reported a systematic review with meta-analysis that showed that multicomponent treatment programs with a moderate or high intensity for overweight or obese young children result in clinical relevant effects [10]. However, the number of studies performed in this age-group was limited, and included studies were of very low (<10 hours) or moderate to high intensity (>26 hours). No studies were included with a low intensity (10-26 hours)[10]. Therefore, the effects of low intensity treatment programs in young children and the success and failure factors in these programs are unknown.
In 2009 we developed the treatment program *AanTafel!* (English: 'To the Table') that is based on clinical guidelines, scientific literature, interviews with parents of young obese children and expert opinion [11]. The process evaluation of *AanTafel!* showed that this treatment program is perceived as highly acceptable by parents and therapists [12].
Childhood obesity impairs physical, psychological and social health and well-being, the effectiveness of obesity treatment is determined not only by the effect on overweight, but also by the effect on cardiometabolic risk, HRQoL, eating behavior and physical activity [13].
The goal of our study was to assess the effectivity of the multicomponent, multidisciplinary treatment program *AanTafel!* focused to the parents of obese young children. The face-to-face contact of this one year treatment program has a low intensity and is complemented with a web-based learning module. We hypothesize that this treatment program reduces overweight, improves cardiometabolic risk profile, increases HRQoL, improves eating behavior, and increases levels of physical activity. The BMI z-score over time in a reference population will be used to observe the natural course of BMI z-score in overweight or obese children.

Methods

Study Design

We used a pre-post design for the evaluation of the treatment program *AanTafel!* on the primary outcome measure (BMI z-score). Measurements were performed at baseline (t=0), after 4 months of intensive treatment (t=4), and at the end of one year treatment (t=12). The medical ethical committee of the Wageningen University approved the study protocol.
After the intervention in the first four (out of six) treatment groups (n=23) bi-annual follow-up visits (consultation without other intervention) with weight and height measurements took place until two years after finishing treatment (t=36). For all of these children at least 1 year follow-up was available, last measure carried forward was used for missing data at t=36 months (n=6).

Participants

Participants were enrolled in a regional hospital (Gelderse Vallei Hospital, Ede, The Netherlands) from March 2010 to May 2013. Participants were referred for treatment by their general practitioner, youth health care physician, or pediatrician. Inclusion criteria were overweight or obesity according to the IOTF criteria [14], age 3 to <8 years old, and having a caregiver willing to attend the sessions and able to speak Dutch (or able to bring along a translator). Exclusion criteria were an endocrine, chromosomal or syndromic cause of obesity and psychological or social problems of the parents interfering with treatment. In the study period, 76 patients in this age range were registered in our hospital with the diagnosis severe overweight. Forty patients started *AanTafel!* (Figure 1) in six different treatment groups with 5 to 9 families per group. In general families were two-parent families (83%) and most (86%) parents were born in The Netherlands. Other native countries of mothers were Morocco or Turkey. In most (87%) families at least one parent was overweight or obese. In 22.5% of the families the highest education of parent(s) was lower secondary education, in 47.5% upper secondary education, and in 20% tertiary education. Reasons for not starting *AanTafel!* were parents not willing to start treatment (n=27), already other care for overweight (n=7), or syndrome diagnosis (n=2).
Written informed consent was obtained from each child's parent or caregiver. There was additional informed consent obtained for the extra measurements (additional blood sampling n=29). Reasons for no extra measurements were technical problems with blood sampling (n=6), or not willing additional blood sampling (n=5).

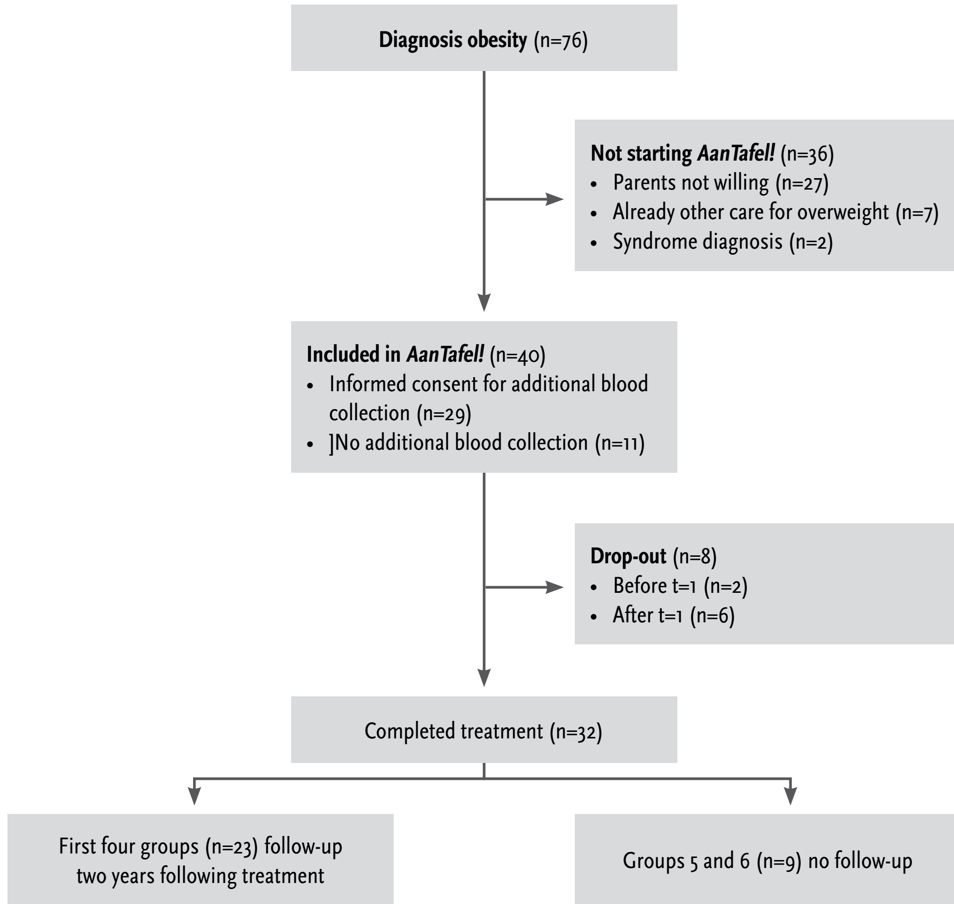

Figure 1 | Flow chart of *AanTafel!* evaluation study

Intervention

The development process and the outline and content of the treatment program *AanTafel!* have been reported earlier [11, 12]. Briefly, *AanTafel!* is focused primarily on parents and tailored to the family's situation and lifestyle. *AanTafel!* is multicomponent with behavioral modification techniques to change dietary intake and physical activity. It is also multidisciplinary and involves a pediatrician, child psychologist, pediatric dietician and child physiotherapist. The treatment program consists of seven group sessions with parents, four physical activity sessions with parents and children, one cooking and tasting workshop with parents and children, and three individual sessions with parent(s) and child. It covers a period of one year and provides a total of 22.5 contact hours. Eight sessions take place in the first four months (intensive phase), in the next eight months six sessions take place (less-intensive phase). Furthermore, parents work at home using a web-based learning module containing information, assignments and movie-clips. Therapists can directly evaluate the completed assignments in the learning module and discuss the outcomes with parents during the next session. Emails were sent to remind parents to visit the session and to use the web-based learning module.

Outcome measures

All measurements in the intervention group were performed at the start of treatment (t=0), after the intensive phase of treatment (t=4), and at the end of treatment (t=12).

Anthropometry

Our primary outcome was change in BMI z-score. Trained staff measured children's weight in underwear without shoes using an electronic calibrated scale (Seca 761), and height without shoes using a stadiometer (Holtain Ltd., Crymych, Cryfed, UK). Body Mass Index (BMI) was calculated from weight (kg)/(height (m)^2) and age and sex-specific BMI z-scores were calculated using Dutch growth curves of 2010 based on the LMS-methods [15]. The mid-upper arm circumference (MUAC) and the waist circumference were measured with a non-stretchable tape measure. Biceps, triceps, subscapular, and suprailiacal skinfold thickness were measured with a skinfold caliper (Holtain Ltd., Crymych UK). All these measurements were performed by one trained person. Age and sex-specific z-scores for MUAC, waist circumference, and the sum of the four skinfold thicknesses were calculated using the program Growth Analyser Research Calculation Tools (version 4.0, Growth Analyser B.V.) with Dutch growth curves from 2001, 2010 and 2001 respectively [15, 16].

Cardiometabolic risk

Supine blood pressure was measured after 5 minutes rest with an automated blood pressure monitor (Welch Allyn VSM 300, Skaneateles Falls, NY, USA) at the left arm. Repeated measurement after two minutes was performed and the measure was repeated until the value was stable. The percentile scores of blood pressure were used in analysis to take age, sex, and height into account [17].
Blood was collected in the morning after the children had fasted overnight and analyzed for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, glycated hemoglobin (HbA1c), and insulin in the Laboratory of Clinical Chemistry of the Gelderse Vallei Hospital. The laboratory joins the external quality control program in The Netherlands (SKML). All analyses were done using Dimension Vista 1500 automated analyser (Siemens, Erlangen, Germany) except for HbA1c, fasting glucose, and insulin.

Total cholesterol, HDL-cholesterol, triglycerides and glucose were determined in plasma with enzymatic methods [18]. LDL-cholesterol was calculated with the Friedewald equation [19]. HbA1c was determined in EDTA-treated plasma with HPLC measurement technology using an ADAMS™ A1c HA-8160 analyser (A. Menarini Diagnostics). Insulin was measured in serum using immulite automated analyzer (Siemens, Erlangen, Germany).
As a measure of insulin resistance, we used the homeostasis model assessment (HOMA IR), this was calculated by the formula (glucose (mmol/L) * insulin (mU/L))/22.5 [20]. The individual components of the metabolic syndrome (waist circumference, blood pressure, lipids, glucose) were recorded as defined by Ahrens et al [21].
The markers of cardiometabolic risk were predefined. The concentrations of the markers vascular endothelial growth factor (VEGF) and hsCRP were measured in a fasting serum sample at the Laboratory of the Division of Human Nutrition, Wageningen University by the V-PLEX Plus Human Biomarker 40-Plex Kit (Meso Scale Diagnostics, Rockville, Maryland). The concentrations of the other markers of cardiometabolic risk interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), tumor necrosis factor (TNF), monocyte chemoattractant protein-1 (MCP-1), e-selectin, leptin, chemerin, plasminogen activator inhibitor-1 (PAI-1), retinol binding protein-4 (RBP-4), soluble intercellular adhesion molecule (sICAM), soluble vascular cell adhesion molecule (sVCAM), TIMP metallopeptidase inhibitor 1 (TIMP-1), cathepsin S, adiponectin were measured in a fasting serum sample at the Laboratory of Translational Immunology of the University Medical Center Utrecht using a previously developed and validated multiplex immunoassay [22] To correct for disturbance in these markers in case of acute infection the results of cases with a CRP of >10 were not taken into account. In case of > 25% of values of a variable below the lower detection limit we excluded the variable from analysis. Therefore, chemerin, leptin and TIMP-1 were excluded. In case of ≤25% of values below the lower detection limit we used 50% of this limit as imputed value in subsequent analysis.

Health related quality of life

The health related quality of life (HRQoL) in children of 5 years and older was measured by the parent form of the Child Health Questionnaire (CHQ-PF50) and in children below the age of 5 years by the Toddler version of the CHQ (Infant Toddler Quality of Life Questionnaire (ITQOL)), both were completed by one of the parents [23, 24]. The CHQ-PF50 consists of 50 items on 14 domains, with a 0 to 100 scale. Lower scores correspond to lower HRQoL. The scores of different domains were combined to a physical and psychosocial summary score [23]. The ITQoL has 97 items and measures 12 domains, also with a 0 to 100 scale [24]. Some children turned five during the study period, the domains which appear in both the CHQ-PF50 and ITQoL (physical functioning, bodily pain, family cohesions, general health, emotional parental impact, parental impact time) were merged and evaluated in all children over time.

Eating behavior
Eating behavior was measured by the Children's Eating Behaviour Questionnaire (CEBQ), a 35-items validated tool that assesses eating style in young children [25, 26]. It covers the main eight dimensions of eating style that are indicated to influence body weight. The questionnaire has previously been used among children aged three years and older and was completed by one of the parents [25, 26]. Dietary intake was assessed using a 3-day dairy (including one weekend day). Daily energy and macronutrients intake were assessed using Evry Dietist software (Evry B.V. 2012) based on the Dutch food table (NEVO online 2011/3.0). Mean daily intake of snacks (fruit or vegetables or non-healthy snacks) and sweet drinks (containing sugar or sugar free) was calculated and use of daily breakfast was recorded. These are dietary pattern elements that are known to influence overweight in children [27, 28].

Physical activity
Physical activity was assessed using the tri-axial accelerometers Actigraph (GT3x) on four consecutive days (including two weekend days). Accelerometers were programmed to measure in 15 second epochs. The children were instructed to wear the accelerometer on the right hip during daytime. The children were also instructed to record physical activity and wearing time to make it possible to check unusual results. Only data of children with at least 480 min of registration time per day for at least three days were included. Actilife software (version 5, ActiGraph, Pensacola, Florida) was used to process the data. Median counts per minute and median time in moderate or vigorous physical activity (MVPA) per day were calculated according to age specific validated cut-off points [29-32].

Reference population
For the primary outcome variable (BMI z-score) a retrospective control group with overweight or obesity (criteria IOTF) at baseline was derived from the Amsterdam Born Children and their Development (ABCD) study [33]. The ABCD study is a prospective cohort study from fetal life onward, which started in 2003-2004. Weight and height were available from Youth Health Care (age 0 to 7) performed by trained nurses and at the age 5 years performed by trained co-workers of the ABCD study. A total of 6575 mothers of the original 8266 pregnant woman who participated in

this cohort study consented to follow-up their child's growth data. At age 5 years 3321 children were measured [33]. Included were in total 249 overweight (including obese) children, 36 of these children were obese.
Included children had at least two measurements available with approximately 1 year time interval, were age 3 to <8 years old, and had mother born in The Netherlands, Morocco or Turkey (because these ethnic groups are included in our intervention group) was used. [14] Age and sex-specific BMI z-scores were calculated as described earlier. Exclusion criteria were having a known endocrine, chromosomal or syndromal disease. These children were in primary care, assumed to be no multidisciplinary treatment program, and these data are therefore used to observe the natural course of BMI z-score.

Statistical analysis
Analyses were performed by using IBM SPSS statistics for Windows version 22 (IBM Corp, Armork, NY). Normally distributed variables were reported as mean with standard deviation (SD), non-normal distributed variables were preferably reported as median with interquartile range (IQR), and independent t-test resp. Mann-Whitney U test were used to compare characteristics of boys and girls; between completers and drop-outs; and between responders and non-responders. Paired t-test or the Wilcoxon signed rank test in case of skewed variables, were used to assess differences between time points. A p-value less than 0.05 was considered statistically significant.

Results

Baseline characteristics
At baseline 6 children (15%) were overweight, 13 (32.5%) had obesity grade 1, and 7 (17.5%) had obesity grade 2, and 14 (35%) had obesity grade 3. Thirteen boys and 27 girls were included with mean age 5.7 years. The mean BMI z-score was 4.2 in boys and 3.3 in girls (Table 1). Girls had higher systolic blood pressure levels and lower HDL-cholesterol.
Eight children (20%) dropped-out during treatment (Figure 1). The children who completed treatment did not significantly differ from the drop-outs regarding age, BMI z-score or educational level. The drop-outs had higher systolic blood pressure percentile (97.5 vs 75.0, p=0.01) and HOMA IR (1.65 vs 0.47, p=0.033) than the completers.

Table 1 | Baseline characteristics of children in *AanTafel!* evaluation study (n=40).

	Boys (n=13) Median [IQR]	Girls (n=27) Median [IQR]
Age (year)	5.6 [4.5-6.3]	5.8 [4.7-7.0]
Height (cm)	119.3 [111.0-124.4]	123.6 [110.9-131.1]
Weight (kg)	31.3 [28.2-37.3]	33.6 [27.0-38.1]
BMI (kg/m²)	22.9 [20.6-24.8]	22.1 [20.4-25.0]
BMI z-score	4.2 [3.4-5.1]	3.3* [2.6-4.0]
MUAC (cm)	23.6 [22.3-25.1]	23.8 [16.4-27.4][b]
MUAC z-score	5.3 [4.1-6.5]	4.5 [3.4-5.9][b]
Waist circumference (cm)	69.9 [67.2-72.9]	71.1 [63.8-74.35][b]
Waist circumference z-score	3.1 [2.7-3.7]	2.8 [2.4-3.5][b]
Sum of four skinfold thicknesses z-score	8.7 [6.1-11.4][a]	7.7 [5.3-10.3][c]
Systolic blood pressure percentile score	67.0 [61.0-82.5]	90.0** [53.0-98.0]
Diastolic blood pressure percentile score	56.0 [26.5-62.0]	57.0 [39.0-73.0]
Total cholesterol (mmol/l)	4.2 [4.0-4.8]	4.5 [3.7-5.2]
HDL cholesterol(mmol/l)	1.3 [1.2-1.5]	1.1***[1.0-1.3]
LDL cholesterol (mmol/l)	2.6 [2.3-3.1]	2.8 [2.1-3.4]
Triglycerides (mmol/l)	0.69 [0.52-0.92]	1.07 [0.64-1.43]
HbA1c (mmol/mol)	33.0 [32.1-34.7	34.00 [33.0-35.5]
HOMA IR	0.47 [0.44-0.98]	0.78 [0.42-1.57]

* p=0.007; ** p=0.043; *** p=0.023; [a] n=9; [b] n=24; [c] n=22

Anthropometry

BMI z-score significantly decreased over time (Table 2, Figure 2). The mean reduction between t=0 and t= 4 is 0.30 (0.30 SD), and 0.45 (SD 0.49) between t=0 and t=12. Boys and girls showed similar reductions in BMI z-score over time. Follow-up data of the first 23 children were available at 36 months (n=6, last measure carried forward). In this group the reduction in BMI z-score sustained and was 0.39 (SD 0.30) until t=4, 0.56 (SD 0.54) until t=12 and 0.61 (SD 0.86) until t=36.
The z-scores of the waist circumference and sum of four skinfold thickness significantly decreased in the intensive phase of treatment and remained stable in the less intensive phase of treatment (Table 2, Figure 2). The reduction in MUAC z-score was non-significant.

Cardiometabolic risk

HDL-cholesterol significantly increased after the less-intensive phase and at the end of the treatment program (Table 2). In addition, a small increase was found in total cholesterol in the less intensive phase of treatment, but not at the end of treatment. No clear changes were found in HbA1c, HOMA-IR or blood pressure.
At baseline 16.7% of the children had all four components of metabolic syndrome. This decreased to 0% at the end of treatment (Figure 3). The percentage of children with no or one component of metabolic syndrome increased from 30.5% at baseline to 70.8% at t=12. Overall the improvement in components of metabolic syndrome was borderline significant (p=0.052, t=0 to t=12 months).
Concentrations of IL18, e-selectin, and sICAM significantly decreased from baseline to the end of treatment (Table 3), indicating a reduction in inflammation. TNF and PAI-1 showed significant reductions in the less-intensive phase. A significant increase was seen in IL-8 in the intensive phase of treatment and sVCAM in the less-intensive phase.

Health related quality of life

For all domains, except parental impact of time, the scores showed a non-significant improvement during treatment. The psychosocial summary score increased from 48.9 at baseline to 50.1 at the end of treatment with significant improvement after the intensive phase of the treatment (Table 4). The physical summary score increased from 49.7 to 53.2. This improvement is clinically relevant [34].

Eating behavior and physical activity

The dimensions desire to drink and food fussiness of the CEBQ showed a significant decrease during overall treatment (Table 5), but no significant changes were seen in the other dimensions of eating behavior.

Table 2 | Biomedical parameters during *AanTafel!* evaluation study.

	t=0 (n=38) Median [IQR]	t=4 (n=38) Median [IQR]	t=12 (n=32) Median [IQR]	t=0 to t=4 p-value	t=4 to t=12 p-value	t=0 to t=12 p-value
BMI z-score	3.41 [2.95-4.28]	3.08 [2.70-3.99]	2.86 [2.54-3.63]	0.000	0.10	0.000
MUAC z-score	4.8 [3.6-6.0][a]	4.5 [3.7-5.4][d]	4.3 [3.3-5.6]	0.40	0.81	0.37
Waist circumference z-score	2.9 [2.6-3.5][a]	2.8 [2.3-3.2][e]	2.7 [2.3-3.2]	0.016	0.66	0.049
Sum of four skinfold thicknesses z-score	7.7 [5.4-10.3][b]	6.7 [4.6-9.3][f]	6.6 [4.3-8.5][h]	0.001	0.23	0.028
Systolic blood pressure percentile score	82.0 [54.8-96.5]	75.0 [45.0-87.0][a]	76.0 [44.0-83.0][b]	0.26	0.75	0.32
Diastolic blood pressure percentile score	56.5 [36.8-70.3]	48.0 [34.0-64.5][a]	59.0 [41.0-67.0][b]	0.06	0.06	0.97
Total cholesterol (mmol/l)	4.45 [3.80-5.00][c]	4.40 [3,65-4.83][g]	4.50 [3.83-5.05]	0.16	0.040	0.38
HDL cholesterol (mmol/l)	1.18 [0.98-1.31][c]	1.25 [1.10-1.34][g]	1.27 [1.09-1.61]	0.11	0.018	0.001
LDL cholesterol (mmol/l)	2.75 [2.19-3.19][c]	2.77 [1.88-3.17][g]	2.73 [2.08-3.21]	0.12	0.41	0.30
Triglycerides (mmol/l)	0.88 [0.62-1.29][c]	0.72 [0.57-0.95][g]	0.68 [0.49-1.14]	0.06	0.39	0.80
HbA1c (mmol/mol)	34.0 [32.2-35.5][c]	33.3 [32.2-34.1][g]	34.0 [32.0-35.4]	0.89	0.13	0.19
HOMA IR	0.67 [0.43-1.47]c	0.46 [0.43-1.16]g	0.45 [0.42-1.25]i	0.77	0.09	0.99

[a] n=37; [b] n=31; [c] n=39; [d] n=36; [e] n=35; [f] n=32; [g] n=34; [h] n=38; [i] n=25.

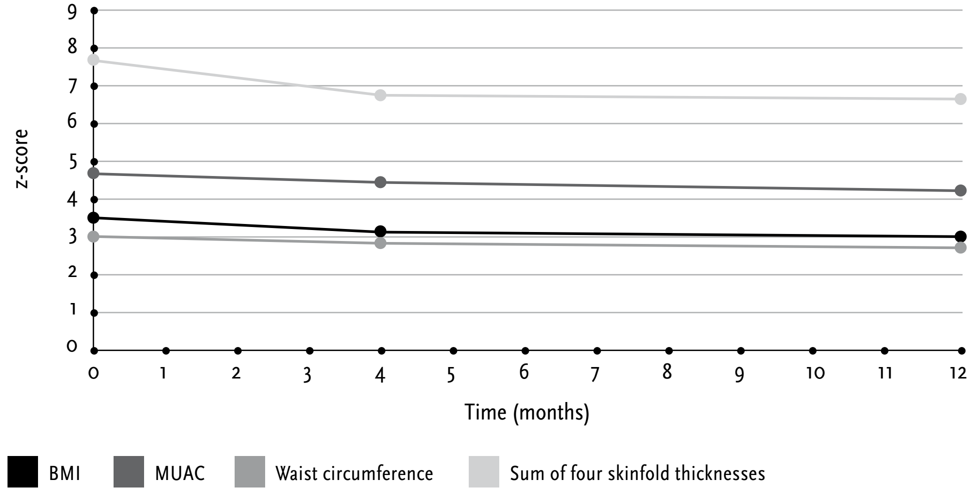

Figure 2 | Measurements of BMI, MUAC, waist circumference, and sum of four skinfold thicknesses during *AanTafel!* evaluation study.

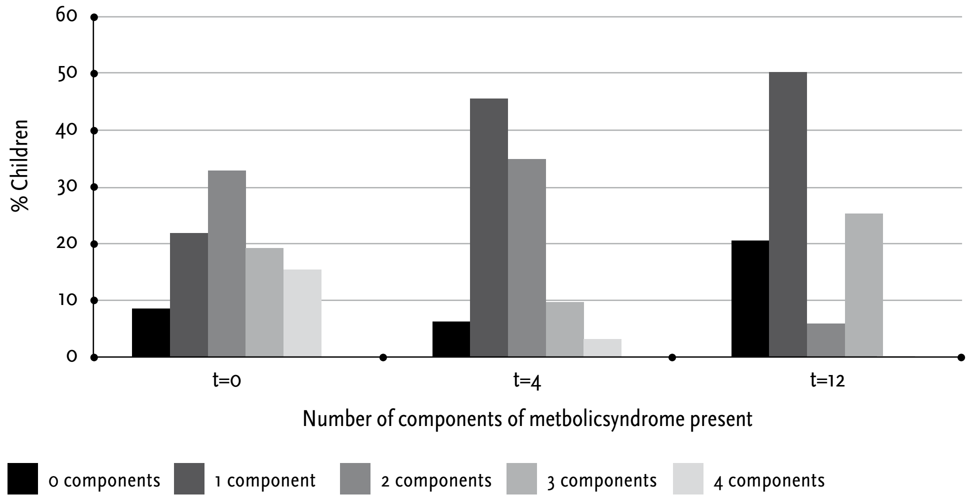

Figure 3 | Prevalence of metabolic syndrome components during the *AanTafel!* evaluation study at baseline (t=0), four months (t=4), and twelve months (t=12)

t=0 to t=4, p-value=0.021; t=4 to t=12, p-value=0.95; t=0 to t=12, p-value= 0.052

Table 3 | Cardiometabolic markers during the *AanTafel!* evaluation study.

	t=0 (n=27) Median [IQR]	t=4 (n=22) Median [IQR]	t=12 (n=19) Median [IQR]	t=0 to t=4 p-value	t=4 to t=12 p-value	t=0 to t=12 p-value
VEGF (pg/ml)	289.2 [190.5-445.9][a]	318.4 [271.8-437.4][b]	366.1 [218.3- 443.8][c]	0.23	0.06	0.18
hsCRP (mg/l)	1.96 [0.44-3.47][a]	1.94 [1.01-4.64][b]	0.72 [0.40-2.79][c]	0.27	0.78	0.92
IL-6 (pg/ml)	0.504 [0.333-0.871][a]	0.575 [0.393-0.836][b]	0.494 [0.304-0.730][c]	0.78	0.22	0.80
IL-8 (pg/ml)	6.93 [5.09-10,05][a]	11.60 [7.60-21.89][b]	9.38 [6.44-12.04][c]	0.002	0.75	0.07
IL-18 (pg/ml)	200.3 [108.2-252.6]	232.7 [125.6-266.1]	149.2 [114.6-221.6]	0.41	0.10	0.040
TNF (pg/ml)	2.79 [2.30-3.32][a]	2.94 [2.27-4.11][b]	2.69 [2.21-2.99][c]	0.16	0.023	0.31
MCP-1 (pg/ml)	151.6 [121.4-226.4]	180.4 [133.3-205.5]	157.7 [135.0-204.8]	0.55	0.80	0.87
e-selectin (pg/l)	71.2 [59.3-84.2]	61.4 [46.7-74.1]	59.3 [53.2-81.4]	0.16	0.18	0.007
PAI-1 (pg/l)	329.1 [202.7-446.5]	435.6 [281.0-590.3]	240.1 [142.4-504.9]	0.39	0.039	0.52
RBP-4 (mg/l)	29.7 [26.9-32.7]	30.2 [26.4-33.2]	30.4 [28.2-32.7]	0.78	0.38	1.00
sICAM (pg/l)	789.6 [711.6-832.8]	734.0 [652.6-818.9]	707.4 [643.3-770.3]	0.21	0.49	0.020
sVCAM (mg/l)	2.53 [1.65-2.93]	2.03 [1.28-2.60]	2.63 [2.06-3.15]	0.25	0.049	0.26
Cathepsin S (pg/l)	11.5 [9.6-16.6]	15.0 [10.6-19.0]	14.3 [9.6-17.2]	0.31	0.31	0.78
Adiponectin (mg/ml)	0.216 [0.138-2818.800]	0.204 [0.141- 2901.300]	0.215 [0.162-2730.800]	0.94	0.80	0.40

hsCRP high sensitive C-reactive protein; IL-6 interleukin-6; IL-8 interleukin-8; IL-18 interleukin-18; MCP-1 monocyte chemoattractant protein-1; PAI-1 plasminogen activator inhibitor-1; RBP-4 retinol binding protein-4; sICAM soluble intercellular adhesion molecule; sVCAM vascular cell adhesion molecule; TNF tumor necrosis factor; VEGF vascular endothelial growth factor
[a] n=24; [b] n=19; [c] n=18

Table 4 | Health related quality of life during the *AanTafel!* evaluation study.

	t=0 Mean (SD)	t=4 Mean (SD)	t=12 Mean (SD)	t=0 to t=4 p-value	t=4 to t=12 p-value	t=0 to t=12 p-value
Merged domains CHQ-PF50 and ITQoL	*n=40*	*n=34*	*n=32*			
Physical functioning	87.4 (17.1)	88.4 (12.6)	91.2 (12.2)	0.99	0.07	0.17
Bodily pain	80.2 (18.7)[a]	87.5 (16.5)	86.4 (18.6)	0.26	0.45	0.32
Family cohesions	72.1 (18.4)	72.2 (16.3)	75.8 (20.5)[b]	0.62	0.44	0.37
General health	66.7 (18.3)	70.5 (16.9)	72.1 (15.8)	0.22	0.85	0.06
Emotional parental impact	78.0 (21.6)	81.5 (17.3)	83.0 (16.5)	0.12	0.86	0.10
Parental impact time	87.1 (20.7)	88.7 (17.6)	83.9 (22.8)	0.95	0.44	0.70
Summary scores CHQ-PF50	*n=26*	*n=29*	*n=30*			
Physical summary score	49.7 (7.7)	53.0 (7.3)	53.2 (6.9)	0.08	0.20	0.16
Psychosocial summary score	48.9 (8.6)	52.5 (5.6)	50.1 (8.7)	0.003	0.16	0.63

[a] n=39; [b] n=31

Table 5 | Results of the Child Eating Behaviour Questionnaire during *AanTafel!* evaluation study.

	t=0 (n=40) Median [IQR]	t=4 (n=34) Median [IQR]	t=12 (n=32) Median [IQR]	t=0 to t=4 p-value	t=4 to t=12 p-value	t=0 to t=12 p-value
Food Responsiveness	3.00 [2.00-3.90]	2.80 [2.15-3.80]	3.00 [2.00-3.60]	0.58	0.50	0.32
Emotional overeating	2.00 [1.50-2.94]	2.25 [1.50-2.75]	2.00 [1.50-2.94]	0.91	0.83	0.83
Enjoyment of Food	3.75 [3.50-4.25][a]	3.75 [3.50-4.25][c]	3.88 [3.50-4.25]	0.71	0.26	0.97
Desire to Drink	3.33 [2.33-3.75][b]	2.67 [2.00-4.00]	2.60 [2.00-2.80]	0.25	0.11	0.001
Satiety responsiveness	2.60 [2.00-2.80][a]	2.40 [2.05-3.00][d]	2.40 [2.00-3.00][e]	0.81	0.88	0.70
Slowness in eating	2.50 [1.50-3.00][a]	2.50 [2.00-2.81]	2.50 [1.75-3.00][e]	0.07	0.63	0.71
Emotional undereating	2.50 [2.00-3.00]	2.75 [2.00-3.00]	2.38 [1.75-2.75]	0.24	0.24	0.84
Food fussiness	2.92 [2.21-3.50]	2.67 [2.00-3.83][c]	2.67 [1.96-3.17][f]	0.37	0.046	0.029

[a] n=39; [b] n=38; [c] n=33; [d] n=32; [e] n=31; [f] n=30

Table 6 | Dietary intake during *AanTafel!* evaluation study.

	t=0 (n=28) Median [IQR]	t=4 (n=18) Median [IQR]	t=12 (n=12) Median [IQR]	t=0 to t=4 p-value	t=4 to t=12 p-value	t=0 to t=12 p-value
Energy (kcal)	1436.2 [1110.9-1634.5]	1176.7 [1041.4-1425.3]	1148.0 [941.7-1330.7]	0.39	0.29	0.035
Protein (en%)	14.9 [13.4-16.7]	16.0 [15.3-18.1]	16.3 [13.8-18.7]	0.43	0.25	0.76
Fat (en%)	12.4 [11.2-14.0]	12.0 [10.3-13.4]	11.7 [10.4-13.6]	0.034	0.050	0.12
Saturated fat (en%)	4.7 [3.9-5.3]	4.4 [3.9-4.8]	4.3 [3.5-5.2]	0.272	0.11	0.33
Carbohydrates (en%)	55.0 [51.9-57.2]	54.6 [50.5-58.2]	55.0 [48.8-57.8]	0.347	0.08	0.41
Fibers (g)	11.5 [10.1-15.6]	12.6 [11.2-14.2]	12.0 [9.4-14.4]	0.88	0.53	0.27
Snack, total (n)	2.5 [2.0-3.6]	2.8 [1.9-3.3]	2.3 [2.0-3.0]	0.59	0.92	0.27
Snack, fruit or vegetables (n)	1.0 [0.7-1.3]	1.0 [0.7-1.0]	1.0 [0.7-1.3]	0.24	0.26	0.81
Snack, non-healthy (n)	1.7 [1.1-2.6]	1.8 [1.0-2.1]	1.3 [1.0-2.0]	0.57	0.57	0.39
Sweet drinks, total (n)	3.3 [2.4-4.9]	1.7 [1.3-3.7]	3.0 [1.8-3.8]	0.40	0.91	0.14
Sweet drinks, sugar containing (n)	2.5 [1.1-3.7]	1.3 [0.7-1.8]	1.2 [0.3-2.7]	0.02	0.38	0.046
Sweet drinks, sugar free (n)	0.8 [0.0-2.3]	0.5 [0-2.4]	0.7 [0-2.8]	0.027	0.52	0.23
Breakfast taken (%)	82	94	100	0.66	0.32	0.06

Table 7 | Characteristics (mean and SD) at baseline and after 1 year of follow-up in overweight (including obese) children from the ABCD study [33].

Age	n	Sex (n)		Country of birth mother			BMI z-score (mean (SD))	1 year change in BMI z-score (mean (SD))
		Boys	Girls	Netherlands	Turkey	Morocco		
3 yr	128	46	82	105	9	14	2.15 (0.61)	-0.13 (0.65)
4 yr	92	31	61	79	4	9	2.16 (0.65)	-0.13 (0.64)
5 yr	29	8	21	26	1	2	2.34 (0.66)	0.03 (0.45)

Table 8 | Characteristics (mean and SD) at baseline and after 1 year of follow-up in obese children from the ABCD study [33]

Age	n	Sex (n)		Country of birth mother			BMI z-score (mean (SD))	1 year change in BMI z-score (mean (SD))
		Boys	Girls	Netherlands	Turkey	Morocco		
3 yr	29	8	21	25	3	1	3.06 (0.45)	-0.17 (0.51)
4 yr	26	9	17	23	1	2	3.04 (0.41)	-0.05 (0.59)
5 yr	8	0	8	7	1	0	3.24 (0.46)	-0.05 (0.20)

At baseline, a higher energy intake was reported than recommended by the Dutch Health Council (Table 6) [35]. Median energy intake significantly decreased with approximately 300 kcal. Median fat intake reduced during the intensive phase. The children used more than the recommended maximum of 2 sweet drinks per day. This number did not change from baseline to the end of treatment. But children decreased their intake of sugar containing sweet drinks from baseline 2.5 drinks/day to 1.2 drinks/day at the end of treatment. Furthermore, the use of breakfast increased from 82% of the children to 100%.

Regarding physical activity a non-significant increase was seen in the median counts per minute during the treatment, from 241 counts/min at baseline, to 258 counts/min at t=12 (p=0.387, data not shown). Median time in MVPA per day reduced non-significantly from 43 min at baseline to 38 min at t=12 (p=0.178).

Reference population

Two-hundred forty-nine children of the ABCD study had overweight or obesity at age 3, 4 or 5 years (Table 7). At the age of 3 or 4 years, the change in BMI z-score during the next 12 months amounted to -0.13 (SD 0.65). At the age of 5 years the BMI z-score was stable. Among the few children with obesity the reductions were slightly different (-0.17 for age 3 year, -0.05 for age 4 and 5 years, Table 8).

Discussion

This study showed that the multicomponent, multidisciplinary treatment program *AanTafel!* with low intensity face-to-face contact and a complementary web-based learning module reduces weight gain in overweight and obese young children at short and long term. Furthermore, it improves their cardiometabolic risk profile and eating behavior, with a reduction of children having all four components of metabolic syndrome to 0%. HRQoL showed a non-significant improvement and physical activity measured by accelerometry did not appear to change much.

The strength of this study is that it evaluates a treatment program based on multiple indicators, providing insight in the physical and psychosocial health and well-being of the children. This is recommended in the literature, but not common practice [10, 13]. Another strength of our study is that the evaluation is carried out in clinical practice rather than a research setting, and provides insight in t the effect of treatment is a 'real-world' setting [36]. Similar to normal practice, children were referred by their physician rather than recruited through for example newspapers, as is the case for most research studies. Participation in the study was not required for starting this treatment program. However, all parents gave consent. Therefore, the study population is representative for the obese population which is normally treated in our hospital. The clinical relevant decrease of BMI z-score in short and in long term is therefore promising.

A limitation of research in real-world practice is the more frequent loss of data and the higher drop-out compared to a controlled research setting [37]. All parents of the children participating in this study were willing to start treatment, but their motivation was not assessed. The drop-out rate could have been lowered when a more extensive selection procedure was applied [37]. However, this could cause some families to refrain from starting treatment. The drop-out rate of 20% is comparable to what is found in the literature [38, 39]. Our study however has less controlled conditions and a reference group that is less comparable than control groups used in randomized controlled trials (RCTs). In a RCT the likelihood of observing an intervention effect (if one exist) is maximized [36]. However, the intervention effect of a RCT is not generalizable to the effect that the intervention will have in clinical practice, because of low external validity [36, 40].

A mean reduction in BMI z-score of 0.45 was found. A reduction of 0.5 in BMI z-score is clinically relevant given that it is associated with a reduction in cardiovascular risk factors and insulin resistance in children 4-15 years of age [13, 41, 42]. The reduction in BMI z-score remains at long term. Probably, this results in also at long term lower chronic inflammation and better cardiometabolic risk profile and therefore lower risk for cardiometabolic diseases for the future adults. The reduction in BMI z-score is comparable with that of multicomponent moderate or high intensity programs treating overweight (including obese) young children [10, 38, 39, 43]. Our intervention was of low intensity and therefore probably more cost-effective. Possibly, the web-based learning module played a role in maintaining results with a treatment program of lower intensity. To examine whether our result is not due to secular changes we described natural course of the reference population, a cohort of Amsterdam children, which showed a small decrease in BMI z-score in 3 and 4 years old overweight or obese children and a stable BMI z-score in the 5 year old children. Indeed, other studies showed that without treatment the BMI z-score of overweight and obese children does not change [10]. The observed change in BMI z-score in our intervention group can therefore be seen as treatment effect.

In this study, we showed that the achieved change in BMI z-score sustained at long term with last measurement 2 years after treatment. Evidence on long term effects of overweight treatment programs for children is limited [44]. However, the study of Kleber et al. with a high intensity treatment program showed that improvement of BMI z-score can be maintained in long term (3 year follow up) in young children [38].

At baseline 16.7% of our study population had all four components of the metabolic syndrome; abnormal waist circumference, blood pressure, triglycerides or HDL-cholesterol, HOMA IR or fasting glucose. At the end of this study this decreased to 0%, this is in agreement with the reduction in BMI. Metabolic syndrome is defined as having three out of four components, and at baseline 36.1% of our study population had metabolic syndrome compared to 1.5% in a population-based survey with European children 2.0-10.9 years [21]. The prevalence of the metabolic syndrome decreased during intervention to 25%.

Kleber at al. evaluated a multicomponent moderate to high intensity treatment programs with comparable result in BMI z-score (-0.46) an observed an increase in HDL and triglycerides was observed as well [38]. Kleber at al. also observed a significant decrease of HOMA IR of approximately 15%, but in our study no change in HOMA IR was observed. The mean HOMA IR at baseline in this study was 2.49, compared to mean HOMA IR of 1.01 (data not shown) in our study. Possibly, the lower HOMA IR at baseline explains the difference in effect on this point.

Little is known about the effects of an overweight treatment program on markers of cardiovascular risk that mediate low-grade inflammation, endothelial dysfunction, or coagulation in young children. In 3 to 5 year old children, a decrease in serum TNF concentration was found in a multidisciplinary intervention group (n=33), but no changes were observed in levels of adiponectin, leptin, hsCRP and IL-6 [43]. In prepubertal children aged 6-9 years (n=24) with a decrease in BMI z-score of ≥0.5 (group of responders in multidisciplinary treatment) a decrease in CRP and borderline significant decrease in IL-6 was observed [45]. In sICAM no changes were observed. We observed significant decreases in IL-18, e-selectin and sICAM over time during treatment. This indicates that successful treatment of obese prepubertal children improves inflammation status. However, additional studies are needed to elucidate which markers of cardiometabolic risk are the most sensitive for changes of cardiometabolic risk in these children.

The children in our study had lower HRQoL than the general Dutch population. On the domains emotional parental impact, physical functioning and general health their mean score was more than 10 points (approximately 1 SD) lower than the scores of a sample of general Dutch preschool children [46]. In general, a HRQoL difference of 0.5 SD is regarded clinically relevant [34]. Also the physical summary score our population scored approximately 1 SD lower than the general population, and more than 0.5 SD lower than a severely obese non-treatment-seeking population [4]. These data point at a generally low quality of life of our study population and give an addition call for effective treatment. During our treatment program HRQoL increased over time in all domains, except from the domain parental impact time, which may be due to time investment in the treatment of their obese child. The changes in HRQoL were not statistically significant, but (close to) clinical relevant with a mean change in the physical summary score of approximately 0.5 SD (SD of the general Dutch children population) and 0.4 SD in the domains physical functioning, bodily pain, and general health [4].

An advantage of using a generic questionnaire for measuring HRQoL is that the score can be compared to other study populations [47]. However, a disadvantage of such a general questionnaire instead of a disease specific questionnaire is that changes in HRQoL are more difficult to detect [47]. However, as there is no obesity HRQoL questionnaire available for young children below the age of 5 we used generic HRQoL questionnaires, possibly due to this no significant changes were observed in HRQoL in this study.

Children in this study were less active than recommended, less than 60 min/day MVPA. We found a non-significant decrease in time spent in MVPA and a non-significant increase in mean counts per minute. This conflicting results may be caused by the choices for the cutoff levels, because these are higher for older children. Also, it can be hypothesized that children have increased their low intensity physical activity instead of MVPA, for example by increasing active transport (walking or cycling) as was intended in this treatment program. Many of our parents set not only a goal to increase physical activity in daily life for example increasing active transport, but also stimulated their child to participate in organized sports. Because of their young age, most children started with swimming lessons, and also judo was advised by our physiotherapist because it helps to build self-confidence and overweight is not a disadvantage in this sport. However, during both sports the accelerometer cannot be used and thus, no data was available. This missing data may have resulted in the absence of significant changes in the level of physical activity.

In conclusion, we observed that a treatment program with low intensity and complementary a web-based learning module is an effective strategy to improve health and well-being of obese children aged three to eight years. Beneficial changes in eating behavior were observed. The BMI z-score showed a clinically relevant change, which remains at 2 years follow-up. This is supposed to decrease the risk of cardiometabolic diseases for these future adults. Approximately, one sixth of our treatment group was having all four components of metabolic syndrome at baseline, this decreased to 0% at the end of treatment, also pointing at a decrease of risk of cardiometabolic diseases.

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Chapter 6

Epicardial adipose tissue thickness is increased in obese young children; a pilot study

E. van Hoek, L.P. Koopman, E.J.M. Feskens, A.J. Janse

Submitted

ABSTRACT

Introduction
In adults, epicardial adipose tissue (EAT) appears to act as endocrine organ and to play a role in atherosclerosis. In children and adolescents epicardial adipose tissue thickness (EATT) is correlated with BMI z-score, cardiovascular risk factors, and pro- and anti-inflammatory markers. So far EATT has not been assessed in young (3 to 8 years old) children.

Objective
To compare EATT in overweight and obese young children with normal weight peers. Furthermore, correlations between EATT, and cardiometabolic risk factors are assessed, and EATT is measured during treatment of overweight and obese children.

Methods
Children who visited the pediatrician because of overweight or obesity and children who visited the pediatrician because of cardiologic evaluation and were diagnosed with an innocent heart murmur were invited to participate in the study. Eligibility criteria for the study were age 3 to 8 years, and having no known endocrine or chromosomal disorder. Included were 8 overweight, 25 obese, and 15 normal weight children. Overweight and obesity were diagnosed by the IOTF criteria. EATT was measured by echocardiography. In the overweight and obese children also blood pressure, (fasting) lipid profile, glucose, insulin, high sensitive C reactive protein (hsCRP), and adiponectin concentrations were measured. In the overweight and obese children that completed treatment (n=20) measurements were repeated after 4 months and at the end of 12 months of multidisciplinary treatment.

Results
EATT was significantly higher in the overweight (median 1.38 mm) and obese (median 1.57 mm) children compared to the children with normal weight (median 0.87 mm). EATT was significantly correlated with adiponectin (r = -0.485), but not with other risk factors. EATT did not significantly change during treatment (0.02 mm, SD 0.68 mm), despite a decrease of BMI z-score of approximately -0.4 (SD 0.57).

Conclusion
EATT is increased in overweight and obese young children compared to their normal weight peers. This is important, because of the supposed function of EAT in the development of cardiovascular diseases. Additionally, EATT was negatively correlated with adiponectin, but correlations with cardiovascular risk factors were not statistically significant. EATT did not change during multidisciplinary treatment, while treatment did reduce BMI z-score.

Introduction

Obesity among children and adolescents is widely considered as an important public health problem [1]. Obese children are at increased risk of becoming obese adults [2, 3], they frequently have components of the metabolic syndrome during childhood, and have an increased risk to develop cardiovascular diseases later in life [4]. Not only the total amount of fat, but also specific fat depots, mainly visceral fat, have distinct metabolic characteristics and secrete and produce inflammatory markers and therefore cause low grade inflammation and higher risk of cardiovascular and metabolic (type 2 diabetes) diseases [5, 6].
Epicardial adipose tissue thickness (EATT) is recently identified as an additional cardiovascular risk factor since epicardial adipose tissue (EAT) functions as an endocrine organ. EAT could locally contribute to the development of coronary artery disease [7]. EAT is located between the visceral layer of the pericardium and the outer wall of the myocardium, no structure besides a fascia separates the EAT from the myocardium and coronary vessels [7, 8]. It shares the same microcirculation and innervation as the myocardium, is supplied by branches of the coronary arteries, and can therefore interact with the myocardium through vasocrine and paracrine pathways [8, 9]. It has the same embryonical origin as visceral omental fat and expresses and secretes cytokines, pro- and anti-inflammatory adipokines and vasoactive factors [7, 9]. EAT may provide protection to the myocardium and coronary arteries. However, in obesity EAT may become an adverse lipotoxic and proinflammatory organ, and increased EATT is associated with coronary artery disease in adults [7, 8].
Several studies in children and adolescents showed that EATT measured by echocardiography is correlated with BMI z-score and other cardiovascular risk factors such as blood pressure, homeostatic model assessment for insulin resistance (HOMA IR), high triglycerides, and low high-density lipoprotein cholesterol (HDL) [10-12]. Furthermore, EATT was associated with the pro- and anti-inflammatory markers leptin, adiponectin, and high sensitive C reactive protein (hsCRP) in adolescents [13, 14]. Finally, EATT in children from the age of nine years was found to be an independent predictor of carotid intima-media thickness, which is a surrogate marker of early atherosclerosis [10, 11, 15]. EATT is mostly studied in adults and adolescents. As far as we know EATT is not studied on children with mean age below the age of eight. Therefore, it is unknown whether EATT is already increased in young children and is correlated to cardiovascular and metabolic risk at this early age.
The main goal of this study is to assess whether EATT in young overweight and obese children is increased compared to normal weight young children. Secondary, our goal is to observe the correlation between EATT and the cardiovascular risk

factors and pro- and anti-inflammatory markers in overweight and obese young children, and if EATT changes in those children participating in a multidisciplinary treatment program.

Subjects and methods

Participants were enrolled in a regional hospital (Gelderse Vallei Hospital, Ede, Netherlands) from March 2010 to January 2015. Children who visited the pediatrician because of overweight or obesity and children who visited the pediatrician because of cardiologic evaluation and were diagnosed with an innocent heart murmur were invited to participate in the study. Eligibility criteria participants were age 3 to 8 years, and having no known endocrine or chromosomal disorder. In addition, cases started treatment if parent(s)/guardian(s) were willing to start treatment, were Dutch speaking (or possibility to bring along a translator), and there were no psychological or social problems of the parents interfering with treatment.
Participants were diagnosed as having overweight or obesity according to the IOTF criteria [16]. The study group consisted of 8 overweight and 25 obese children (cases) and 15 normal weight children (controls). In all children measurements were performed at baseline. Measurements in cases which started treatment were performed at baseline (t=0), after the 4 months intensive phase of treatment (t=1), and at the end of one-year-treatment (t=2).
Written informed consent was obtained from the parents/ guardians of all participants.
The medical ethical committee of the Wageningen University approved the study protocol.

Treatment program

Overweight and obese children were treated by the multidisciplinary, multicomponent, family-based treatment program *AanTafel!*. This treatment is age-specific, tailored to individual children and families, focussed on the parents and has a duration of one year by using a combination of individual and group sessions and a web-based learning module. Eight sessions take place in the first four months (intensive phase), afterwards six sessions take place in the next eight months (less-intensive phase).

Measurements

In all participating children the BMI z-score and EATT were measured at baseline (t=0).

Trained staff measured children's weight without shoes, using an electronic, calibrated scale (Seca 761) and height without shoes using a stadiometer (Holtain limited, Crymych, Cryfed, UK). For calculating the Body Mass Index (BMI) the formula weight (kg)/[height (m)]^2 was used. Age and sex-specific BMI z-scores were calculated [17].
Echocardiographic investigations were performed using *GE Healthcare Vivid S6 (General Electric Company, United Kingdom)* by three experienced and trained echocardiographers. Epicardial fat was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. EATT was measured in left decubitus position in the parasternal long axis perpendicular to the aortic annulus, which was used as the anatomical landmark, according to the method proposed by Iacobellis et al. [18, 19]. All measurements were taken end-systolic when the EATT is highest. The average value of three cardiac cycles was calculated. The coefficient of interobserver variation was 14.4% (EvH) and the coefficient of intraobserver variation was 19.5% (blinded measurements by LPK and EvH). Measurements were performed in anonymized images by one observer (EvH).
In the group cases (screened for intervention) additionally, blood pressure, and blood samples were taken at baseline, at the end of the intensive phase of treatment (t=1) and at the end of one-year-treatment (t=2).
Supine blood pressure was measured after 5 minutes rest with an automated blood pressure monitor (Welch Allyn VSM 300, Skaneateles Falls, NY, USA) at the left arm. Repeated measurement after two minutes was performed and the measure was repeated until the value was stable. The percentile scores of blood pressure were used in the analysis to take age, height, and sex into account [20].
Blood samples were taken after overnight fasting and analyzed for total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, and insulin in the Laboratory of Clinical Chemistry of the Gelderse Vallei Hospital. The laboratory joins the external quality control program in The Netherlands (SKML). All analyses were done using Dimension Vista 1500 automated analyser (Siemens, Erlangen, Germany) except for fasting glucose, and insulin. Total cholesterol, HDL-cholesterol, triglycerides and glucose were determined in plasma with enzymatic methods [21]. LDL-cholesterol was calculated with the Friedewald equation [22]. Insulin was measured in serum using immulite automated analyzer (Siemens, Erlangen, Germany). As a measure of insulin resistance, we used the HOMA IR, this was calculated by the formula (glucose (mmol/L) * insulin (mU/L))/22.5 [23].
Concentrations of hsCRP were measured in serum at the Laboratory of the Division of Human Nutrition, Wageningen University by the V-PLEX Plus Human Biomarker 40-Plex Kit (Meso Scale Diagnostics, Rockville, Maryland). Leptin and adiponectin

concentrations were measured at the Laboratory of Translational Immunology of the University Medical Center Utrecht using a validated multiplex immunoassay [24]. In case of > 25% of values of a variable below the lower detection limit we excluded the variable from further analysis. This was the case for leptin and hence leptin levels were excluded from the study. In case of ≤25% of values below the lower detection limit we used 50% of this limit as imputed value in subsequent data analysis.

Statistical analysis

Analyses were performed by using IBM SPSS statistics for Windows version 22 (IBM Corp, Armork, NY). Baseline characteristics are presented as mean ± standard deviation (SD) in case of Normal distribution, otherwise values are presented as median with interquartile range (IQR). Because of non-normal distribution difference between groups were tested by the Mann-Whitney U test in case of two groups and Kruskal-Wallis test in case of more groups. For categorical variables a Chi-Square test was used. To test differences in variables over time the Wilcoxon signed rank test was used. Spearman's rho was calculated to assess correlations. Multivariate analysis was performed using a multiple linear regression model with forced entry. The level of significance was set at $p<0.05$.

Results

Baseline characteristics

Participants flow is shown in Figure 1 and baseline characteristics in Table 1. At baseline in the normal weight group consisted of 9 boys and 6 girls, the overweight group of 2 boys and 6 girls, and the obese group of 6 boys and 19 girls. The children in both weight groups were not significantly different regarding age and borderline significantly different on height. They differed significantly regarding sex, weight, BMI, and BMI z-score.

Thirty-one children (7 boys, 24 girls) with median age 5.8 years were screened to start the multidisciplinary treatment program. Parents of five children were not willing to start treatment and 6 children dropped out during treatment. Drop-outs did not differ on age and BMI z-score, but had significantly higher systolic blood pressure and HOMA IR (data not shown).

Relation of EATT with weight status

The children with overweight or obesity had significantly higher EATT compared to the children with normal weight (Table 1). BMI z-score was significantly associated with EATT (Table 3, Figure 2). Multiple regression analysis showed that EATT was

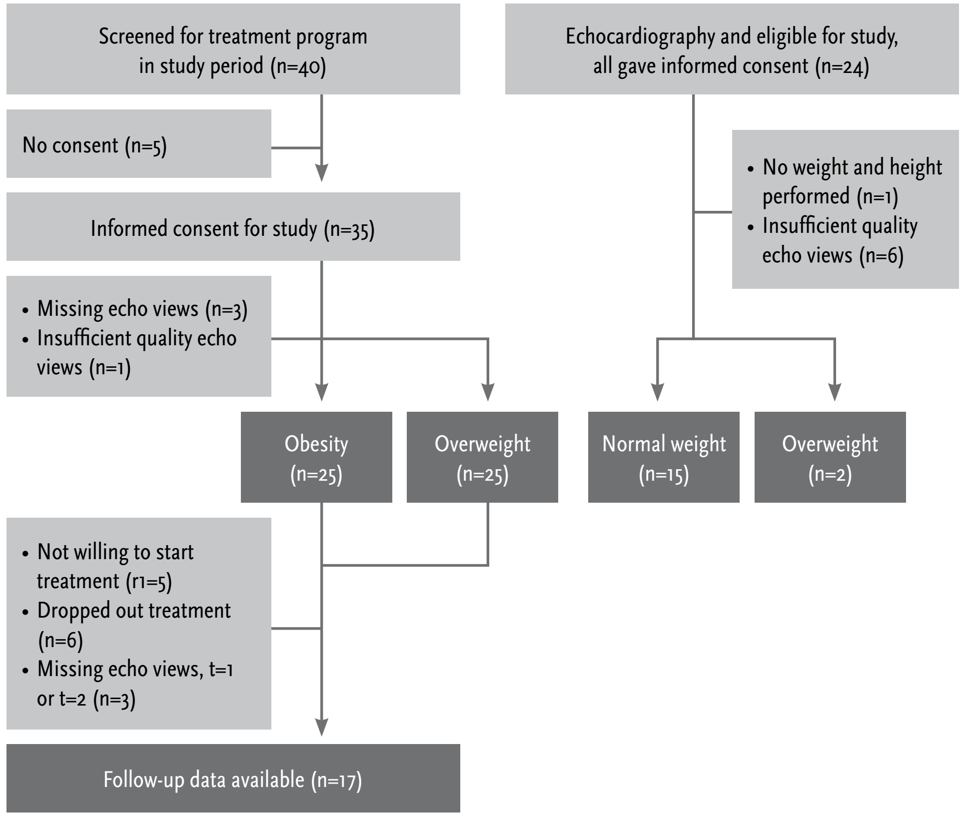

Figure 1 | Flow participants.

Table 1 | Baseline characteristics of children aged 3-8 year addressed for EATT.

	Normal weight (n=15) Median [IQR]	Overweight (n=8) Median [IQR]	Obesity (n=25) Median [IQR]	p-value
Sex (n)	9 M, 6 F	2 M, 6 F	6 M, 19 F	0.021
Age (y)	4.3 [4.2-5.3]	4.3 [4.2-4.8]	6.4 [4.9-7.3]	0.23
Height (cm)	109.6 [99.0-119.3]	111.4 [107.7-118.0]	126.7 [110.9-131.0]	0.052
Weight (kg)	17.1 [15.1-23.2]	22.6 [21.4-26.7]	35.9 [29.9-40.1]	0.000
BMI (kg/m²)	15.8 [14.8-16.4]	18.9 [17.9-19.2]	23.2 [21.8-25.4]	0.000
BMI z-score	0.24 [-0.77-0.92]	2.24 [1.74-2.37]	3.76 [3.25-4.25]	0.000
EATT (mm)	0.87 [0.53-1.00]	1.38 [0.68-1.93]	1.57 [1.20-2.57]	0.002

BMI Body mass index; EATT Epicardial adipose tissue thickness; F Female; M Male

Table 2 | Results of multiple regression analysis of EATT on BMI z-score, age, and sex (n=48).

	Unstandardized coefficients B (se)	Standardized coefficients Beta	p-value
Intercept	-0.73 (0.51)		
BMI z-score	0.17 (0.06)	.40	0.004
Age (yr)	0.07 (0.07)	.12	0.359
Sex (1=M 2=F)	0.44 (0.21)	.27	0.040

F Female; M Male; se standard error

Table 3 | Correlation between EATT and cardiovascular risk factors in 31 children age 3-8 yr with overweight (n=6) or obesity (n=25).

	EATT	
	Spearman's rho	p-value
BMI z-score[a]	0.472	0.001
Systolic blood pressure	0.240	0.15
Diastolic blood pressure	0.312	0.09
HOMA IR[b]	0.169	0.38
Total cholesterol[c]	0.071	0.71
HDL cholesterol[c]	-0.348	0.06
LDL cholesterol[c]	0.159	0.40
Triglycerides[c]	0.129	0.50
Adiponectin[b]	-0.444	0.016
hsCRP[d]	-0.190	0.36

BMI Body mass index; EATT epicardial adipose tissue thickness
[a] n=48, all children participating in this study taken in account, also normal weight children;
[b] n=29; [c] n=30; [d] n=25

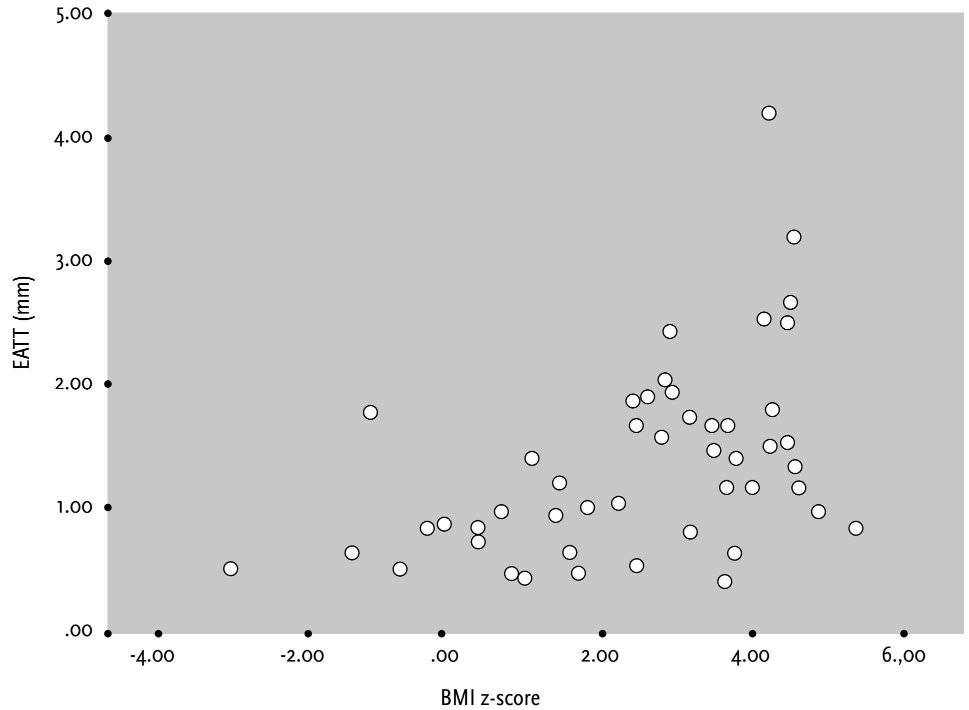

Figure 2 | Correlation between BMI z-score and EATT.

BMI Body mass index; EATT Epicardial adipose tissue thickness

independently related to BMI z-score (Table 2, standardized beta coefficient=0.40, p=0.004) and sex (standardized beta coefficient 0.27, p=0.040, indicating that girls have higher EATT than boys), but not age.

Correlation of EATT with cardiovascular and metabolic risk

EATT was not significantly correlated with regular cardiovascular and metabolic risk factors (Table 3). However, all correlation coefficients indicated that cardiovascular risk was higher with higher EATT and associations with diastolic blood pressure (0.31) and HDL cholesterol (-0.35) were borderline significant. No association was observed between EATT and hsCRP but a clear inverse association was observed with adiponectin (r=-0.49, p=0.008).

EATT during multidisciplinary treatment

Multidisciplinary treatment of the children decreased BMI z-score and increased HDL cholesterol. However EATT did not change during treatment (0.02 mm, SD

Table 4 | Longitudinal data of cases (n=17).

	t=0, mean (SD)	t=1, mean (SD)	t=2, mean (SD)	t=0 to t=1 p-value	t=1 to t=2 p-value	t=0 to t=2 p-value
BMI z-score	3.43 (0.91)	3.16 (0.81)	3.01 (0.76)	0.019	0.28	0.006
EATT (mm)	1.47 (0.75)	1.24 (0.49)	1.56 (0.64)	0.21	0.06	0.62
Systolic blood pressure percentile	68.1 (23.7)	61.2 (23.6)[a]	68.6 (22.3)	0.38	0.23	0.78
Diastolic blood pressure percentile	52.0 (23.7)	41.9 (26.6)[a]	56.2 (20.6)	0.66	0.005	0.015
HOMA IR[a]	0.83 (0.67)[a]	0.68 (0.52)[a]	0.94 (0.45)[a]	0.41	0.16	0.57
Total cholesterol (mmol/l)[a]	4.04 (0.69)[a]	3.99 (0.84)[a]	4.13 (0.90)[a]	0.69	0.42	0.39
HDL cholesterol (mmol/l)[a]	1.24 (0.22)[a]	1.28 (0.27)[a]	1.42 (0.31)[a]	0.61	0.025	0.026
LDL cholesterol (mmol/l)[a]	2.43 (0.57)[a]	2.41 (0.81)[a]	2.41 (0.72)[a]	0.82	0.54	0.65
Triglycerides (mmol/l)[a]	0.81 (0.30)[a]	0.66 (0.19)[a]	0.69 (0.27)[a]	0.08	0.33	0.19
Components metabolic syndrome (n)[b]	1.87 (0.99)[b]	1.40 (0.91)[b]	1.31 (0.95)[a]	0.19	0.91	0.14

[a] n=16; [b] n=17

0.68 mm), despite a decrease of BMI z-score of approximately -0.4 (SD 0.57) (Table 4). The diastolic blood pressure percentile increased during treatment. The EATT on different time points (pairwise) did not correlate significantly (t=0 to t=2 -0.08, p=0.60). Also, there were no significant correlations between change in EATT and change in BMI z-score (t=0 to t=2 r=-0.12, p=0.63).

Discussion

As far as we know this is the first study reporting on EATT of overweight and obese young children and we found that EATT in those children is increased compared

to normal weight young children. Additionally, EATT was negatively correlated with adiponectin, but correlations with cardiovascular risk factors were not statistically significant. EATT did not change during multidisciplinary treatment, despite that treatment did reduce BMI z-score.

We found an independent relationship of EATT with BMI z-score and sex with females having a higher EATT, but not with age. In earlier research a correlation with age was found. The EATT measured in older children was higher compared to the EATT we found [25]. Possibly, in our sample there was no relationship between age and EATT due to the small age range and the small sample size. We found an inverse association between EATT and adiponectin. Adiponectin is an anti-inflammatory adipokine, which is lower in overweight and obese children compared to normal weight children [26]. In adults who underwent cardiac surgery, adiponectin expression measured in EAT was lower in the patients with severe coronary artery disease compared to those without coronary artery disease, suggesting that adiponectine produced by EAT may have a protective role on the coronary artery [27]. Also in children, low adiponectin level is considered a marker of metabolic syndrome in and cardiovascular risk [26] and hence our results indicate that already at young age EATT is an indicator of increased risk for cardiometabolic diseases.

We did not find a change of EATT during effective treatment based on the change of BMI z-score. As far as we know, this is not investigated in children before. Additional studies are needed to confirm our findings. In adults, weight loss following dietary intervention was significantly associated with reductions in EATT of 0.8 to 4.0 mm [28]. Possibly, EATT in young children is too small or our sample size was too small to detect the effect of decrease of overweight on EATT in these young children. If age is correlated to EATT as discussed above, this is a positive correlation, and therefore age could possibly act as a confounder in the effect of treatment on EATT as the children were overall less overweight at the end of treatment, but also one year older.

A strong feature of our study is that it gives insight in EATT in young children. In adults EAT has received more attention the last years. The location, innervation, and circulation of EAT make that EAT could locally interact with the myocardium and coronary arteries through paracrine and vasocrine pathways [7-9]. Current evidence supports the hypothesis that, in obese persons EAT may become an adverse lipotoxic and proinflammatory organ that contributes to the in the development of coronary atherosclerosis [8]. Therefore, it is of high importance to know that the EATT is already increased in obese young children. Tracking will possibly take place, children with obesity and increased EATT will then become adults with obesity, with increased EATT, and increased risk for cardiovascular diseases. Measuring EATT by echography is non-invasive, fast, cheap, and more applicable for testing in the field compared to the alternative of measuring it by magnetic resonance imaging (MRI) [29]. However, MRI is also non-invasive and has the possibility to assess not only the EATT, but also the volume of EAT, which is possibly a more reliable indicator for the amount of EAT [30]. The correlation between EATT measurements by echocardiography and volume measurement of EAT and the correlation of both measurements with cardiovascular risk factors needs to be assessed.

Inter-observer and intra-observer variability were considerable. This might have affected our results for example those comparing EATT before and after treatment. Another possible explanation might be that variability occurs due to how the echo views were made. For example, the way the transducer was placed can affect the results [29]. We tried to minimize this by using three experienced and well trained echocardiographers and by using a standardized protocol. The control group was not age and sex matched. Because girls were more prevalent in the obese group and multiple regression indicated that girls had higher EATT than boys, sex could act as a confounder. But from the multiple regression analyses it was observed that EATT was independently related to BMI z-score. The sample with longitudinal data was small, so more research is needed to observe whether EATT changes during effective obesity treatment.

Conclusion

This study shows that EATT is correlated to BMI z-score in young children, and increased in children with overweight or obesity. This is of high importance, because of the supposed endocrine function of EAT and the possible role of EAT in cardiovascular diseases. A higher EATT in obese young children compared to normal weight children points at the need for effective treatment of those children. We also found an inverse correlation of EATT with adiponectin, which implicates that higher EATT correlates with adipokine responses already in young children.

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Chapter 7

General discussion

Main findings

The overall objective of this project was to contribute to effective treatment programs targeting overweight and its comorbidities in young children (defined as age 3 to 8 years). Effective treatment programs can potentially lower the high short- and long-term burden of obesity on health and wellbeing of young children. Previous research suggests that the age interval from 3 to 7 years is a critical growth period with increased risk of persistent obesity [1, 2]. Therefore, this period provides an important window of opportunity for treatment. However, no evaluated treatment programs were available in The Netherlands in 2009 when this study was started. The main findings of this research project as described in **chapters 2 to 6** are summarized in Table 1.

The systematic review with meta-analysis showed that multicomponent treatment programs (combining dietary education, physical activity education, and behavioral therapy) of moderate or high intensity (≥ 26 hours of face-to-face contact) were the most effective in reducing overweight in young children (**chapter 2**). These treatment programs showed a reduction in BMI z-score of approximately -0.5, which is associated with a decrease in cardiometabolic risk factors in children ages 4-12 years and is, hence, likely to be clinically relevant.

To develop a novel treatment program for young obese children, evidence from scientific literature was integrated with insights from practice with regard to effective childhood obesity treatment. This process involved the collection of data on six requirements: theory, influencing factors, tailoring, multi-disciplinarity, duration/frequency, and evaluation and monitoring. In five steps the development process took place: the inquiry of evidence from (I) clinical guidelines, (II) systematic review with meta-analysis (chapter 2), and (III) extended literature review, was supplemented with (IV) parental interviews and afterward (V) these findings were integrated by the involved therapists as described in **chapter 3**. This method was useful because review of clinical guidelines (step I) did not result in data on all requirements. The resulting treatment program *AanTafel!* has the following key characteristics: multicomponent, multidisciplinary, family-based with focus on the parents, age-specific, tailored to individual children and families, a duration of one year by using a combination of individual and group sessions, and complementary a web-based learning module.

Parental and multidisciplinary involvement seem to be important factors in effective treatment, but it was not clear how to involve parents and how to involve multiple disciplines. A pilot study with process evaluation of the treatment program *AanTafel!* was carried out to gain insight in both factors (**chapter 4**). The pilot study showed that parental peer support, individual family tailoring, and highly participative elements (such as self-monitoring of diet, visit to the supermarket) are important strategies to involve parents in the treatment program. Regarding multidisciplinary involvement, multidisciplinary presence at most meetings was viewed as positive by both parents and therapists. However, therapists put forward that the high costs should be considered as well and expressed the possibility of decreasing the multidisciplinary presence to the required disciplines necessary for each respective session. Minor changes to the treatment program *AanTafel!* were implemented after this pilot study. To increase the level of family tailoring, one extra individual session was added at the start of the program to determine family goals and develop a plan how to reach these goals. Furthermore, strategies for activating the extended family were more extensively discussed during the sessions, to help parents accomplishing the required changes in their lifestyle. The extended family (for example grandparents) was also invited to the sessions. The multidisciplinary presence was reduced to the required disciplines necessary for each respective session, and contact was increased between therapists between the sessions to keep all therapists up to date on the progress of the families.

The effect of the treatment program *AanTafel!* on overweight (primary outcome BMI z-score), cardiometabolic risk profile, HRQoL, eating behavior, and physical activity was evaluated in **chapter 5**. We found that overweight decreased from baseline till the end of treatment. The significant mean decrease in BMI z-score was 0.45. A significant increase from baseline to the end of the treatment was seen in HDL cholesterol. No significant changes were observed in the other cardiometabolic risk factors, but, an overall reduction was observed in the number of components of metabolic syndrome. Regarding markers of inflammation, an overall significant decrease was seen in IL18, e-selectin, and sICAM. The other markers did not change. HRQoL showed a non-significant improvement in most domains and the change in the physical summary score can be considered clinically relevant. Energy intake decreased but in general macronutrient composition of the diet was unaffected. The number of sugar containing sweet drinks decreased from 2.5 to 1.2 units per day and the use of breakfast increased to 100%. Physical activity as measured with accelerometers showed no significant change. A final promising finding was that the change in BMI z-score lasted at long term (-0.61, SD 0.86), i.e.2 yrs after finishing treatment as measured in first 23 children who finished treatment.

As described in **chapter 6,** epicardial adipose tissue thickness (EATT) was higher in overweight and obese young children compared to their normal weight peers. EATT was negatively correlated with adiponectin, but correlations of EATT with other cardiometabolic risk factors were not statistically significant. EATT did not change during multidisciplinary treatment, despite that treatment did reduce BMI z-score by 0.5 unit.

Table 1 | Summary of the main findings of this thesis.

Research question	What is the effectiveness of treatment programs in overweight and obese young children and what are the general characteristics of effective treatment programs for overweight or obese young children?
Methods	Systematic review and meta-analysis
Findings	• Overall positive effect on the BMI z-score of overweight young children in treatment programs targeting lifestyle. • Multicomponent treatment programs of moderate or high intensity are the most effective. • These treatment programs changed BMI z-score with -0.46 (95% CI -0.53 to -0.39).
Research question	How to develop a treatment program for young overweight or obese young children using evidence from science and practice?
Methods	Literature review, target group interviews, and professional judgements
Findings	• (1) Retrieve evidence from literature review and target group interviews. • (2) Integrate evidence with professional judgement. • Gaps in evidence in the clinical guidelines were overcome by this method.
Methods	Process evaluation
Findings	• Parental involvement strategies: peer support, family tailoring, highly participative elements. • Multidisciplinary presence at all meetings: positive, but has to be reconsidered to reduce costs; frequent therapist-interaction to stay up-to-date with participants' progress is necessary.
Research question	What is the effect of the treatment program *AanTafel!* on body composition, cardiometabolic risk, psychosocial wellbeing (HRQoL) and behavior of overweight or obese young children?
Methods	Pre-post design (with independent reference group)
Findings	• Improvement of body composition - Significant decrease of BMI z-score (0.45, SD 0.49), waist circumference z-score, and sum of four skinfolds z-score. - In the reference group a change of BMI was observed of -0.13, -0.13 and 0.03 in children of respectively 3, 4, and 5 years old. - MUAC: non-significant decrease. - Long term decrease of BMI z-score in cohort of first 23 children (0.61, SD 0.86). • Indicators of cardiometabolic risk improved partly - Risk factors: HDL cholesterol: significant increase; other no significant changes; improved number of components of metabolic syndrome. - Markers of inflammation: significant decrease of IL18, e-selectin, and sICAM. • HRQoL non-significant improvement in most domains - Physical summary score: clinically relevant improvement. • Behavior showed improvement of dietary intake and eating behavior - Dietary intake: significant decrease of energy; no significant changes of macronutrients; significant decrease of number of sugar containing sweet drinks; Increase of use of breakfast to 100%. - Eating behavior: decrease of food fuzziness and desire to drink. - Physical activity: non-significant decrease in time spent in moderate or vigorous physical activity; non-significant increase in mean counts per minute.

Research question	Is EATT increased in overweight and obese young children compared to normal weight young children, is it correlated to cardiometabolic risk factors, and does it change during multidisciplinary overweight treatment?
Methods	Case-control and pre-post design
Findings	• Increased EATT in overweight and obese young children compared to normal weight young children. • EATT was negatively correlated with adiponectin; no significant correlations of EATT with other cardiometabolic risk factors. • No change of EATT during multidisciplinary treatment (0.02 mm, SD 0.68 mm), despite a -0.5 change in BMI z-score.

BMI Body Mass Index; CI Confidence Interval; EATT Epicardial adipose tissue thickness; HDL High Density Lipoprotein; HRQoL Health Related Quality of Life; IL Interleukin; MUAC middle upper arm circumference; SD standard deviation; sICAM soluble intercellular adhesion molecule.

Methodological issues

Performing research in practice

We developed and evaluated the intervention *AanTafel!* in secondary care practice. Intervention studies can be subdivided in effectiveness and efficacy trials [3]. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under 'real-world' conditions. In efficacy research the likelihood of observing an intervention effect (if one exists) is maximized, by highly controlled conditions and therefore high internal validity. A placebo-controlled randomized controlled trial (RCT) design is ideal for efficacy evaluation as it minimizes bias. On the other hand, an intervention effect measured by an efficacy trial is not generalizable to the effect that the intervention will have in clinical practice [3, 4]. Results of treatment programs for obese children in RCTs have often a lower drop-out rate compared to clinical practice [5]. The higher drop-out rate in clinical practice suggests that more motivated families participate in RCTs. Effectiveness studies are performed in real-world everyday secondary care settings, and therefore the outcomes are probably more close to the results of real clinical practice [3]. The study population is more heterogeneous, and therefore the internal validity is lower. However, the external validity is higher resulting in generalizability. In effectiveness studies, as in clinical practice, a grade of tailored therapy for each child in the intervention is possible.

An example to illustrate potential difference between results of effectiveness and efficacy studies is the evaluation of the MEND program for children 8-12 years in the UK. The intervention is multicomponent with moderate intensity. This program is first evaluated in a RCT in a research-setting within the community with well trained staff, which can be seen as an efficacy study [6]. In this RCT a decrease of BMI z-score was found of about 0.2 at six and twelve months (longer term not available). The effectiveness of this intervention was measured in a community setting at long term (2.4 years after baseline, short term not available), but no significant changes in BMI z-score (-0.07) were observed [7]. This difference may be explained by the measurement at long- rather than short-term in the community setting, but can also be due to the non-RCT setting and the difference in staff used in the community setting.

The distinction between efficacy and effectiveness is not strict, but it is a continuum [3]. The evaluation of *AanTafel!* can be seen on this continuum more close to an effectiveness study. The study is performed in clinical practice, with the usual providers of obesity treatment in practice, and a heterogeneous study population. Children were referred by their physician as is normal practice, instead of recruitment by for example newspapers. Participation in the study was not required for starting this treatment program. No extra inclusion criteria except from starting the treatment program were used for participation in the study. All parents of children enrolled in treatment gave consent for the evaluation study of *AanTafel!*. Therefore, the study population is generally representative for the obese population which is normally treated in our hospital. We did not perform a RCT, because we thought it not ethical to refuse obese young children to participate in the available best-practice, best-evidence treatment program due to study design. In addition, we would have needed more participating children for a RCT, which means increased time and cost. Also, we wanted to evaluate the results of treatment in 'real world' practice. As a reference population children of a large Dutch cohort study were included, the ABCD study [8]. In this reference population a smaller change in BMI z-score was observed compared to our intervention group (-0.13, -0.13, and 0.03 in respectively children of 3, 4, and 5 years old). Also, in our meta-analysis the control population (groups without any treatment or lifestyle education) showed no change in BMI z-score (chapter 2) [9]. This indicates that the decrease of BMI z-score observed in the *AanTafel!* group intervention is a treatment effect and not due to secular changes.

Generalizability: setting and patient characteristics

The studies presented in this thesis were performed in secondary care. It can be argued that obese children with a high likelihood for co-morbidities have to be assessed and treated in secondary or tertiary care because of the seriousness of the consequences [10, 11]. Possibly, parents perceive the therapists in the hospital as real experts and their child's obesity as a real disease as it is diagnosed by the pediatrician, this can help to follow the treatment program, however evidence is

missing on this point. On the other hand, the shift from the clinical to the community setting is assumed to reduce costs and reach more patients [12]. The predictors of overweight are rooted within the community context, as shown in the ecological model of Davison and Birch (chapter 1, Figure 3) [13]. A community setting may make better use of local knowledge and facilities and higher involvement of local health professionals compared to the secondary care setting.
As described in chapter two, all studies in the review that were performed in primary health care achieved no or low (< 0.2 decrease in BMI z-score) effect [9]. Possibly this is not (only) due to the setting, but (also) due to the lower intensity of performed treatment. However, evidence is missing on this point. There was no comprehensive treatment available in our region in primary care. Children were referred to secondary care for obesity treatment, and an experienced multidisciplinary treatment team and resources for research were available. Currently, it is being investigated whether a transition of *AanTafel!* from secondary to primary care is possible and what the effects will be.
The results of a study must be clinically useful to a group of patients, which is termed as external validity or generalizability. The results can be very dependent on factors as setting and patient characteristics [14]. Children were referred by their primary care physician, general physician of pediatrician for obesity treatment. Consequently it is a selective study population with obesity or severe overweight. A reasonable proportion (53%) of the children diagnosed with obesity in our hospital started the treatment program *AanTafel!*. Based on the national prevalence of childhood obesity [15, 16], the number of young children that we reached by *AanTafel!* makes up for a small proportion of the obese young children in the region of Gelderse Vallei Hospital. Most children had an additional reason for starting obesity treatment other than 'just' having a BMI in the obese range. These reasons were on somatic or psychosocial fields, for example children also were diagnosed with asthma, had severe obesity with physical disabilities, or had a sibling with underweight (and therefore a very challenging situation for parents). Therefore, our study population was a specific complex group of children. Probably, these children need other treatment options (probably more tailored and intensive) than those children that will be reached in primary care. The American Academy of Pediatrics (AAP) advises a staged-care approach and *AanTafel!* can be seen as a stage 3 treatment, a comprehensive multidisciplinary intervention, which is used for children who are severely overweight and in who other approaches did not help, or children who already have comorbidity or obese parents [17].

The prevalence of childhood obesity differs between ethnic and socioeconomic groups in The Netherlands [16, 18]. Possibly, also appropriate treatment strategies

are different for different ethnic groups, careful consideration of and tailoring to the target group needs and contextual factors potentially improves acceptability and satisfaction, and lowers drop-out [19]. In our pilot study (chapter 3), all parents perceived the multicomponent composition, multidisciplinary approach, and the web-based characteristic of the learning module positive regardless of their ethnic or socioeconomic background. Never the less, parents preferred more tailoring to their situation, they perceived that eating in social and cultural settings (e.g. visit to extended family or Ramadan) required more attention in treatment. Most parents included in the studies described in this thesis were born in The Netherlands. Other native countries of mothers were Morocco or Turkey. Our conclusions may not apply to other ethnic groups. Furthermore, parents of children included in this study all took the step to start with their child the treatment program in the hospital, therefore they were all (more or less) motivated parents.

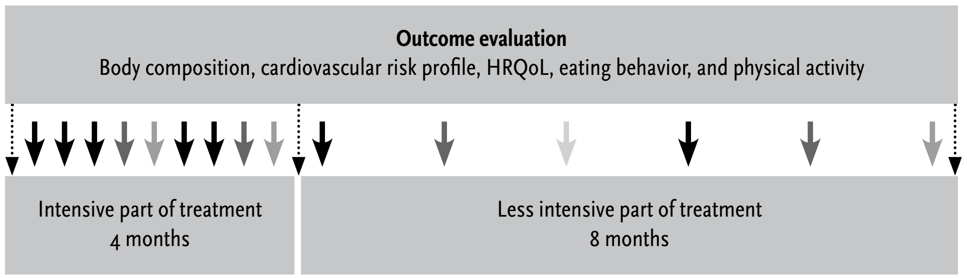
Lessons learned

Insights in the development of a science and practice based treatment program

As described in chapter 3 and 4, the current version of the treatment program *AanTafel!* was developed in several steps. Clinical guidelines and scientific evidence from literature were searched. Despite the abundance of literature on childhood obesity, it appeared that there were still gaps in essential evidence for the development of an intervention tailored to those young children. Next, parental interviews were performed. With professional judgement, the scientific evidence and the findings from parental interviews were integrated and the treatment program *AanTafel!* was constructed. In practice, the latter was a natural process with conscious and unconscious considerations, which was hard to describe for scientific purposes. The important information that professionals have collected by their own experience, but also by the experiences of other professionals in their networks will be lost if only the published evidence is used [20]. In our opinion, the views of the target group (in our case the parents) and therapists are essential in a development process of an intervention to overcome the existing gap between evidence and practice.
After the pilot study with process evaluation (described in chapter 4), including the assessment of views of participating parents and therapists minor changes to the treatment program *AanTafel!* were made. In our opinion, this process evaluation is an important step to see if the intervention can be implemented as planned and were improvements can be made [21].

The resulting treatment program *AanTafel!*

The resulting program *AanTafel!* covers 22.5 contact hours over one year with complementary a web-based learning module (Figure 1). *AanTafel!* is multicomponent with behavioral modification techniques to change dietary intake and physical activity. The pediatrician, child psychologist, pediatric dietician, and child physiotherapist are involved and therefore it is multidisciplinary. The behavioral modification techniques used are for example goal-setting and modelling. For dietary intake and physical activity some key themes are discussed in the sessions as the importance of breakfast taking and reducing sedentary behavior, but the main focus is that parents (with help of the therapists) set their own family dietarian and physical activity goals and design a plan to get these goals. Because parents are setting their own goals based on the dietary record and physical activity of their child, *AanTafel!* is tailored to their child and family situation. The treatment program consists of seven group sessions with parents, four physical activity sessions with parents and children, one cooking and tasting workshop with parents and children, and three individual sessions with parent(s) and child over a period of one year covering in total 22.5 contact hours. Nine sessions take place in the first four months (intensive phase), in the next eight months six sessions take place (less-intensive phase).



HRQoL Health Related Quality of Life

- Group meeting for parents
- Physical activity meeting for parents and children
- Individual session for parent(s) and child
- Cooking or tasting workshop for parents and children

Between every meeting/session new information and assignment(s) are available in the Internet workbook.

Figure 1 | Structure and evaluation of *AanTafel!*.

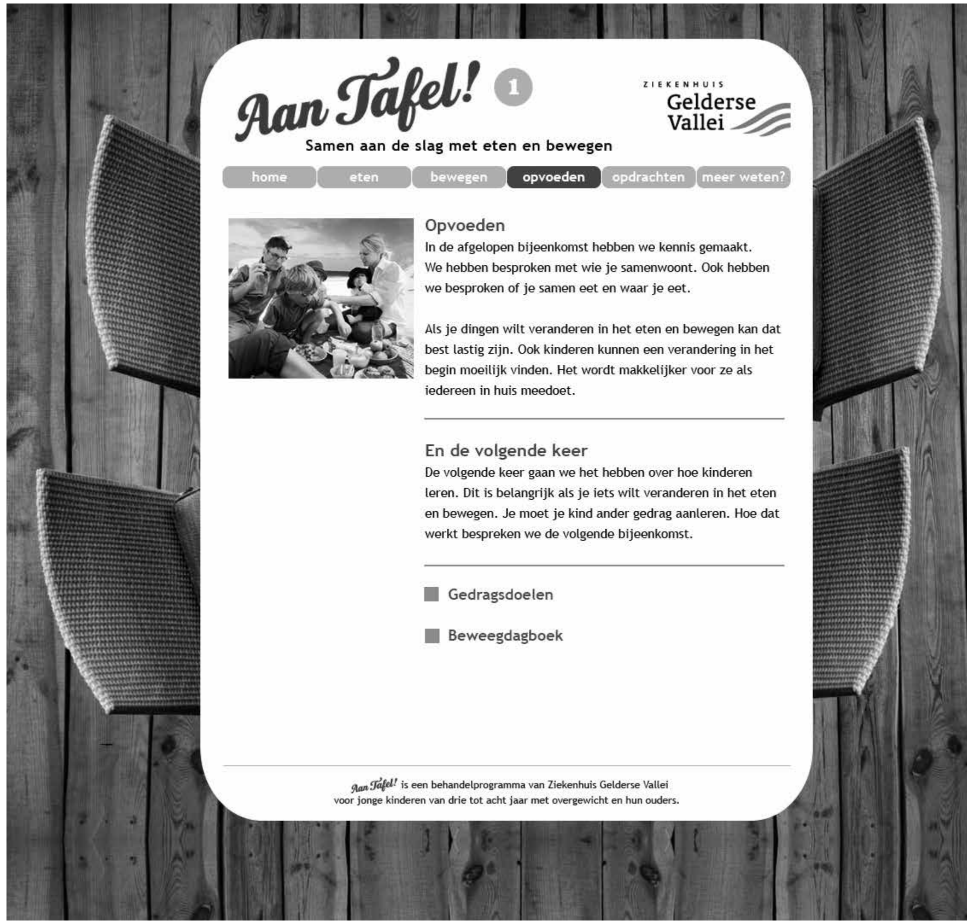


Figure 2 | An example of an Internet page part of the web-based learning module of *AanTafel!* for parents.

Web-based learning module

The web-based learning module that is part of *AanTafel!* intends to reduce participation barriers such as travel time, transportation difficulties, and enhance adherence by allowing for a self-chosen time and location for the participants [22, 23]. As described in chapter 3 parents of overweight young children were positive about the use of Internet in the treatment and added to the above mentioned reasons that they are used to work on the Internet, because everything nowadays is there to find. The web-based learning module consists of information, assignments and movie-clips (Figure 2). After each session, the corresponding chapter in their personal (log-in code per family) web-based learning module is accessible for the parents. At the end of the program, all 13 chapters are accessible. Therapists can directly evaluate the completed assignments, for example a nutritional diary, in the learning module and discuss these with parents during the next session. Therefore, the group and individual sessions were more tailored to the problems the parents faced in daily life. In practice, as described in chapter 4, it was well accepted by parents and therapists.

Studies that isolate the effects of interactive electronic media interventions for example as substitute to face-to-face treatment, are generally lacking [24]. Therefore, it is not known if it is possible to substitute part of the face-to-face contact with Internet treatment. But the fact that *AanTafel!* is a low intensity program and yielded the same change in BMI z-score as other moderate or high intensity programs is promising. This will have a positive effect on the cost-effectiveness of the treatment program.

Indicators for evaluation of the effectiveness of a treatment program

Several questions can be placed with regards to the assessment of interventions: were objectives achieved [21]? Did treatment lead to undesirable side-effects? What occurs between treatment and effect? In line with the objectives of the *AanTafel!,* indicators for overweight and the comorbidities (cardiometabolic and psychosocial) were used. Side-effects of obesity treatment such as an undesirable change in eating behavior, were also covered [5]. What happens between the treatment and the effect is also referred to as the 'black box' [21], in this case this 'black box' can be change of eating behavior and physical activity, which are also evaluated.

Indicator applicability in practice

BMI z-score was used as main indicator in the studies presented in this thesis. This indicator accounts for height, age, and sex [25]. Because it accounts for age it is an appropriate method for pre- and post-test. BMI z-score is easy to perform and did not lead to problems in practice. The other measures of overweight (waist circumference, MUAC, and skinfold thickness) that we have used were less easy to perform. Especially the youngest children in our study sometimes feared the skinfold thickness measurements and were not cooperative to these measurements which led to missing values in some cases. In our study all these measures indicated the same effect, i.e. a decrease of overweight. In planning the evaluation of *AanTafel!* we decided not only to measure BMI z-score, but also waist circumference, MUAC and skinfold thickness. The reason for this was that these can provide useful additional information, for example when fat mass decreased and fat free mass increased, BMI z-sore possibly remained stable and waist circumference decreased [26]. However, the effect of increasing fat free mass (muscle mass) may have a more important role in pubertal compared to pre-pubertal children. From the

review (chapter 2) we learned that no common outcome indicator was used in all studies, and hence some studies had to be excluded from meta-analysis [9]. For future treatment programs, we recommend to include the BMI z-score as the outcome measure to enable comparison between studies.

For measuring the effect on cardiometabolic risk profile, we measured blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, HBA1c and HOMA IR. Blood pressure measurements were easy to perform with an automated blood pressure monitor. Blood collection caused some difficulties for children with fear for venapunction and failed venapunction occurred in some in very obese young children. However, we experienced that these indicators were not only important for providing a broad view on the effects of treatment, but were also important for parents whose child already had positive cardiometabolic risk factors. For those parents this knowledge was sometimes an extra motivator for starting treatment.

We used HRQoL as the indicator for psychosocial well-being in the studies presented in this thesis. Therefore, the validated generic questionnaires Child Health Questionnaire-Parent Form with 50 items (CHQ-PF50) for children aged ≥ 5 years and the 103-item Infant Toddler Quality of Life questionnaire (ITQoL) in children < 5 years were used [27-29]. All parents were able to fill in this questionnaire, but because of time constraints of parents not all were returned. We did not observe significant changes in HRQoL, but we found (non-significant) improvement in most domains, which was sometimes clinically relevant. The children in our study were too young to complete the questionnaire themselves. Possibly, the improvement that was observed in HRQoL was not significant because of low power of the study. The validation of these questionnaires is based on large populations [27, 29]. There was no disease specific questionnaire available for this young age-group. Therefore, we had to use generic HRQoL questionnaires, instead of a disease specific HRQoL questionnaire. Disease-specific HRQoL questionnaires provide a more detailed measurement of dimensions specific to the health problem and are therefore more sensitive to change [28, 30]. It is advisable to use a HRQoL questionnaires to measure the effect of treatment on population level. If available, disease-specific questionnaires must be used to measure effects in small populations.

For *AanTafel!* the cost-effectiveness is not evaluated. Childhood obesity is a problem with not only short term, but also very serious long term consequences. Because of the long term consequences with increased health care costs and decreased productivity at work for the future adults, the total societal cost burden of childhood obesity is enormous [31]. The lifetime cost effectiveness of lifestyle interventions to treat overweight and obese children is estimated using an adaptation of the

National Heart Forum economic model [32]. This shows that interventions to treat childhood obesity are potentially cost effective, but cost savings and health benefits appear at long term, after 30-60 years. The financing of this kind of programs is in our current health system a challenge, because health care providers need to negotiate with health insurance companies on the financing possibilities [33]. The available resources may therefore differ from year to year.

Novel indicators

In our studies we used several indicators that are not common practice. The significance for the individual and therefore clinical practice is unknown without normal values (which are expected to be method dependent) and missing information on the exact effects of these indicators. Validating a biomarker for clinical practice is a challenging process and needs large-scale studies [34]. In this project, concentrations of biomarkers for cardiometabolic risk were measured in fasting blood samples. These were adipokines (e.g. adiponectin), pro-inflammatory cytokines (e.g. tumor necrosis factor, TNF), pro-coagulation factors (e.g. plasminogen activator inhibitor-1, PAI-I) and factors of endothelial dysfunction (e.g. intercellular cell adhesion molecule-1, ICAM-I). In our case, chemerin, leptin and TIMP metallopeptidase inhibitor-1(TIMP-1) were excluded, because of > 25% of values of a variable below the lower detection limit of these markers. As far as we know, chemerin is not measured in young children before, and TIMP-I not in overweight or obese young children. However, leptin is extensively studied in preadolescent children [35]. Due to a technical problem we could not measure serum leptin concentration. The advantage of measuring those biomarkers would be that, together with the other indicators, they give a broad view on the effect of the treatment program *AanTafel!* on the cardiometabolic risk of the children. This effect is summarized in Figure 3.

In chapter 6 we evaluated the EATT, the thickness of adipose tissue that is located between the visceral layer of the pericardium and the outer wall of the myocardium, as possible new biomarker for cardiometabolic risk. In older children and adolescents, EATT was correlated with BMI z-score, several cardiovascular risk factors, pro-inflammatory markers, and carotid-intima media thickness (as early indicator of atherosclerosis) [37-42]. We observed that EATT was higher in overweight and obese young children compared to their normal weight peers. However, even in the obese group the layer of EAT was very small (median 1.57, interquartile range 1.20-2.57). Intra-observer and inter-observer variability were acceptable, but not excellent. Also, the direction of the transducer can affect the results [43]. Possibly, this caused that no correlation was found between EATT at different time points.

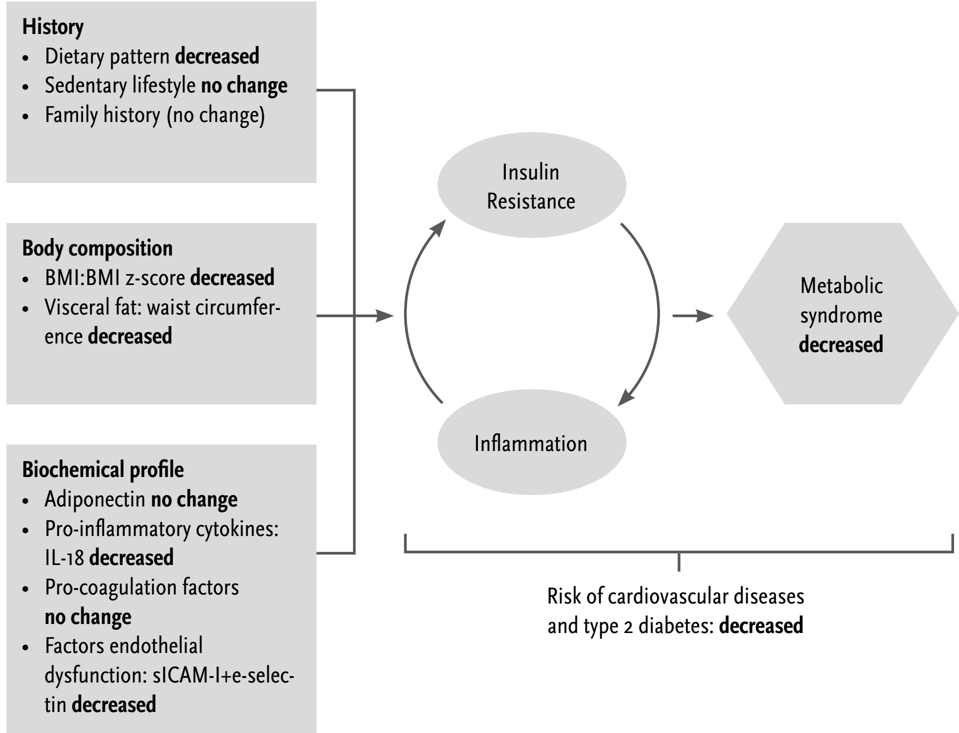


Figure 3 | The change of cardiometabolic risk in obese children participating in *AanTafel!*.

Most environmental and physical factors shown at the left that promote development of low-grade inflammation and insulin resistance are decreased at the end of the obesity treatment *AanTafel!*. This influences the development of the metabolic syndrome. The metabolic syndrome is also decreased in *AanTafel!*. The change in these factors together is supposed to lower the child's cardiometabolic risk (i.e. risk or cardiovascular diseases and type 2 diabetes). This figure was adapted from the figure of Weiss [36].

Because of the role EATT is supposed to have in the development of cardiovascular diseases, more studies are needed to determine the exact role of this fat layer. But so far, it cannot be used as a novel biomarker for cardiometabolic disease in young children.

Effective cooperation between science and practice

In this project a gap was found between what practice needs and what is delivered by science. The discussion in the literature about how to bridge this gap continues unabated [44]. Chatterje, Green and Kumanyika (2013) present the L.E.A.D. framework (Locate, Evaluate and Assemble evidence and inform Decisions) for evidence gathering and use for obesity prevention [44]. This framework guides the

application of a wide variety of evidence sources and is applicable to childhood obesity treatment as well.
Such efforts should use a collaborative approach in which practice works closely together with science, similar to the development of *AanTafel!*. A main task is to indicate differences in the working principles and solutions to bridge gaps with regards to the limitations of using causal models which focus on obesity as a result of individual energy imbalance rather than a result of set of societal rooted factors. Another topic is the use of the golden standard RCT study design that may safeguard internal but compromise external validity [44, 45].

Current evaluated treatment programs for obese young children in The Netherlands

Since the systematic review, which summarized the effectiveness of treatment programs for obese young children as indicated in the literature up to April 15, in 2012 [9] (chapter 2), as far as we know two Dutch treatment programs tailored to overweight and obese young children were evaluated and published. Besides this, also other initiatives run in The Netherlands, but the effect of these programs is not evaluated (or not reported) and fall therefore out the scope of this thesis. The first evaluated treatment program is a multidisciplinary intervention program that is evaluated in a RCT called the GECKO-Outpatients Clinic Study [46]. Children (n=75) were randomly assigned to the multidisciplinary intervention program or usual care. The multidisciplinary treatment program consisted of dietary advice and physical activity sessions for parents and children, and psychological counseling for parents only. The program had a total duration of 30 hours within 16 weeks, and therefore is a moderate intensity treatment. The children in the usual-care group were seen three times 30-60 min by their pediatrician within 16 weeks. The inclusion criteria for this study were more or less the same as the *AanTafel!* inclusion criteria, except from the age of the children included in this RCT who were 3 to 5 years old. The children in this study were less overweight at baseline compared to the *AanTafel!* evaluation (respectively BMI z-score 2.7 and 3.6). At the end of intervention (16 weeks) the BMI z-score decreased with 0.5 in the intervention group, compared to 0.3 in the usual care group, 12 months after intervention this was 0.6 and 0.3 respectively [46]. In the intervention group twenty percent drop-out was observed and not included in analysis. The change of HRQoL was measured with the CHQ-PF50 and showed a significant reduction of the domain bodily pain, but not of the other domains [47]. At baseline, the medians of several domains appeared to be higher in the GECKO compared to the *AanTafel!* population, for example 100 on physical functioning compared to 91.7 in the *AanTafel!* population and respectively 76.7 and 67.5 on general health. At long term, i.e. 36 months after baseline, data on body composition of less than 50% of the children were available, a non-significant estimated effect size was found between the groups of 0.39 (95% CI -0.002 to 0.79) [48]. This multidisciplinary intervention program is only used for research and currently does not run in practice.
The second treatment program is the Lifestyle Triple P intervention, a family intervention that is focused on the parents and consists of active skills training methods based of self-regulation principles [49]. It is multicomponent with nutrition, physical activity, and positive parenting strategies and has a low intensity (15 hours of parental group sessions and additional telephone contact within 14 weeks). Groups are led by well-trained health professionals. This intervention is evaluated in a RCT (n=86). In the control condition parents received information (brochure and web-based tailored advice) [49]. Overweight or obese children in the age of 4-8 years were included (baseline BMI z-score 1.8) [50]. No significant effects were found on BMI z-score (-0.06 in intervention and control group at 16 weeks). Positive effects were observed in physical activity and eating behavior [50]. This intervention is still used in practice in The Netherlands.
In conclusion, as far as we know there are only three evaluated treatment programs (including *AanTafel!*) that were tailored to overweight and obese young children. One moderate intensity multicomponent treatment (the GECKO-Outpatients Clinic Study) with clinical relevant effects, which is currently not used in practice. Two multicomponent low intensity treatment programs (Lifestyle Triple P and *AanTafel!*) are available in The Netherlands. *AanTafel!* showed a clinical relevant decrease in BMI z-score in contrary to Lifestyle Triple P. Possibly the multidisciplinary aspect, the combination of group and individual sessions, and the complementary web-based learning module of *AanTafel!* played a role in the clinical relevant results. It is of high importance to evaluate the treatment programs that are used to treat young overweight or obese children and use proven-effective treatment programs, as consequences of childhood overweight or obesity are serious. Not (only) in research setting but (also) in real-world practice these evaluation should take place. To save time and money proven-effective treatment programs should be expanded in The Netherlands, instead of developing several new programs. Furthermore, after evaluation results should be reported, to avoid loss of information.

Recommendations for science and practice

Recommendations for science

More research is needed on treatment programs for young overweight and obese children, as the number of studies is currently limited. The following issues has to be addressed:

- What is the appropriate setting for which children?
- What is the appropriate treatment for different populations (f.e. overweight vs. obese children with comorbidity)?
- Ideally, the studies should report content and theory of the treatment program, the effect on somatic and psychosocial parameters, the effect on knowledge and behavior, and long-term effects.

The role of EATT in young children has to be unraveled:

- Higher powered research is needed to study if EATT at young age is correlated to cardiometabolic risk factors and if EATT changes during decrease of overweight.
- Research is needed to study if EATT by MRI is superior to echocardiography in young children.

Improved cooperation with practice in:

- Discussion with practice what practical questions are still unanswered.
- Perform a RCT when the question is if an intervention potentially can have an effect, or to compare two conditions. Also, realize that external validity is important and therefore evaluation of interventions in practice are not per se inferior.

Recommendations for practice

For the development of an obesity treatment program:

- The evidence from literature is essential, but also the view of the target group and the knowledge of professionals should be taken into account.
- The process of integrating evidence from science and practice is a useful method to overcome the gaps in clinical guidelines.
- Treatment should be tailored to the target group.

For treating obese young children:

- To involve parents to the treatment, parental peer support, tailoring to individual families are important
- Multidisciplinary treatment is well perceived by parents
- Complementary web-based treatment can help to tailor treatment to the family situation, but the advantages of face-to-face treatment (f.e. peer support) still remain
- The treatment program *AanTafel!* in secondary care for young obese children shows clinical relevant effects on body composition, risk profile for cardiometabolic diseases, HRQoL, and eating behavior. Further evaluation is needed to find out what the effects are in different settings.

Improved cooperation with research in:

- Discussion for practice relevant research questions.
- Design and perform, together with researchers, high level effectiveness studies.

Overall conclusion

This research project aimed to contribute to effective treatment programs targeting overweight and its comorbidities in young children (defined as age 3 to 8 years). Our systematic literature review showed that multicomponent treatment programs with moderate to high intensity for overweight or obese young children appear to result in clinically relevant results, but the of number studies is limited. Clinical guidelines did not provide the information necessary for the development of a treatment program. Never the less, the combination of the information from clinical guidelines, literature review, parental interviews, and professional judgement was helpful to develop the treatment program *AanTafel!*. The use of this program showed a clinically relevant improvement of body composition, cardiometabolic risk profile (Figure 3), HRQoL (mainly the physical summary score), and eating behavior. To make research more relevant for practice the cooperation between practice and research should be increased. EATT, a layer of adipose tissue around the heart that is in adults correlated to atherosclerosis, was higher in overweight and obese young children compared to their normal weight peers. EATT was negatively correlated with adiponectin, but correlations of EATT with other cardiometabolic risk factors were not statistically significant. Higher powered studies are needed to further unravel the role of EATT in obese young children.

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Abbreviations

BMI	Body mass index
BT	Behavioral therapy
CEBQ	Children's Eating Behaviour Questionnaire
CHQ-PF28	Child Health Questionnaire-parent form with 28 items
CHQ-PF50	Child Health Questionnaire-parent form with 50 items
CI	Confidence interval
CRP	C-reactive protein
CVR	Cardiovascular
DE	Dietary
DEXA	Dual energy X-ray absorptiometry
EAT	Epicardial adipose tissue
EATT	Epicardial adipose tissue thickness
HDL cholesterol	High-density lipoprotein cholesterol
HOMA IR	Homeostasis model assessment
HRQoL	Health-related quality of life
hsCRP	High sensitive C-reactive protein
ICAM-I	Intercellular cell adhesion molecule-1
IDF	International Diabetes Federation
IL	Interleukin
IOTF	International Obesity Task Force
IQR	Interquartile range
IR	Insulin resistance
ITQoL	Infant Toddles Quality of Life Questionnaire
MCP-I	Monocyte chemoattractant protein-I
MRI	Magnetic resonance imaging
MUAC	Mid-upper arm circumference
OSAS	Obstructive sleep apnea
PA	Physical activity
PAI-1	Plasminogen activator inhibitor-1
PedsQL	Paediatric Quality of Life Inventory
RBP-4	Retinol binding protein-4
RCT	Randomized controlled trial
SD	Standard deviation
SE	Standard error
TIMP-1	TIMP metallopeptidase inhibitor 1
TNF	Tumor necrosis factor-a
VCAM-I	Vascular cell adhesion molecule-I
VEGF	Vascular endothelial growth factor
WC	Waist circumference
WHO	World Health Organization

About the author

Curriculum Vitae

Esther van Hoek was born on the 24th of January (Deurne, The Netherlands). After completing secondary school (VWO) at the Maasland College in Oss (2001), she studied Medicine at the Radboud University in Nijmegen. As part of her studies she performed an internship Tropical Medicine in Biharamulo District Designated Hospital in Tanzania. After her graduation (2007), she started working as a Resident Pedatrics (ANIOS) in the Gelderse Vallei Hospital (ZGV). In 2009 she was engaged in the development of a novel treatment program for young obese children (*AanTafel!*) in the ZGV. In 2011, this treatment program won the Special Distinction Award at The Obese Species International Conference (Erice, Sicily). The research project investigating the development, implementation, and evaluation of the treatment program *AanTafel!* was under supervision of Prof. Dr E.J.M. Feskens, Dr A.J. Janse, and Dr L.I. Bouwman and resulted in this thesis. During this period, Esther stayed appointed at the ZGV and was external PhD-student at the Division of Human Nutrition of Wageningen University. As a PhD-student, Esther joined the educational program of the graduate school VLAG, attended several international conferences, and was involved in the supervision of bachelor and master students. April 2015, Esther started her specialist training in Pediatrics at the Amalia Children's Hospital of the Radboud University Medical Center in Nijmegen under the supervision of Dr. J.M.T. Draaisma. Esther is living together with Mattijs Julsing. Together they have one daughter: Elke (2013).

List of publications

Scientific Papers

van Hoek E, Feskens EJ, Bouwman LI, Janse AJ: Effective interventions in overweight or obese young children: systematic review and meta-analysis. *Child Obes* 2014 (10):448-460

van Hoek E, Bouwman LI, Koelen MA, Lutt MAJ, Feskens EJM, Janse AJ: *Development of a Dutch intervention for obese young children.* Submitted.

van Hoek E, Janse AJ, Bouwman LI, Feskens EJM: *Process evaluation of a family-tailored, multi-method childhood obesity treatment program in a secondary care setting.* Submitted.

van Hoek E, Feskens EJM, Bouwman LI, Verburgt WH, de Jager W, Schipper HS, Vrijkotte TGM, Janse AJ: *A novel multidisciplinary treatment program with web-based learning module for young obese children.* Submitted.

van Hoek E, Koopman LP, Feskens EJM, Janse AJ: *Epicardial adipose tissue thickness is increased in obese young children; a pilot study.* Submitted.

Other

van Hoek E, van Mierlo TD: 'Verdraaid, een spugende zuigeling'. Praktische pediatrie 2009 (2).

Abstracts in scientific journals or proceedings

van Hoek E, Koopman LP, Feskens EJM, Janse AJ: *Het epicardiale vet is verdikt bij kinderen met overgewicht of obesitas.* Congress of the Dutch Pediatric Society (NVK) (Abstract accepted for oral presentation).

van Hoek E, Feskens EJM, Bouwman LI, Janse AJ: *Multidisciplinaire behandeling (AanTafel!) van jonge kinderen met obesitas leidt tot daling BMI z-score en afname metabool syndroom.* NVK-Congress, 2015 (Abstract accepted for oral presentation).

van Hoek E, Feskens EJM, Bouwman LI, Janse AJ: *Effectiviteit van behandelprogramma's voor jonge kinderen met overgewicht of obesitas systematische review en meta-analyse.* NVK-Congress, Veldhoven, The Netherlands, 2013. (Abstract and poster presentation).

van Hoek E, Feskens EJM, Janse AJ: *AanTafel! Een nieuw behandelprogramma voor jonge kinderen met overgewicht, voorlopige resultaten evaluatie.* NVK-Congress, Veldhoven, The Netherlands, 2013. (Abstract and poster presentation).

van Hoek E, Feskens EJM, Bouwman LI, Janse AJ: *Effectiveness of interventions in young children with overweight or obesity: systematic review and meta-analysis.* European Congress on Obesity (ECO), Liverpool, United Kingdom, 2013
(Abstract and poster presentation).

van Hoek E, Feskens EJM, Janse AJ: *Treating young obese children: a pilot study.* ECO, Lyon, France, 2012 (Abstract).

van Hoek E, Feskens EJM, Bouwman LI, Janse AJ: *Pilot Study: A novel multidisciplinary approach for young obese children.* 20th workshop of The European Childhood Obesity Group (ECOG),

Brussels, Belgian, 2010 (Abstract and oral presentation).

van Hoek E, van den Berg A, Rasmussen E, de Blaauw I, Tolboom J, Damen G: *Ondervoeding bij kinderen: hoe stellen we dit vast?* NVK-Congress, Veldhoven, The Netherlands (Abstract and oral presentation).

van den Berg A, van Hoek E, de Blaauw I, Rasmussen E, Damen G: *Inadequate screening tools for malnutrition in children.* The European Society for Clinical Nutrition and Metabolism (ESPEN), Florence, Italy (Abstract).

Overview of completed training activities

Discipline specific activities

- 19th workshop of the European Childhood Obesity Group (ECOG), ECOG, 2009 (Dublin, Ireland).
- 20th workshop of the ECOG, ECOG, 2009 (Brussels, Belgium).
- 4th national nutritional congress, Gelderse Vallei Nutrition Alliance (AVGV), 2011 (Ede, The Netherlands).
- Chronic Inflammation: new insights and challenges, Federa, 2011 (Leiden, The Netherlands).
- National Congress on Childhood Obesity, AVGV/Wageningen University (WU)/Gelderse Vallei Hospital (ZGV)/Interactie, 2012 (Ede, the Netherlands)
- NVK-congress, Dutch Pediatric Society (NVK), 2012 (Veldhoven, The Netherlands)
- Master class Regulation of Energy Intake, VLAG, 2012 (Wageningen, The Netherlands)
- NASO symposium, The Netherlands Association for the Study of Obesity (NASO), 2013 (Utrecht, The Netherlands)
- Master class Public Health Research in Practice, VLAG, 2013 (Wageningen, The Netherlands)
- European Congress on Obesity, European Association for the study of Obesity (EASO), 2013 (Liverpool, UK)
- NVK-congress 2013, NVK, 2013 (Veldhoven, The Netherlands)
- National Congress on Childhood Obesity, AVGV/WU/ZGV/Interactie, 2013 (Ede, The Netherlands)
- Als alles is geprobeerd - Kinderen met ernstige obesitas - Symposium, SCEM, 2014 (Ede, The Netherlands)
- National Congress on Childhood Obesity, AVGV/WU/ZGV/Interactie, 2015 (Lunteren, the Netherlands)

General courses and activities

- Grant writing, TULIPS, 2010 (Schoorl, The Netherlands)
- Masterclass Linear and logistic regression, VLAG/chair of epidemiology, 2010 (Wageningen, The Netherlands)
- Erasmus Summer Programme, Netherlands Institute for Health Science (NIHES), 2011 (Rotterdam, The Netherlands)
- Principles of Research in Medicine
- Introduction to Data-analyses
- ICH-GCP Good Clinical Practice, Clinical Trial Service (CTS), 2010 (Ede, The Netherlands)
- Improve your Writing, WUR Language Services, 2012 (Wageningen, The Netherlands)
- Masterclass longitudinal data analysis, VLAG, 2013 (Wageningen, The Netherlands)
- Scientific Writing, Wageningen in'to Languages, 2014 (Wageningen, The Netherlands)

Optional courses and activities

- Preparing a PhD research proposal, 2010
- Food for Thought meetings, AVGV, 2010-2014 (Ede, The Netherlands)
- Journal Club Pediatrics, ZGV, 2010-2014 (Ede, The Netherlands)
- Staff seminars, WU, 2010-2014 (Wageningen, The Netherlands)
- Reference meetings, Postacademic training Pediatrics (PAOK), 2010-2014 (Utrecht, The Netherlands)

Samenvatting

Obesitas komt steeds vaker voor bij kinderen. Kinderen met obesitas hebben een verhoogd risico op het ontstaan van hart- en vaatziekten en diabetes mellitus type 2 (gezamenlijk hierna te noemen cardiometabool risico) op latere leeftijd. Daarnaast worden kinderen met obesitas vaker gepest en hebben zij een verminderde kwaliteit van leven.
Het is belangrijk kinderen met obesitas op jonge leeftijd te behandelen, omdat de behandeling van obesitas bij jonge kinderen vaker succesvol is dan van oudere kinderen. Daarnaast is de gewichtsgroei in de leeftijdscategorie 3 tot 7 jaar voorspellend voor de kans op obesitas op latere leeftijd. Toen dit project in 2009 werd gestart, was er nog geen geëvalueerd behandelprogramma voor jonge kinderen (in de leeftijd van 3 tot 8 jaar oud) met obesitas in Nederland beschikbaar.
Het cardiometabool risico bij kinderen kan worden vastgesteld door het meten van de risicofactoren: veranderd vetprofiel (dyslipidemie), hoge bloeddruk, insuline resistentie en toegenomen vet rondom de buikorganen (abdominale obesitas). De clustering van deze risicofactoren wordt het metabool syndroom genoemd. Ook andere factoren, zoals de aanwezigheid van laaggradige ontsteking bepalen het cardiometabool risico. Stoffen die deze laaggradige ontsteking veroorzaken worden onder andere door vetcellen geproduceerd. Het epicardiale vet is een laagje vet rondom het hart dat deze ontstekingsveroorzakende stoffen produceert en daarmee een rol lijkt te spelen bij het ontstaan van verhoogd cardiometabool risico. Bij volwassenen met obesitas is het epicardiale vet verdikt en is dit gecorreleerd met cardiovasculaire ziekten. Het is echter nog onduidelijk of dit ook voor jonge kinderen geldt.
Het doel van dit project was om een behandelprogramma voor jonge kinderen met obesitas te ontwikkelen, implementeren en evalueren. Daarnaast wilden we weten of het epicardiale vet bij jonge kinderen verdikt is, of dit correleert met het cardiometabool risicoprofiel en of de dikte van het epicardiale vet verandert tijdens de behandeling van hun obesitas.

Hoofdstuk 2 geeft een overzicht van gepubliceerde behandelprogramma's voor jonge kinderen met overgewicht of obesitas. Door middel van een systematisch literatuuronderzoek en meta-analyse hebben we de effectiviteit van deze behandelprogramma's (20 behandelprogramma's met in totaal 1015 kinderen) onderzocht. In het algemeen bleken de programma's een gunstig effect te hebben op de body mass index (BMI, maat voor overgewicht). Er waren echter grote verschillen tussen de verschillende behandelprogramma's in opzet en in effect. De matig en hoog intensieve (>25 contacturen in het programma) behandelprogramma's, die zich met behulp van gedragsveranderende technieken richten op eten en bewegen (multicomponent), bleken te leiden tot het beste en bovendien klinisch relevant effect. Deze subgroep bestond echter slechts uit twee behandelprogramma's. Er waren geen laagintensieve multicomponent behandelprogramma's in de literatuur beschreven voor deze leeftijdsgroep.

Hoofdstuk 3 beschrijft het ontwikkelproces van het behandelprogramma *AanTafel!*. Bestaande nationale en internationale richtlijnen voor behandeling van kinderen met obesitas bleken onvoldoende informatie te bevatten voor het ontwikkelen van een behandelprogramma. Daarom werd er bij de ontwikkeling van *AanTafel!* gebruik gemaakt van aanvullend literatuuronderzoek (onder meer het in hoofdstuk 2 beschreven systematische review) en van interviews met ouders van kinderen met obesitas, die op de wachtlijst stonden voor behandeling. Deze informatie is geïntegreerd door professionals en waar nodig aangevuld met hun kennis en ervaring. Deze methode was behulpzaam om de missende informatie in de richtlijnen op te vullen. Het resulterende behandelprogramma *AanTafel!* is primair gericht op de ouders en toegespitst op de situatie en de levensstijl van de gezinnen. *AanTafel!* is een multicomponent en multidisciplinair behandelprogramma gericht op het verbeteren van eet- en beweeggedrag. Een kinderarts, kinderpsycholoog, kinderdiëtist en kinderfysiotherapeut zijn erbij betrokken. Het programma bestaat in totaal uit 15 bijeenkomsten in 1 jaar (22.5 contacturen, laagintensief): groepsbijeenkomsten voor ouders, beweegbijeenkomsten voor ouders en kinderen, individuele bezoeken en 1 kook- en smaakworkshop voor ouders en kinderen. Daarnaast is er een digitale leermodule voor ouders onderdeel van het programma, hierin staan informatie, filmpjes en opdrachten voor ouders. De behandelaars kunnen de gemaakte opdrachten direct inzien en bespreken.

Hoofdstuk 4 geeft inzicht in de procesevaluatie van de pilot van het behandelprogramma *AanTafel!* waarbij we de aanwezigheid van ouders bij de bijeenkomsten en het gebruik van het digitale werkboek geëvalueerd hebben, interviews hebben afgenomen met ouders (n=7 gezinnen) en de betrokken behandelaars vragenlijsten hebben ingevuld. Hierbij lag de focus op strategieën om de ouders te betrekken bij het behandelprogramma en op de samenwerking tussen de verschillende zorgverleners, omdat praktische informatie op deze gebieden in de literatuur ontbrak. Eén gezin maakte het behandelprogramma niet af. De gemiddelde aanwezigheid van ouders was 86%. De ouders logden regelmatig in op de digitale leermodule en maakten hierbij driekwart van de opdrachten. De elementen van het programma met een hoge ouderbetrokkenheid (zoals het invullen van een eetdagboek) werden hoog gewaardeerd zowel door ouders als behandelaars. Daarnaast ervaarden ouders het contact met de andere ouders als zeer positief. Van zowel de behandelaars als ook de ouders kwam de suggestie om de behandeling nog verder toe te

spitsen op de deelnemende gezinnen en de interactieve elementen in de digitale leermodule uit te breiden. Ouders waardeerden het contact met de andere ouders in de groep. Vanuit de zorgverleners werd tevens gesuggereerd de kosten te kunnen verminderen door minder zorgverleners aanwezig te laten zijn bij de bijeenkomsten. Op basis van deze procesevaluatie werd het programma op kleine punten aangepast.

Hoofdstuk 5 geeft een overzicht van de resultaten van het behandelprogramma *AanTafel!* op het gebied van lichaamssamenstelling, cardiometabool risico en kwaliteit van leven. Dit werd onderzocht door middel van een voor-na opzet in de praktijk onder 40 kinderen met overgewicht of obesitas. Tachtig procent van de kinderen maakte het behandelprogramma volledig af. Bij hen verbeterde de BMI (klinisch relevante verbetering) van baseline tot het eind van behandeling en deze verbetering was nog steeds aanwezig op 3 jaar na baseline (gemeten in het eerste cohort, 23 kinderen). Aan het begin van het behandelprogramma had een zesde van de kinderen alle vier de componenten van het metabool syndroom, maar na behandeling waren er geen kinderen meer met alle vier de componenten. Tevens werd een afname in laaggradige ontsteking gezien: de concentraties van de markers IL18, e-selectin, en sICAM namen significant af. De kwaliteit van leven steeg (niet significant) in vrijwel alle domeinen, met een klinisch relevante stijging in de fysieke score.

Hoofdstuk 6 beschrijft de dikte van het epicardiale vet gemeten met echocardiografie bij jonge kinderen met overgewicht of obesitas. Het epicardiale vet bleek verdikt te zijn bij kinderen met overgewicht (n=8) of obesitas (n=25) vergeleken met het epicardiale vet bij leeftijdsgenoten met normaal gewicht (n=15). Dit is van belang vanwege de veronderstelde rol van het epicardiale vet bij de ontwikkeling van hart- en vaatziekten. Het epicardiale vet was negatief gecorreleerd met adiponectine, maar correlaties met andere cardiometabole risicofactoren waren niet significant. Ondanks een significante verbetering van BMI, werd geen verandering in de dikte van het epicardiale vet tijdens behandeling gevonden.

Samenvattend is er veel literatuur over obesitas bij kinderen verschenen, maar gaf de literatuur onvoldoende informatie om een behandelprogramma voor jonge kinderen te ontwikkelen. Om het onderzoek dat wordt verricht relevanter te maken voor het ontwikkelen van richtlijnen voor de praktijk is meer samenwerking nodig tussen zorgprofessionals en onderzoekers. Het behandelprogramma *AanTafel!* werd ontwikkeld door de combinatie van informatie uit richtlijnen, literatuuronderzoek, interviews met ouders en kennis en ervaring van professionals. Dit program-

ma is laagintensief, maar bevat aanvullend een digitale leermodule en is specifiek gericht op gezinnen met jonge kinderen met obesitas. *AanTafel!* bleek te leiden tot een klinisch relevante verbetering van lichaamssamenstelling, cardiometabool risicoprofiel en kwaliteit van leven van de kinderen (voornamelijk op het fysieke domein). Daarnaast bleek het epicardiale vet dikker bij jonge kinderen met overgewicht of obesitas vergeleken met leeftijdsgenoten met een normaal gewicht. Welke betekenis deze vetlaag heeft voor deze jonge kinderen en welke rol behandeling hierin kan spelen moet nog verder worden onderzocht.
Obesitas is een toenemend probleem onder jonge kinderen met ernstige gevolgen. In dit proefschrift hebben wij laten zien dat dit probleem zowel op korte als lange termijn effectief kan worden behandeld met een multicomponent en multidisciplinair behandelprogramma met lage intensiteit en aanvullend een digitale leermodule.

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