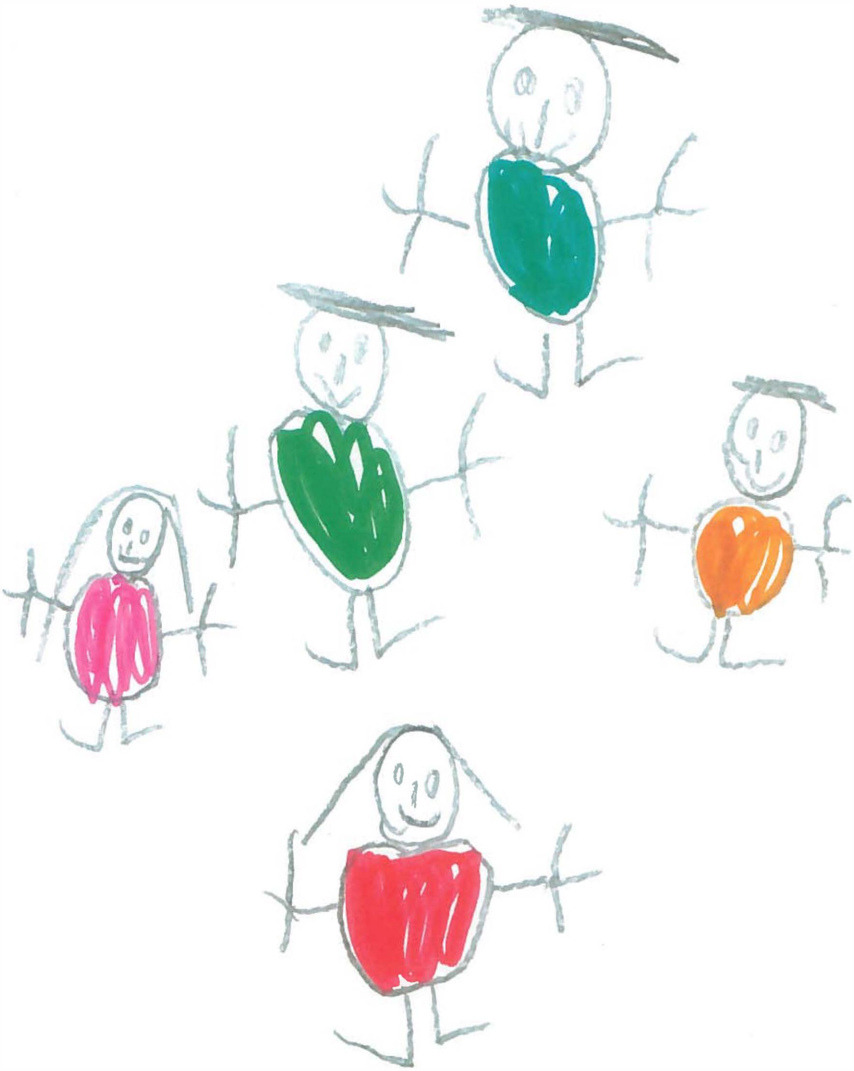
Effects of a multidisciplinary treatment program in overweight and obese preschool children

Bocca, Gianlorenzo

Effects of a Multidisciplinary Treatment Program in Overweight and Obese Preschool Children



Gianlorenzo Bocca

Effects of a Multidisciplinary Treatment Program in Overweight and Obese Preschool Children

Gianlorenzo Bocca

Stellingen behorende bij het proefschrift:

Effects of a Multidisciplinary Treatment Program in Overweight and Obese Preschool Children

1. Insuline ongevoeligheid en risicofactoren voor cardiovasculaire aandoeningen zijn bij 3- t/m 5-jarige kinderen met overgewicht of obesitas gerelateerd aan het vetgehalte. (dit proefschrift)
2. Een multidisciplinaire behandeling van 3- t/m 5-jarige kinderen met overgewicht of obesitas geeft betere resultaten dan een standaard aanpak. (dit proefschrift)
3. Interventieprogramma's bij 3- t/m 5-jarige kinderen met overgewicht of obesitas leiden tot een afname van het lichaamsvet en verbetering van de insuline gevoeligheid. (dit proefschrift)
4. Kwaliteit van leven van 3- t/m 5-jarige kinderen met overgewicht of obesitas verbetert na een interventieprogramma. (dit proefschrift)
5. Interventieprogramma's voor 3- t/m 5-jarige kinderen met overgewicht of obesitas hebben ook 3 jaar na de start een positief effect op de body mass index z-score. (dit proefschrift)
6. Vincere non è importante, è l'unica cosa che conta. Winnen is niet belangrijk, het is het enige dat telt. (Giampiero Boniperti, honorary president Juventus FC)
7. Driving a Porsche is like having children, you only know when you've had one yourself. (Porsche commercial)
8. Als alles tegen lijkt te zitten, bedenk dan dat een vliegtuig opstijgt bij tegenwind, niet met de wind mee. (Henry Ford)
9. Bezuinigingen in academische ziekenhuizen zijn eenvoudig te realiseren door het verminderen van de bureaucratie.
10. Meten is weten, als je weet wat je meet.
11. Fino alla fine!

Gianlorenzo Bocca, 20 november 2013

Bocca, G.
Effects of a multidisciplinary treatment program in overweight and obese preschool children.
Thesis, Rijksuniversiteit Groningen

The studies presented in this thesis were financially supported by an unrestricted grant from Hutchison Whampoa Limited, Hong Kong.

The printing of this thesis was financially supported by the Graduate School of Medical Sciences GUIDE, University Medical Center Groningen, University of Groningen and by Ferring BV and Pfizer BV.

Cover design: Anne Bocca

Printing and lay-out: Drukkerij elite, Lommel - Belgium

ISBN: 978-90-367-6464-3

RIJKSUNIVERSITEIT GRONINGEN

Effects of a multidisciplinary treatment program in overweight and obese preschool children

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. E. Sterken,
in het openbaar te verdedigen op
woensdag 20 november 2013
om 12.45 uur

door

Gianlorenzo Bocca

geboren op 31 mei 1969
te Goirle

Promotores: Prof. dr. P.J.J. Sauer
Prof. dr. R.P. Stolk

Co-promotor: Dr. ir. E. Corpeleijn

Beoordelingscommissie: Prof. dr. H.A. Delemarre-van de Waal
Prof. dr. S.A. Reijneveld
Prof. dr. B.H.R. Wolffenbuttel

ISBN: 978-90-367-6464-3

Paranimfen: Nynke Doornebal-Pietersen
Bas Zegers

Table of contents

1

General Introduction and Outline of the Thesis

Prevalence of obesity

During the last decades, the prevalence of childhood obesity has increased dramatically, also in the Netherlands.[1] Multiple factors may contribute to the development of obesity in children. The genetic background,[2] intra-uterine growth restriction resulting in low birth weight,[3] and early postnatal catch-up growth,[4] have all been identified as risk factors for childhood obesity. An unhealthy lifestyle, characterized by inactivity, a high-fat diet and excess caloric intake, is mainly responsible for the increase in obesity, also in children.[5] The increase in childhood obesity has been especially observed in children younger than the age of 8 years.[6] Increases in weight and body mass index (BMI) between the ages of 2 to 7 years are associated with an increased BMI in adolescence,[7] and obese children and adolescents have an increased risk to remain so into adulthood.[8,9] According to the international cut-off values on BMI,[10] defined as weight in kg/(height in m)^2, the prevalence of overweight in Dutch boys between the ages of 3 to 5 years is 7.8 to 12.8% and in Dutch girls 12.8 to 18.1%.[1] For obesity, the prevalence in Dutch boys and girls aged 3 to 5 years is 0.8-2.0% and 1.6-3.3%, respectively.[1]

Consequences of obesity

Childhood obesity imposes severe health risks. A decreased insulin sensitivity, dyslipidemia, low-grade systemic inflammation, and hypertension have been demonstrated, potentially leading to metabolic syndrome and type 2 diabetes at a later age.[11] The tracking from childhood to adolescence of cardiovascular risk factors associated with obesity has recently been demonstrated.[12] According to international consensus guidelines, metabolic syndrome cannot be diagnosed in children under the age of 10 years.[13] However, separate elevated cardiovascular risk factors have been described in obese children aged 7-9 years.[14] At present time, it remains unclear whether elevated cardiovascular risk factors can be found in preschool-aged overweight or obese children. Other complications of childhood obesity include non-alcoholic fatty liver disease,[15] obstructive sleep apnea syndrome,[16] and orthopedic disorders.[17]

Besides physical complications of obesity, overweight and obese children are at risk to obtain psychosocial problems, thereby impairing their quality of life.[18,19] A lower psychosocial health has been demonstrated in preschool-aged children.[20] Caretakers should therefore also assess the quality of life in children with overweight or obesity, and not only focus on weight. Since, it has been demonstrated that parents may underestimate the degree of overweight or obesity in their children.[21]

Treatment of obesity

Prevention of childhood obesity should have a high priority. When prevention of obesity has failed, treatment should already be started at a young age.[22] Moreover, younger children generally achieve a larger reduction in weight during obesity treatment programs.[23] Multidisciplinary lifestyle intervention programs in 5- to 12-year-old children with obesity have proven to be able to reduce weight.[24] However, little is known on the effect of multidisciplinary obesity treatment programs on weight reduction in preschool-aged children.

It has been demonstrated that multidisciplinary intervention programs in overweight or obese children, by inducing weight loss, can improve insulin sensitivity, reduce signs of systemic low-grade inflammation, and lower triglyceride concentrations in blood.[25] Also, these lifestyle intervention programs have shown positive effects on health-related quality of life, at least in adolescents.[26] However, the effects of multidisciplinary intervention programs on cardiovascular risk factors, psychosocial aspects and health-related quality of life in overweight or obese preschool-aged children are largely unknown.

The GECKO-Outpatients Clinic

Overweight and obese children aged 3-5 years, and their parents were seen at the Groningen Expert Center for Kids with Obesity at the Beatrix Children's Hospital, University Medical Center Groningen, Groningen, the Netherlands. Between October 2006 and March 2008, 75 children participated in a randomized controlled clinical trial studying the effect of a multidisciplinary obesity treatment program. The effect was compared with a group of overweight and obese children receiving a usual-care treatment program.

The multidisciplinary intervention program lasted 16 weeks and consisted of the following elements:

- **Dietary advice.** In 6 sessions of 30 minutes each, a dietician gave education and advised on improving eating behavior. For example, children and parents were advised to have breakfast every morning, abstain from soft drinks and have at most 3 snacks per day. Personal goals were set for the children and their parents and, on consecutive sessions, feedback was given on these goals. Special diaries were developed to document eating patterns (type and amount of food consumed), and they were used during 4 consecutive days, 2 weekdays and 2 weekend days. A normocaloric diet, based on the required daily intake for this age group, was advised.
- **Physical activity**. The physical activity sessions consisted of 12 group sessions of 60 minutes each and were supervised by a physiotherapist. The exercise program mimicked the type and intensity of elementary school exercise, thereby focusing on an active lifestyle. Also, the

sessions aimed at having fun during exercise and improving the child's well being. Parents and children were advised to reduce sedentary activities and to stimulate the children's daily physical activity to at least 60 minutes, according to the Dutch Standard of Healthy Activities. Physical activity of the children was measured using a pedometer (Yamax Digi-Walker SW-200, Yamax USA Inc.). The pedometer was worn at least 3 weekdays and 1 weekend day and the daily amount of steps was documented in a diary.

- **Behavioral therapy.** Behavioral therapy sessions (6 group sessions of 120 minutes each) were for parents only and were guided by a psychologist. During these sessions, parents learned to be a healthy role model and to change family attitudes toward healthy eating and physical activity. They learned ways to remove unhealthy food triggers and know the difference between hunger and cravings. Parents were taught to use sticker charts to motivate the children and to follow their progress. A schematic overview of the multidisciplinary intervention program is provided in Table 1.

The usual-care program also lasted 16 weeks. During this period, the children and their parents were seen by a resident in pediatrics who advised on a healthy lifestyle. In 3 sessions of 30-60 minutes each, children and parents received information on healthy eating behavior and children were advised to perform physical activity for 1 hour per day, according to the Dutch Standard of Healthy Activities. Also, children were advised to minimize their sedentary activities (television watching, playing with the computer) to at most 2 hours per day. The children and parents in the usual-care group documented their eating patterns and physical activity in diaries, in an identical way as the children in the multidisciplinary intervention group. A schematic overview of the usual-care program is provided in Table 1.

Table 1. Schematic representation of weekly activities in the multidisciplinary intervention and usual-care groups.

Multidisciplinary intervention group	baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Measurements	v																v
Dietary advice by dietician		v	v		v				v			v			v		
Physical activity session by physiotherapist				v	v	v	v	v	v	v	v	v	v	v	v		
Parental behavioral therapy by psychologist						v		v		v		v		v		v	
Usual-care group	baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Measurements	v																v
Visit to resident in pediatrics			v					v					v				

Numbers indicate the weeks of the program.

After the end of both programs, the children were followed-up during a period of 3 years.

The first aim of this thesis is to determine the effect of a multidisciplinary intervention program in 3-year-old to 5-year-old overweight or obese children on anthropometry and body composition. We compare the effect with a group of overweight or obese children of the same age, receiving a usual-care treatment program.

The following questions are addressed:
- What is the effect of a multidisciplinary intervention program in overweight or obese children 3-5 years old on anthropometry and body composition, at the end of the treatment program and 1 year after the start of the program? (**Chapter 3**)
- Does a multidisciplinary intervention program in overweight or obese children 3-5 years old have positive effects on physical activity and energy intake and do they remain 1 year after the start of the program? (**Chapter 3**)
- What is the effect of a multidisciplinary intervention program in overweight or obese children 3-5 years old on anthropometry and body composition, 1½ and 3 years after the start of the program? (**Chapter 6**)
- Does the effect of a multidisciplinary intervention program on physical activity and energy intake in overweight or obese children 3-5 years old remain 1½ and 3 years after the start of the program? (**Chapter 6**)

The second aim of this thesis is to determine the prevalence of insulin resistance and cardiovascular risk factors in 3-year-old to 5-year-old overweight or obese children and to determine the effect of a multidisciplinary intervention program on insulin resistance, cardiovascular risk factors, low-grade systemic inflammation, and adipokines. Again, we compare the effect with a group of overweight or obese children of the same age, receiving a usual-care treatment program.

The following questions are addressed:
- What is the prevalence of insulin resistance and cardiovascular risk factors in 3-year-old to 5-year-old overweight or obese children and are insulin resistance and cardiovascular risk factors in these children related to body weight or body composition? (**Chapter 2**)
- Does a multidisciplinary intervention program in 3-year-old to 5-year-old overweight or obese children have positive effects on insulin resistance, lipid profile, markers of low-grade systemic inflammation and adipokines and are these effects related to changes in body weight and body composition? (**Chapter 4**)

The third aim of this thesis is to determine the effect of a multidisciplinary intervention program in 3-year-old to 5-year-old overweight or obese children on health-related quality of life and to compare the effect with a group of overweight or obese children aged 3-5 years receiving a usual-care treatment program.

The following questions are addressed:

- Does a multidisciplinary intervention program in 3-year-old to 5-year-old overweight or obese children improve health-related quality of life? (**Chapter 5**)
- Are changes in body weight and body composition related to changes in health-related quality of life? (**Chapter 5**)

In chapter 7 we discuss the main findings of this thesis and provide future perspectives and recommendations regarding obesity intervention programs in children.

References

1. Schönbeck Y, Talma H, van Dommelen P, Bakker B, Buitendijk SE, Hirasing RA, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. PLoS One 2011;6:e27608.
2. Fernandez JR, Klimentidis YC, Dulin-Keita A, Casazza K. Genetic influences in childhood obesity: recent progress and recommendations for experimental designs. Int J Obes (Lond) 2012;36:479-484.
3. Druet C, Ong KK. Early childhood predictors of adult body composition. Best Pract Res Clin Endocrinol Metab 2008;22:489-502.
4. Ong KK. Size at birth, postnatal growth and risk of obesity. Horm Res 2006;65 Suppl 3:65-69.
5. Speiser PW, Rudolf MC, Anhalt H, Camacho-Hubner C, Chiarelli F, Eliakim A, et al. Consensus statement: Childhood obesity. J Clin Endocrinol Metab 2005;90:1871-1887.
6. Van den Hurk K, van Dommelen P, van Buuren S, Verkerk PH, Hirasing RA. Prevalence of overweight and obesity in the Netherlands in 2003 compared to 1980 and 1997. Arch Dis Child 2007;92:992-995.
7. Liem ET, van Buuren S, Sauer PJ, Jaspers M, Stolk RP, Reijneveld SA. Growth during infancy and childhood, and adiposity at age 16 years: ages 2 to 7 years are pivotal. J Pediatr 2013;162:287-292.
8. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. Int J Pediatr Obes 2009;4:281-288.
9. Gordon-Larsen P, The NS, Adair LS. Longitudinal trends in obesity in the United States from adolescence to the third decade of life. Obesity (Silver Spring) 2010;18:1801-1804.
10. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-1243.
11. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002;360:473-482.
12. Bugge A, El-Naaman B, McMurray RG, Froberg K, Andersen LB. Tracking of clustered cardiovascular disease risk factors from childhood to adolescence. Pediatr Res 2013;73:245-249.
13. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al; IDF Consensus Group. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007;8:299-306.
14. Pedrosa C, Oliveira BM, Albuquerque I, Simões-Pereira C, Vaz-de-Almeida MD, Correia F. Obesity and metabolic syndrome in 7-9 years-old Portuguese schoolchildren. Diabetol Metab Syndr 2010;2:40.
15. D'Adamo E, Impicciatore M, Capanna R, Marcovecchio ML, Masuccio FG, Chiarelli F, et al. Liver steatosis in obese prepubertal children: a possible role of insulin resistance. Obesity (Silver Spring) 2008;16:677-683.
16. Arens R, Muzumdar H. Childhood obesity and obstructive sleep apnea syndrome. J Appl Physiol 2010;108:436-444.
17. Novais EN, Millis MB. Slipped capital femoral epiphysis: prevalence, pathogenesis, and natural history. Clin Orthop Relat Res 2012;470:3432-3438.
18. Griffiths LJ, Parsons TJ, Hill AJ. Self-esteem and quality of life in obese children and adolescents: a systematic review. Int J Pediatr Obes 2010;5:282-304.
19. Friedlander SL, Larkin EK, Rosen CL, Palermo TM, Redline S. Decreased quality of life associated with obesity in school-aged children. Arch Pediatr Adolesc Med 2003;157:1206-1211.
20. Kuhl ES, Rausch JR, Varni JW, Stark LJ. Impaired health-related quality of life in preschoolers with obesity. J Pediatr Psychol 2012;37:1148-1156.
21. Oude Luttikhuis HG, Stolk RP, Sauer PJ. How do parents of 4- to 5-year-old children perceive the weight of their children? Acta Paediatr 2010;99:263-267.
22. Baidal J A, Taveras EM. Childhood obesity: shifting the focus to early prevention. Arch Pediatr Adolesc Med 2012;166:1179-1181.
23. Sabin MA, Ford A, Hunt L, Jamal R, Crowne EC, Shield JP. Which factors are associated with a successful outcome in a weight management programme for obese children? J Eval Clin Pract 2007;13:364-368.
24. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev 2009;CD001872.
25. Martos R, Valle M, Morales RM, Cañete R, Gascón F, Urbano MM. Changes in body mass index are associated with changes in inflammatory and endothelial dysfunction markers in obese prepubertal children after 9 months of body mass index SD score loss. Metabolism 2009;58:1153-1160.
26. Vos RC, Huisman SD, Houdijk EC, Pijl H, Wit JM. The effect of family-based multidisciplinary cognitive behavioral treatment on health-related quality of life in childhood obesity. Qual Life Res 2012;21:1587-1594.

2

Insulin Resistance and Cardiovascular Risk Factors in 3- to 5-Year-Old Overweight or Obese Children

Gianni Bocca[1 *]
Eva C. Ongering[1 *]
Ronald P. Stolk[2]
Pieter J.J. Sauer[1]

* both authors contributed equally to the manuscript

[1] Department of Pediatrics, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[2] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Hormone Research in Paediatrics 2013;80:201-206

Abstract

Background: The increasing rate of overweight and obesity is alarming. The complications of overweight and obesity at a young age are largely unknown. We aimed to assess the prevalence of insulin resistance (IR) and cardiovascular risk factors among overweight and obese children aged 3-5 years.

Methods: The study population consisted of 75 children (29 overweight, 46 obese). We performed anthropometry and bioelectrical impedance analysis as an indicator of body composition. IR was determined by the updated Homeostasis Model Assessment of Insulin Resistance (HOMA2-IR). Cardiovascular risk factors were defined by the presence of increased serum triglycerides, blood pressure, and HOMA2-IR and by a decreased serum HDL-cholesterol.

Results: An elevated HOMA2-IR was found in 7.7% of the children. HOMA2-IR was correlated with body mass index (r = 0.63), waist circumference (r = 0.62) and body fat percentage (r = 0.58) (all $p < 0.001$). Cardiovascular risk factors were present in 6.9% (triglycerides) to 74.3% (hypertension) of the children.

Conclusions: IR and cardiovascular risk factors are already evident in many 3- to 5-year-old overweight and obese children. IR is strongly related to body composition.

Introduction

The prevalence of overweight and obesity is growing rapidly worldwide, including the Netherlands.[1] Even at a very young age overweight and obesity are a common problem. Changes in weight and body mass index (BMI) between the ages of 2 to 7 years are associated with an increased BMI in adolescence.[2] Obese adolescents have a high risk of becoming obese adults.[3]

Obesity often coexists with cardiovascular and metabolic disorders. This can be caused by adipocytokines,[4] and by the presence of dyslipidemia and insulin resistance (IR). Adipocytokines are able to create a state of low grade inflammation,[5] oxidative stress,[6] and metabolic syndrome (MS).[7] MS is a combination of different metabolic disorders that can predict the later development of cardiovascular disease (CVD) and type 2 diabetes (T2D).[7] IR plays a central role in the pathophysiology of MS.[8,9] Furthermore, IR is a strong predictive factor for the development of T2D.[10]

According to the International Diabetes Federation consensus report, MS cannot be diagnosed in children under the age of 10 years.[11] However, cardiovascular risk factors in childhood overweight and obesity have been demonstrated.[12,13] Pedrosa et al. considered 16% of on average 8.7 year-old overweight and obese children to have MS,[13] while D'Adamo et al. showed that there were already complications in, on average, 8.5 year-old overweight and obese children.[14] It is important to know if there are cardiovascular risk factors at an even younger age, since this would indicate the urgent need to prevent overweight and obesity in preschool-aged children.

The aims of this study are to evaluate the prevalence of IR and cardiovascular risk factors in 3- to 5-year-old overweight and obese children, and to assess the association between body composition and IR and cardiovascular risk factors.

Methods

Between October 2006 and March 2008, overweight and obese children aged 3 to 5 years and their parents were invited to participate in an intervention study to influence lifestyle and thereby reduce BMI. Details of the study have been described previously.[15] All children were living in the northern part of the Netherlands. The cases were recruited by asking Well Child Clinics to refer children to our outpatient clinic if they were overweight or obese. General practitioners and pediatricians in the northern parts of the Netherlands were also invited to refer 3- to 5-year-old overweight and obese children to our clinic. Overweight and obesity were defined by a BMI above the international cut-off points for overweight and obesity.[16] Children with mental retardation, severe behavioral problems, or other criteria interfering with participation were excluded from the study, and children with obesity due to known medical causes or eating disorders were also excluded. Written informed consent from the parents or legal caretakers was obtained. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

In this study we describe the results of measurements done before the intervention started. During anthropometric measurements the children wore only their underwear. All anthropometric measurements were done *in duplo*. The average of both measurements was calculated. Standard calibrated scales and stadiometers were used to determine height (to the nearest 0.1 cm) and weight (to the nearest 0.05 kg). BMI was calculated and standardized (BMI-z) using age- and sex-specific data from the Fourth Dutch Growth Study (http://www.growthanalyser.org/).[17] Waist circumference (WC) (to the nearest 0.1 cm) was measured in an orthostatic position at the midpoint between the lateral iliac crest and the lowest rib, using a standard measuring tape. WC was standardized (WC-z) as described above. Body composition was measured using a 50 kHz fixed-frequency bio-impedance analyzer (BIA-101, Akern S.r.l./RJL Systems, Florence, Italy). Resistance (Rz) and reactance (Xc) values were collected, corresponding to total body water and extra-cellular water content, respectively. On the same day, all measurements were performed three times and the average was calculated. Body fat percentage (BF%) was determined as described by Horlick and colleagues.[18] After a resting period of 10 minutes and with the children in a supine position, systolic (SBP) and diastolic (DBP) blood pressure were measured *in duplo* using a Dinamap Critikon 1846SX digital sphygmomanometer (Critikon Inc., Tampa, Florida, USA) and an appropriate cuff size. The mean of two readings was calculated. The children's blood pressure (BP) was classified according to sex, height and age.[19]

Blood was drawn after an overnight fast. Total cholesterol (T-C; lower detection limit 0.1 mmol/L, intra- and inter-assay coefficient of variation 1.1 and 1.2%, respectively), HDL-cholesterol (HDL-C; 0.1 mmol/L, 1.2 and 2.1%, respectively), LDL-cholesterol (LDL-C; 0.1 mmol/L, 1.1 and 2.3%, respectively) and triglycerides (TG; 0.05 mmol/L, 1.2 and 1.5%, respectively) were measured using an enzymatic colorimetric method (Roche Modular, Mannheim, Germany). HbA1c (lower limit of detection, intra- and inter-assay coefficient of variation in non-diabetic controls 3.5%, 1.05 and 1.61%, respectively) was determined using high-performance liquid chromatography (Bio-Rad Variant, Bio-Rad Laboratories, Veenendaal, the Netherlands), insulin (1.3 mU/L, 4.5-8.3 and 4.7-12.2%, respectively) by radioimmunoassay (Diagnostic Systems Laboratories, Inc., Webster, TX, USA) and glucose (0.11 mmol/L, 1.0 and 1.7%, respectively) by an enzymatic method (hexokinase-mediated reaction, Roche Modular, Mannheim, Germany). IR was determined by the updated Homeostasis Model Assessment of Insulin Resistance (HOMA2-IR).[20]

Cardiovascular risk factors included serum TG, HDL-C, HOMA2-IR and blood pressure. The cut-off values for TG and HDL-C, as used by Cook and coworkers,[21] were used in the present study, as it has been shown that the distribution of these values is about the same in 5-year-olds from a contemporary cohort of 307 British children.[22] For cut-off values for HOMA2-IR, we used data from Murphy et al.,[22] although the children in this study were 5-8 years old. To our knowledge, no data on HOMA2-IR are available in younger children, so the above mentioned cut-offs were chosen. To diagnose impaired insulin sensitivity, we chose the 97.5th percentile as the cut-off point, a HOMA2-IR for boys of 1.53 and for girls of 1.85. Cardiovascular risk factors were diagnosed if one or more of the following criteria were present: (1) TG ≥ 1.24 mmol/L; (2) HDL-C ≤ 1.03 mmol/L; (3) hypertension (SBP and/or DBP ≥ 90th percentile for age, sex and height); (4) impaired glucose tolerance (HOMA2-IR ≥ 97.5th percentile). Besides HOMA2-IR, fasting glucose (≥ 5.6 mmol/L) and HbA1c (≥ 5.5%) were used to detect impaired glucose tolerance.[23,24]

Statistical analysis was performed using IBM SPSS Statistics version 20. Distribution of normality was tested using the 1-sample Kolmogorov-Smirnov test. Pearson correlation coefficients were calculated to assess the association between variables. BMI-z was used to divide the children into a group with overweight and a group with obesity. We used the non-paired t-test to determine the difference between two independent groups, and the non-parametric version, Mann-Whitney U test, for variables without a normal distribution. The significance level of all tests was 0.05. Primary outcome parameter of the study was the change in BMI in the children receiving a multidisciplinary obesity treatment program, compared with the children receiving a usual-care program. To detect a difference in BMI between both treatment groups of 2 kg/m^2 (approximately 10%), two groups of 63 children were required (SD 4, two-sided alpha 0.05, power 80%).

Results

A total of 75 children with a mean age of 4.7 years were included: 29 children with overweight and 46 obese. Table 1 gives the clinical characteristics of both groups. In the children with overweight and obesity, the mean (SD) BMI was 18.7 (0.8) and 22.7 (2.5) kg/m², and the mean (SD) BMI-z was 1.8 (0.3) and 3.3 (0.8), respectively.

Table 1. Descriptive and anthropometric characteristics of the study population. Data are expressed as mean (SD).

	Overweight (n=29)	Obesity (n=46)	p-value
Boys, n	5 (17.2%)	16 (34.8%)	
Girls, n	24 (82.8%)	30 (65.2%)	
Age, years	4.7 (0.7)	4.7 (0.9)	0.93
BMI, kg/m²	18.7 (0.8)	22.7 (2.5)	< 0.001
BMI z-score	1.8 (0.3)	3.3 (0.8)	< 0.001
Waist circumference, cm	59.2 (3.9)	68.5 (7.0)	< 0.001
Waist circumference z-score	1.8 (0.6)	3.2 (0.7)	< 0.001
Body fat %	23.2 (5.2)	32.3 (5.8)	< 0.001
Systolic blood pressure, mmHg	108 (14)	116 (11)	0.02
Diastolic blood pressure, mmHg	63 (6)	65 (7)	0.11

BMI: body mass index

The biochemical parameters for the total and for the separate groups with overweight or obesity are shown in table 2.

Table 2. Biochemical parameters of the total group of children and for the separate groups with overweight or obesity. Data are expressed as mean (SD).

	Total group	Overweight	Obesity
Glucose, mmol/L	4.2 (0.3)	4.0 (0.4)	4.3 (0.3)*
	(n=68)	(n=26)	(n=42)
HbA1c, %[1]	5.3 (3.3 - 6.0)	5.3 (3.3 - 6.0)	5.4 (3.8 - 5.9)
	(n=73)	(n=29)	(n=44)
Insulin, mU/L	7.9 (4.0)	6.2 (3.5)	8.9 (4.0)**
	(n=65)	(n=25)	(n=40)
HOMA2-IR	1.00 (0.51)	0.79 (0.45)	1.14 (0.50)**
	(n=65)	(n=25)	(n=40)
T-C, mmol/L	3.85 (0.60)	3.79 (0.53)	3.89 (0.65)
	(n=73)	(n=28)	(n=45)
HDL-C, mmol/L	1.28 (0.27)	1.30 (0.30)	1.27 (0.25)
	(n=73)	(n=28)	(n=45)
LDL-C, mmol/L	2.48 (0.54)	2.41 (0.45)	2.52 (0.59)
	(n=72)	(n=28)	(n=44)
TG, mmol/L	0.78 (0.37)	0.70 (0.26)	0.83 (0.43)
	(n=72)	(n=28)	(n=44)

[1] Median (minimum-maximum values)

* significantly higher in the group with obesity compared with the group with overweight (p = 0.01)

** significantly higher in the group with obesity compared with the group with overweight (p < 0.01)

T-C: total cholesterol; HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol; TG: triglycerides

In our study, 5/65 children (7.7%) had a HOMA2-IR above the upper limit of the normal range. This included one overweight child (4.0%) and 4 (10.0%) obese children. In none of the children blood glucose was ≥ 5.6 mmol/L. However, fasting glucose was significantly higher in the group children with obesity, compared with the group children with overweight (p = 0.01). HOMA2-IR and fasting insulin were also significantly higher in the obese than in the overweight children (p < 0.01). HOMA2-IR was significantly correlated with BMI, r = 0.63, WC, r = 0.62 (Figure 1) and BF%, r = 0.58 (all p < 0.001). HbA1c was ≥ 5.5% in 8/29 children (27.6%) of the overweight and in 16/44 (36.4%) of the obese group. The correlation between HbA1c and BMI-z and BF% reached borderline significance (both p = 0.08). In 5/28 overweight (17.9%) and 8/45 obese children (17.8%), HDL-C was below the lower limit of normal. TG were ≥ 1.24 mmol/L in 1/28 (3.6%) of the overweight and in 4/44 (9.1%) of the obese children.

Figure 1. Correlation between the updated Homeostasis Model Assessment of Insulin Resistance (HOMA2-IR) and waist circumference.

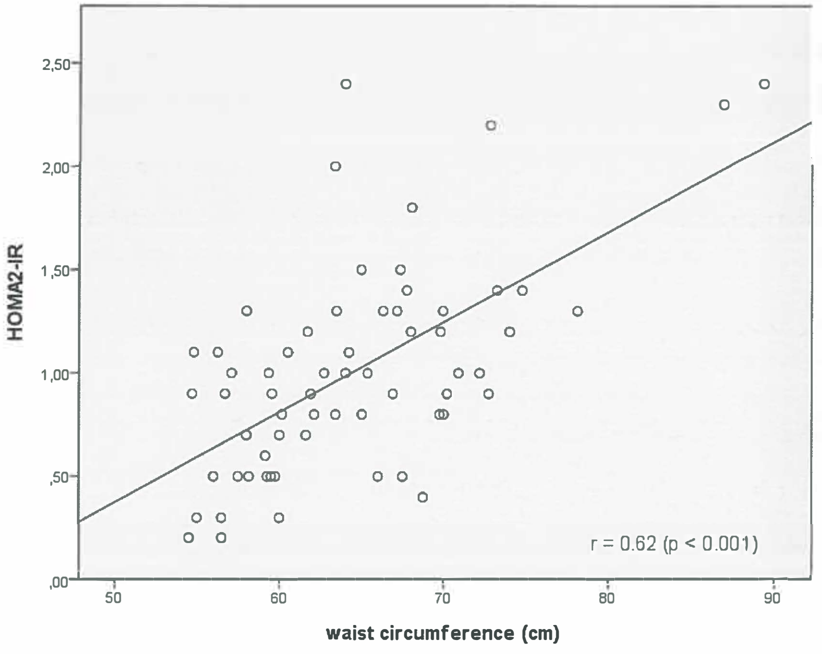


Table 3 shows the number of children with the separate cardiovascular risk factors. In four of the 75 children, data were missing for one of the parameters. Of the four separate cardiovascular risk factors, most of the children had hypertension (74.3%). Impaired glucose tolerance was observed in 7.7% of the children. HDL-C ≤ 1.03 mmol/L and TG ≥ 1.24 mmol/L were seen in 17.8% and 6.9% of the children, respectively.

Table 3. Number (%) of children with cardiovascular risk factors.

Cardiovascular risk factor	Number of children
Hypertension (SBP and/or DBP ≥ 90^{th} percentile)	55/74 (74.3%)
Impaired glucose tolerance (HOMA2-IR ≥ 97.5^{th} percentile)	5/65 (7.7%)
HDL-C ≤ 1.03 mmol/L	13/73 (17.8%)
TG ≥ 1.24 mmol/L	5/72 (6.9%)

SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: HDL-cholesterol; TG: triglycerides

Discussion

Our study shows that cardiovascular risk factors are already evident in overweight and obese children with a mean age of 4.7 years. Furthermore, IR is strongly related to body composition. To our knowledge, this is the first study which focuses on the presence of cardiovascular risk factors in preschool-aged children only, so we cannot compare our results to other studies in children with the same age. Recently it was shown that two third of severely obese Dutch children aged 2 to 17 years had cardiovascular risk factors.[25] In moderately obese 13-year-olds, MS was found in 38.7%, compared with 49.7% in severely obese 11-year-olds.[26] In prepubertal Caucasian children, MS was found in 15-42% of children, using various definitions for MS.[27] Using the definition from Cook et al.,[21] Reinehr et al. found a prevalence of MS of 21% in girls and 15% in boys, aged 4-16 years (mean 11.8 years).[27]

We described the different cardiovascular risk factors separately, as MS per se cannot be diagnosed under the age of 10 years.[11] Pedrosa et al. showed approximately the same prevalence of the different components of MS in 7- to 9-year-old overweight and obese children.[13] Elevated blood pressure was found in 63% (74.3% in our study), IR in 8.5% (7.7%), low HDL-C in 13% (17.8%) and elevated TG in 11% (6.9%). They did not find elevated fasting glucose concentrations in their study and this was neither found in our children. We found a high prevalence of hypertension in our group of overweight and obese children. Although comparable with the study of Pedrosa et al.,[13] this might be partially explained by the cut-offs we chose to define hypertension. Furthermore, the presence of hypertension in our group of children should be regarded with caution, as hypertension can only be diagnosed definitely after a 24-hour continuous blood pressure measurement. The results on the presence of cardiovascular risk factors in our group of 3- to 5-year-old overweight or obese children should be interpreted with care. As no reference values are available for children in this age category, best suitable cut-offs were chosen from the literature, possibly leading to a reference bias. However, the results of our study are supported by a previous study on the prevalence of cardiovascular risk factors in obese children aged 7-9 years.[13]

At present, it is not fully understood what the best parameter is for impaired glucose tolerance. We also determined HbA1c to evaluate glucose tolerance, as it has a higher sensitivity than fasting glucose values.[23] Moreover, fasting glucose values only change at a later stage of impaired glucose tolerance. Even though the results of HbA1c, as an indicator of glucose tolerance, still have to be validated in a larger group, HbA1c seems to be an important parameter.[24] One-third of our children (27.6% of the overweight and 36.4% of the obese children) had an HbA1c $\geq$ 5.5%. We demonstrated a relation between IR and measures of body composition by the significant correlation between BMI, WC, and BF% with HOMA2-IR. The importance of WC to predict IR has been described in children aged 7-17 years.[28]

We cannot compare our data to children with a normal BMI. It was considered unethical to withdraw blood from non-overweight or non-obese children in the fasting state for research purposes only. We therefore compared the obese children with the overweight children. In the obese children, fasting glucose, fasting insulin and HOMA2-IR were significantly higher than in the overweight children. Furthermore, our study shows a clear correlation between IR and BF% and WC. This shows that glucose tolerance is more severely impaired in children with higher fat mass and confirms the results of Calcaterra et al.[12] and Weiss et al.[26] who stated that the risk on metabolic complications increases with increasing obesity and IR.

The present study shows that IR and cardiovascular risk factors are already evident in overweight and obese children with a mean age of 4.7 years. An association exists between IR and BMI, WC and BF%. These results are alarming for the future health of these children, as tracking of obesity and cardiovascular risk factors in children and adolescents have been demonstrated.[29,30] It can be speculated that the chance of developing CVD and T2D is already increased in children who show cardiovascular risk factors at such a young age. It is therefore needed to focus on the prevention and treatment of childhood obesity at such a young age.[31] Also, studies are needed to determine if abnormal metabolic indices at young age are related to an increased risk for CVD and MS at a later age.

References

1. Schönbeck Y, Talma H, van Dommelen P, Bakker B, Buitendijk SE, Hirasing RA, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. PLoS One 2011;6:e27608.
2. Liem ET, van Buuren S, Sauer PJ, Jaspers M, Stolk RP, Reijneveld SA. Growth during infancy and childhood, and adiposity at age 16 years: ages 2 to 7 years are pivotal. J Pediatr 2013;162:287-292.
3. Gordon-Larsen P, The NS, Adair LS. Longitudinal trends in obesity in the United States from adolescence to the third decade of life. Obesity (Silver Spring) 2010;18:1801-1804.
4. Matsuzawa Y, Funahashi T, Nakamura T. Molecular mechanism of metabolic syndrome X: contribution of adipocytokines adipocyte-derived bioactive substances. Ann N Y Acad Sci 1999;892:146-154.
5. Tamakoshi K, Yatsuya H, Kondo T, Hori Y, Ishikawa M, Zhang H, et al. The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. Int J Obes Relat Metab Disord 2003;27:443-449.
6. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol 2004;24:816-823.
7. Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 2008;28:629-636.
8. Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. Diabetes Care 2006;29:2427-2432.
9. Weiss R, Kaufman FR. Metabolic complications of childhood obesity: identifying and mitigating the risk. Diabetes Care 2008;31:S310-S316.
10. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. N Engl J Med 1993;329:1988-1992.
11. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al; IDF Consensus Group. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007;8:299-306.
12. Calcaterra V, Klersy C, Muratori T, Telli S, Caramagna C, Scaglia F, et al. Prevalence of metabolic syndrome (MS) in children and adolescents with varying degrees of obesity. Clin Endocrinol (Oxf) 2008;68:868-872.
13. Pedrosa C, Oliveira BM, Albuquerque I, Simões-Pereira C, Vaz-de-Almeida MD, Correia F. Obesity and metabolic syndrome in 7-9 years-old Portuguese schoolchildren. Diabetol Metab Syndr 2010;2:40.
14. D'Adamo E, Impicciatore M, Capanna R, Marcovecchio ML, Masuccio FG, Chiarelli F, et al. Liver steatosis in obese prepubertal children: a possible role of insulin resistance. Obesity (Silver Spring) 2008;16:677-683.
15. Bocca G, Corpeleijn E, Stolk RP, Sauer PJ. Results of a multidisciplinary treatment program in 3-year-old to 5-year-old overweight or obese children: a randomized controlled clinical trial. Arch Pediatr Adolesc Med 2012;166:1109-1115.
16. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-1243.
17. Fredriks AM, van Buuren S, Fekkes M, Verloove-Vanhorick SP, Wit JM. Are age references for waist circumference, hip circumference and waist-hip ratio in Dutch children useful in clinical practice? Eur J Pediatr 2005;164:216-222.
18. Horlick M, Arpadi SM, Bethel J, Wang J, Moye J Jr, Cuff P, et al. Bioelectrical impedance analysis models for prediction of total body water and fat-free mass in healthy and HIV-infected children and adolescents. Am J Clin Nutr 2002;76:991-999.
19. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114:555-576.
20. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-1495.
21. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. Arch Pediatr Adolesc Med 2003;157:821-827.
22. Murphy MJ, Hosking J, Metcalf BS, Voss LD, Jeffery AN, Sattar N, et al. Distribution of adiponectin, leptin, and metabolic correlates of insulin resistance: a longitudinal study in British children; 1: Prepuberty (EarlyBird 15). Clin Chem 2008;54:1298-1306.
23. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160-3167.
24. Tsay J, Pomeranz C, Hassoun A, Zandieh SO, Rutledge J, Vogiatzi MG, et al. Screening markers of impaired glucose tolerance in the obese pediatric population. Horm Res Paediatr 2010;73:102-107.
25. Van Emmerik NM, Renders CM, van de Veer M, van Buuren S, van der Baan-Slootweg OH, Kist-van Holthe JE, et al. High cardiovascular risk in severely obese young children and adolescents. Arch Dis Child 2012;97:818-821.

26. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 2004;350:2362-2374.
27. Reinehr T, de Sousa G, Toschke AM, Andler W. Comparison of metabolic syndrome prevalence using eight different definitions: a critical approach. Arch Dis Child 2007;92:1067-1072.
28. Daniels SR, Khoury PR, Morrison JA. Utility of different measures of body fat distribution in children and adolescents. Am J Epidemiol 2000;152:1179-1184.
29. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. Int J Pediatr Obes 2009;4:281-288.
30. Bugge A, El-Naaman B, McMurray RG, Froberg K, Andersen LB. Tracking of clustered cardiovascular disease risk factors from childhood to adolescence. Pediatr Res 2013;73:245-249.
31. Baidal JA, Taveras EM. Childhood obesity: shifting the focus to early prevention. Arch Pediatr Adolesc Med 2012;166:1179-1181.

3

Results of a Multidisciplinary Treatment Program in 3- to 5-Year-Old Overweight or Obese Children A Randomized Controlled Clinical Trial

Gianni Bocca[1]
Eva Corpeleijn[2]
Ronald P. Stolk[2]
Pieter J.J. Sauer[1]

[1] Department of Pediatrics, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[2] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Archives of Pediatrics and Adolescent Medicine 2012;166:1109-1115

Abstract

Background: In the Netherlands, as is seen worldwide, the prevalence of childhood obesity has increased, especially under the age of 8 years. Little is known about the results of lifestyle intervention programs in treating obesity in preschool-aged children.We assessed the effects of a multidisciplinary intervention program in 3- to 5-year-old overweight and obese children.

Methods: From October 2006 to March 2008, seventy-five children (29 overweight, 46 obese) aged 3-5 years participated in a randomized controlled clinical trial at the Groningen Expert Center for Kids with Obesity, Beatrix Children's Hospital, University Medical Center Groningen. Children were randomized to a multidisciplinary intervention program or to a usual-care program. Anthropometry was performed and body composition was determined by bioelectrical impedance analysis and ultrasound at the start and at the end of the 16-week program and 12 months after starting the intervention. Main outcome measures were the actual weight reduction, change in body mass index (BMI), BMI z-score, body fat percentage and visceral fat in the multidisciplinary intervention group, compared with the usual-care group.

Results: At the end of the treatment program, children in the multidisciplinary intervention group showed a higher decrease in BMI, BMI z-score and waist circumference (WC) z-score, compared with the children in the usual-care group. At twelve months, the children in the intervention group showed a higher decrease in BMI, BMI z-score, WC and WC z-score, compared with the children in the usual-care group. Visceral fat showed a trend towards a higher decrease.

Conclusions: A multidisciplinary intervention program in 3- to 5-year-old overweight and obese children had beneficial effects on anthropometry and body composition. The positive effects were still present 12 months after the start of the intervention.

Trial Registration: Dutch Trial Registry. Identifier: NTR872 (ISRCTN47185691) (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=872).

Introduction

In the Netherlands, as is seen worldwide, the prevalence of childhood obesity has increased.[1] Between 1980 and 2003, the prevalence of obesity in boys and girls aged 4-16 years has increased especially under the age of 8 years.[1] At present time, the prevalence of overweight in Dutch boys and girls aged 2-21 years is 13.3 and 14.9%, respectively, the prevalence of obesity is 1.8% and 2.2%.[2] A sedentary lifestyle and a high fat and excess caloric intake are considered to be, at least partially, responsible for the epidemic rise in child obesity.[3] The influence of TV viewing and lack of physical activity on body mass index (BMI) in preschool children has thereby been demonstrated.[4] Childhood obesity has extensive health risks, amongst others the development of metabolic syndrome (MS) at a later age.[5]

Treatment of children with overweight or obesity is difficult. A recent meta-analysis on different treatment modalities for obesity in children aged 5-12 years, showed that combined lifestyle interventions with a behavioral component could achieve an important weight reduction.[6] However, little is known about the results of lifestyle intervention programs in treating obesity in preschool children. Treating obesity at a young age is especially important as tracking of obesity exists.[7] Obese adolescents are clearly at risk to become obese adults.[8] Moreover, interventions preventing or reversing obesity in its early stage might be more successful than treating obesity which has been present for a longer period of time. Kindergarten-based interventions have proven to be useful in the prevention of overweight in preschool children.[9]

The aim of this study was to evaluate the effect of a multidisciplinary intervention program in overweight and obese children aged 3-5 years and their families, compared with usual-care. Primary outcome measures were the actual weight reduction, change in BMI and BMI z-score (BMI-z), change in body fat percentage (BF%) and visceral fat (VF) in the intervention group, compared with a usual-care group. Secondary outcome measures were a change in waist circumference (WC) and WC z-score (WC-z), hip circumference (HC) and HC z-score (HC-z), upper arm circumference (UAC), fat-free mass (FFM) and abdominal subcutaneous fat (SCF).

Methods

Study design

The present study, a randomized controlled clinical trial and called "GECKO-Outpatients Clinic", was performed in the Groningen Expert Center for Kids with Obesity (GECKO). Children and their families were randomly assigned to the multidisciplinary intervention program or to a usual-care program.

Inclusion took place between October 2006 and March 2008, and 78 children aged 3-5 years were assessed for eligibility for the study. Children with overweight or obesity, according to the International Obesity Task Force (IOTF) definitions,[10] were referred to the Outpatient Clinic by youth health care physicians, general practitioners or pediatricians. Children with mental retardation, severe behavioral problems, or other criteria interfering with participation were excluded. Also, children with overweight or obesity due to known medical conditions or eating disorders according to the Dutch Eating Behavior Questionnaire, were excluded from the study. Three children did not meet the inclusion criteria for the study because of a BMI-z ≤ 1.1, thus not being overweight. In total, 75 children were included in the study.

Study participants were randomly assigned to the multidisciplinary intervention or usual-care group by our researcher. Computerized randomization was done in groups of twenty, matched by gender. Children and parents in the multidisciplinary intervention program received dietary advice, physical activity sessions and, for parents only, psychological counselling. Dietary advice consisted of six sessions of 30 minutes each, guided by a dietician. During these sessions, a normocaloric diet was advised based on the required daily intake for this age group. In addition, education and advice to improve eating behavior was given. Parents and children were advised to have breakfast every morning, to refrain from soft drinks and to have, at most, three snacks per day. Personal goals regarding the diet were set for parents and children. On consecutive sessions, feedback was given on these goals. The physical activity sessions consisted of twelve group sessions of 60 minutes each and were supervised by a physiotherapist. The exercise program focused on an active lifestyle and mimicked the type and intensity of habitual elementary school exercise (e.g. ball playing and dancing on music). Motor skills were trained and sessions aimed at having fun during exercise, thereby improving the child's well-being. Sedentary activities were advised to be reduced. Every week, parents were asked to stimulate their child's physical activity to achieve a daily physical activity of at least 60 minutes, according to the Dutch Standard of Healthy Activities. Behavioral therapy for parents comprised six group sessions of 120 minutes each that were guided by a psychologist. In these sessions, parents learned to be a healthy role model and to work with feasible goals and healthy rewards. They also learned how to use sticker charts to motivate the children and to keep track of the progress. Parents were taught to change family attitudes towards healthy eating and physical activity, to learn practical ways to remove unhealthy food triggers and to know the difference between hunger and cravings. In total, the multidisciplinary intervention program consisted of 25 sessions, together approximately 30 hours in 16 weeks. Children and parents in the usual-care group were followed by a pediatrician, also during a period of 16 weeks. In this period they were seen three times, 30-60 minutes each time. Information was given on healthy eating behavior and advice to perform physical activity for one hour per day, according to the Dutch Standard of Healthy Activities. Furthermore, children were advised to play outside every day, to go to school walking or biking, and to watch television or to play with the computer at most two hours per day.

In both groups, physical activity was measured using a pedometer (Yamax Digi-Walker SW-200, Yamax USA, Inc., San Antonio, TX, USA). The pedometer was worn at least three weekdays and one weekend-day. After each day the pedometer was worn, parents documented the amount of steps in a diary. The average number of steps per day was calculated. To document eating patterns, again for both groups, special diaries were developed to document the type and amount of food that was consumed. The diaries were used during four consecutive days: two weekdays and two weekend-days. Food records were checked by a dietician and the intake of nutrients was calculated with a validated computer program (Vodisys Medical Software, IP Health Solutions, Groningen, the Netherlands), using the Dutch food composition database (NEVO 2006). The study was approved by the Medical Ethics Committee of the University Medical Center Groningen. Written informed consent from the parents or legal caretakers was obtained.

Anthropometry and assessment of body composition, VF and SCF

Anthropometric measurements were performed at baseline, at the end of the treatment period (16 weeks) and 12 months after treatment started. All anthropometric measurements were done *in duplo*, with the children only wearing their underwear. The average of both measurements was calculated. Standard calibrated scales and stadiometers were used to determine height to the nearest 0.1 cm and weight to the nearest 0.05 kg. Height and weight were used to calculate BMI. WC was measured to the nearest 0.1 cm in orthostatic position at the midpoint between the lateral iliac crest and the lowest rib, using a standard measuring tape. HC was measured to the nearest 0.1 cm at the level of the greater trochanter of both femurs, standing upright. Right UAC was measured to the nearest 0.1 cm at the middle of the upper arm. Z-scores for BMI (BMI-z), WC (WC-z) and HC (HC-z) were calculated using the web-based program Growth Analyser 3 (http://www.growthanalyser.org/), which contains age and sex specific data from the Fourth Dutch Growth Study, obtained in 1996 and 1997.[11]

Measurements for body composition and VF and SCF were performed at baseline, 16 weeks and 12 months using a 50 kHz fixed frequency bio-impedance analyzer (BIA-101, Akern S.r.l./RJL Systems, Florence, Italy). Resistance (Rz) and reactance (Xc) values were collected, corresponding to total body water (TBW) and extracellular water content (ECW), respectively. All measurements were performed three times, the average was calculated. FFM and BF% were determined as described by Horlick and co-workers.[12]

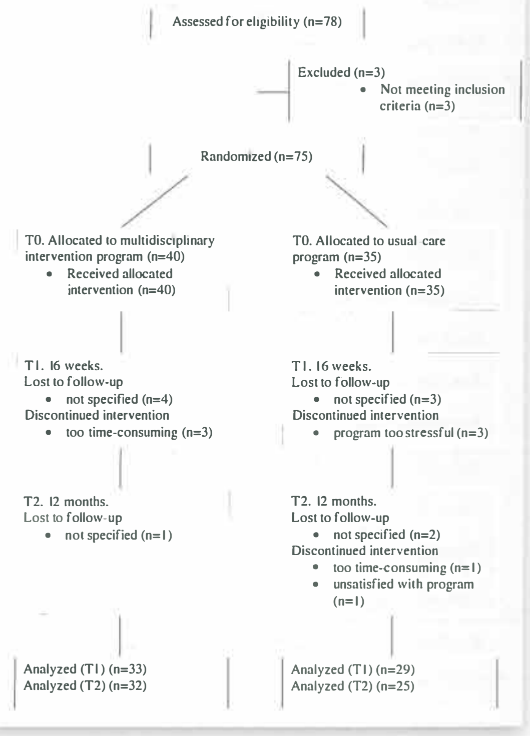
Abdominal SCF and VF were estimated based on distance measurements by standard protocol using a manual ultrasound device (SonoSite Titan, SonoSite, Inc., Bothell, WA, USA).[13,14] Measurements were performed at the middle of the imaginary line between both midpoints between the lateral iliac crest and lowest rib. All measurements were performed twice and to the nearest 0.01 cm. The average of both measurements was taken. SCF was measured at a depth of 4.7 cm with the transducer in a transverse position. The distance between the skin and abdominal muscles was measured on a "freezed" image, after maximum decompression by lifting the transducer and after the child exhaled. VF was measured at a depth of 14 cm with the transducer in a longitudinal position. After the aorta and lumbar spine were visualized, the distance between the peritoneum and the lumbar spine was measured, on a "freezed" image after maximal decompression and exhalation.

Statistical methods and data analysis

Statistical analysis was performed using PASW Statistics version 18.0. Distribution of normality was tested using the one-sample Kolmogorov-Smirnov test. For within-group differences, a paired sample Students T-test was used. For differences between groups, the independent Students T-test was used. Repeated measures ANOVA, taking into account baseline, 16 weeks and 12 months, was used to determine the difference between groups at 12 months. The significance level of all tests was 0.05.

Seventy-five children should have been in the analysis (Figure 1). Due to discontinuation of the intervention or loss to follow-up, data on 62 (82.7%) children were analyzed at the end of the treatment period. Drop-outs at 16 weeks had a slightly lower BMI compared with children who continued the study, however not statistically significant. Data on 57 (76.0%) children were analyzed at 12 months after start of the intervention, 32 out of 40 (80.0%) from the multidisciplinary intervention program and 25 out of 35 (71.4%) from the usual-care group.

Figure 1. Flow diagram of study group assignment and follow-up.



Results

Of the 75 children, with a mean age of 4.7 years, included in the study, 29 had overweight and 46 were obese. For the whole group, BMI ranged from 17.2 to 32.5 kg/m^2 and BMI-z from 1.11 to 6.3. Table 1 shows the descriptive and anthropometric characteristics of the study population. Mean BMI for the intervention group and usual-care group was 21.2 kg/m^2 and 21.0 kg/m^2, respectively. Mean BMI-z for both the intervention and the usual-care group was 2.7.

Table 1. Descriptive and anthropometric characteristics of the study population at baseline. Mean (SD).

	Multidisciplinary Intervention Group n = 40	Usual-care Group n = 35
Boys, No. (%)	12 (30.0)	9 (25.7)
Girls, No. (%)	28 (70.0)	26 (74.3)
Age, y	4.6 (0.8)	4.7 (0.8)
Overweight, No. (%)	14 (35.0)	15 (42.9)
Obese, No. (%)	26 (65.0)	20 (57.1)
Weight, kg	28.4 (6.3)	28.1 (6.8)
Body mass index, kg/m^2	21.2 (2.9)	21.0 (2.7)
Body mass index z-score	2.7 (1.0)	2.7 (1.0)
Waist circumference, cm	64.6 (7.1)	65.2 (8.0)
Waist circumference z-score	2.7 (1.0)	2.7 (1.0)
Hip circumference, cm	69.0 (7.9)	68.6 (7.2)
Hip circumference z-score	2.5 (1.3)	2.4 (1.1)
Upper arm circumference, cm	22.6 (2.3)	22.4 (2.4)
Body fat %	29.0 (7.8)	28.6 (6.3)
Fat-free mass, kg	19.7 (2.4)	19.7 (3.6)
Visceral fat, cm	4.4 (1.4)	4.3 (0.8)
Subcutaneous fat, cm	1.8 (0.7)	1.7 (0.7)
Steps, n/d	11998 (3031	9862 (2729)[a]
Energy intake, kcal/d	1434 (252)	1504 (316)

[a] Statistically significant lower number of steps compared with the multidisciplinary intervention group (independent *t* test, $p < 0.01$).

Figure 1 provides details about inclusion and dropout from the study. In the intervention group, 7 (17.5%) children were lost to follow-up or discontinued the program during the initial treatment period, compared with 6 (17.1%) children in the usual-care group. During the follow-up period after the treatment period, one (2.5%) child in the intervention group and 4 (11.4%) children in the usual-care group, were lost to follow-up or discontinued the program. Main known reasons for discontinuation of the program were the time-consuming aspect and the stressfulness of the intervention.

To assess the direct effects of the two different treatment modalities, we determined the changes in anthropometry and body composition between baseline and 16 weeks for the intervention group and the usual-care group (Table 2).

Table 2. Changes in anthropometry and body composition between baseline and end of the 16-weeks treatment program.

	Multidisciplinary intervention group (n=33)		Usual-care group (n=29)		Difference between groups	
	Mean difference (SD)	95% CI	Mean difference (SD)	95% CI	Mean (SD)	95% CI
Weight, kg	-0.2 (1.4)	-0.69 to 0.29	0.4 (1.4)	-0.15 to 0.93	0.6(0.4)	-0.12 to 1.30
Body mass index, kg/m²	-1.2 (1.0)	-1.50 to -0.81	-0.6 (1.1)	-1.04 to -0.19	0.5 (0.3)	0.01 to 1.07*
Body mass index z-score	-0.5 (0.4)	-0.66 to -0.39	-0.3 (0.4)	-0.47 to -0.14	0.2 (0.1)	0.02 to 0.42*
Waist circumference, cm	-0.9 (3.2)	-2.05 to 0.25	0.9 (5.2)	-1.10 to 2.89	1.8 (1.1)	-0.39 to 3.98
Waist circumference z-score	-0.3 (0.5)	-0.52 to -0.16	0.0 (0.6)	-0.24 to 0.21	0.3 (0.1)	0.04 to 0.60*
Hip circumference, cm	-2.2 (3.9)	-3.60 to -0.86	-0.8 (3.7)	-2.21 to 0.57	1.4 (1.0)	-0.50 to 3.33
Hip circumference z-score	-0.6(0.7)	-0.83 to -0.37	-0.3 (0.6)	-0.57 to -0.08	0.3 (0.2)	-0.06 to 0.60
Upper arm circumference, cm	-0.4 (0.9)	-0.70 to -0.02	0.0 (1.0)	-0.42 to 0.35	0.3 (0.2)	-0.17 to 0.82
Body fat %	-1.5 (3.4)	-2.73 to -0.29	-0.3 (4.0)	-1.81 to 1.26	1.2 (0.9)	-0.66 to 3.13
Fat-free mass, kg	0.3 (0.8)	0.02 to 0.56	0.4(0.9)	0.01 to 0.73	0.1 (0.2)	-0.36 to 0.51
Visceral fat, cm	-0.5 (1.5)	-1.02 to0.06	-0.2 (1.0)	-0.59 to 0.14	0.3 (0.3)	-0.41 to0.91
Subcutaneous fat, cm	-0.2 (0.3)	-0.26 to -0.05	-0.1 (0.3)	-0.22 to 0.02	0.1 (0.1)	-0.10 to 0.21

Positive numbers indicate an increase over time; CI: confidence interval.

* Statistically significant higher decrease in the multidisciplinary intervention group compared to the usual care group.

In the intervention group, a significant decrease was observed for BMI, BMI-z, WC-z, HC, HC-z, UAC, BF% and SCF. There was a significant increase in FFM. In the usual-care group, during the treatment period, a significant decrease was only observed for BMI, BMI-z and HC-z. A significant increase in FFM was also found. Comparing the effect of the two treatment programs between baseline and 16 weeks, a significant higher decrease in BMI (0.5 (0.3) kg/m² (mean (SD)); $p = 0.05$; CI 0.01;1.07), BMI-z (0.2 (0.1); $p = 0.03$; CI 0.02;0.42) and WC-z (0.3 (0.1); $p = 0.02$; CI 0.04;0.60) was demonstrated for the intervention group.

To assess the long-term effects of the two different treatment modalities, we determined the changes in anthropometry and body composition between baseline and 12 months for the intervention group and the usual-care group (Table 3).

Table 3. Changes in anthropometry and body composition from baseline to 12 months after start of the intervention.

	Multidisciplinary intervention group (n=32)		Usual-care group (n=25)		Group x Time
	Mean difference (SD)	**95% CI**	**Mean difference (SD)**	**95% CI**	***P* value[a]**
Weight, kg	1.9 (2.6)	1.00 to 2.85	3.1 (2.2)	2.20 to 4.01	0.12
Body mass index, kg/m²	-1.0 (1.4)	-1.52 to -0.47	0.0 (1.6)	-0.67 to 0.62	0.03*
Body mass index z-score	-0.6 (0.5)	-0.82 to -0.44	-0.3 (0.5)	-0.49 to -0.05	0.02*
Waist circumference, cm	0.9 (4.6)	-0.73 to 2.59	0.3 (5.0)	-1.73 to 2.37	0.02*
Waist circumference z-score	-0.4 (0.6)	-0.57 to -0.14	-0.3 (0.7)	-0.61 to -0.01	0.01*
Hip circumference, cm	0.4 (4.5)	-1.20 to 2.07	2.3 (4.9)	0.29 to 4.37	0.26
Hip circumference z-score	-0.5 (0.7)	-0.78 to -0.25	-0.2 (0.9)	-0.52 to 0.20	0.19
Upper arm circumference, cm	-0.3 (1.3)	-0.71 to 0.22	0.5 (1.5)	-0.16 to 1.10	0.16
Body fat %	-1.7 (4.5)	-3.33 to -0.12	0.3 (4.9)	-1.75 to 2.27	0.25
Fat-free mass, kg	1.8 (1.3)	1.33 to 2.25	2.1 (1.0)	1.69 to 2.55	0.59
Visceral fat, cm	-0.7 (1.5)	-1.21 to -0.14	0.1 (1.2)	-0.40 to 0.62	0.08
Subcutaneous fat, cm	-0.2 (0.4)	-0.30 to -0.02	0.0 (0.4)	-0.17 to 0.12	0.40

Positive numbers indicate an increase over time; CI: confidence interval.

[a] *P* values are based on time x group effect from repeated measures ANOVA taking into account baseline, 16 weeks and 12 months.

* Statistically significant higher decrease in the multidisciplinary intervention group compared to the usual care group.

In the intervention group, 12 months after the initial treatment started, a significant decrease was shown in BMI, BMI-z, WC-z, HC-z, BF%, VF and SCF. FFM had increased significantly. In the usual-care group, a significant decrease was only shown for BMI-z, WC-z and HC. A significant increase in FFM had occurred. Comparing the effect of the two treatment modalities between baseline and 12 months, a significant higher decrease in BMI ($p = 0.03$), BMI-z ($p = 0.02$), WC ($p = 0.02$) and WC-z ($p = 0.01$) was shown for the multidisciplinary treatment program, compared with the usual-care program (Figure 2). VF reached borderline significance ($p = 0.08$).

Figure 2. Body mass index (BMI) z-score, waist circumference (WC) z-score and visceral fat in the multidisciplinary intervention group and usual-care group from baseline to 12 months after start of the intervention.

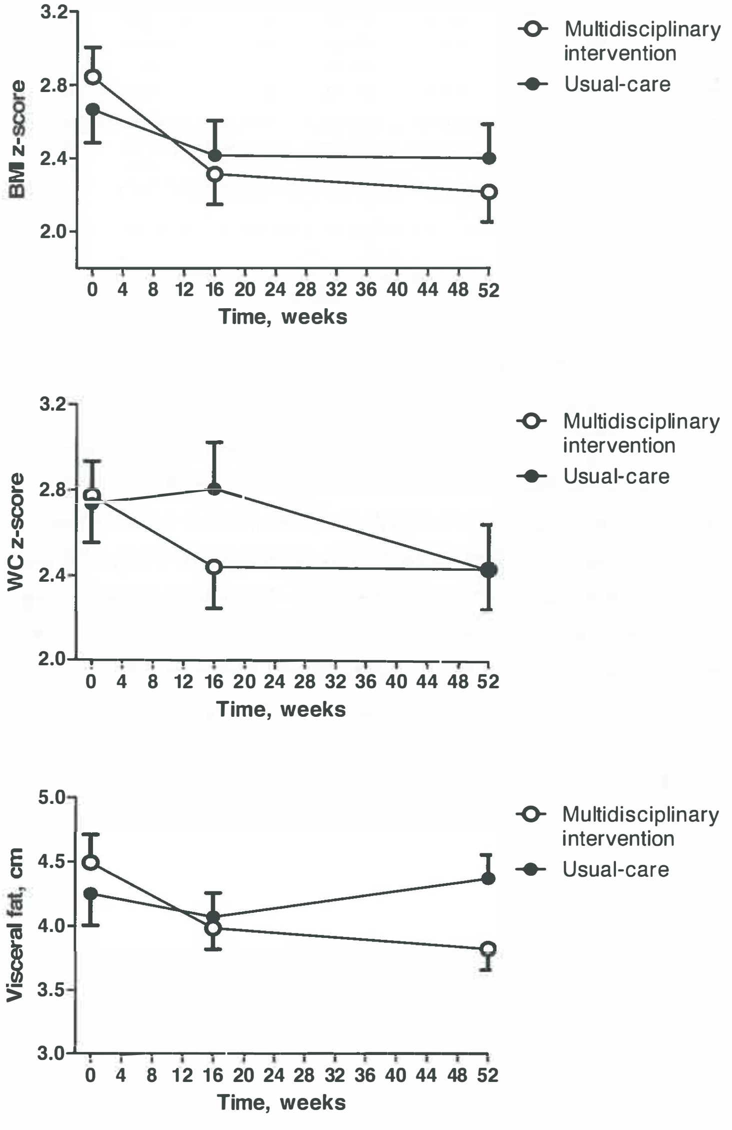


Table 4 shows the results on physical activity and energy intake.

Table 4. Changes in physical activity and energy intake from baseline to end of the 16-weeks treatment program and to 12 months after start of the intervention.

	Multidisciplinary intervention group			Usual-care group			Group x Time	
	Baseline, mean (SD)	16 weeks, mean (SD)	12 months, mean(SD)	Baseline, mean (SD)	16 weeks, mean (SD)	12 months, mean (SD)	*P* value[a]	*P* value[b]
Steps, n/day	11998 (3031)	13823 (2711)	12455 (3185)	9862 (2729)	12039 (2329)*	10308 (2404)	0.50	0.39
Energy intake, kCal/day	1434 (252)	1323 (200)	1369 (244)	1504 (316)	1327 (220)	1429 (265)	0.81	0.87
Fat energy%	27.7 (3.9)	26.5 (5.0)	30.2 (6.2)	27.7 (3.8)	26.9 (4.1)	29.6 (4.0)	0.59	0.87
Saturated fat energy%	11.0 (2.2)	10.1 (2.2)	11.3 (2.7)	10.6 (1.7)	10.5 (1.7)	10.9 (1.6)	0.22	0.71
Unsaturated fat energy%	13.8 (2.0)	13.0 (3.0)	15.5 (3.2)	14.4(2.5)	13.5 (2.8)	15.5 (2.7)	0.98	0.53
Carbohydrate energy%	57.3 (4.7)	57.1 (5.2)	53.8 (6.4)	58.6 (4.3)	58.1 (5.6)	54.8 (4.0)	0.68	0.92
Mono-/disaccharide energy%	32.8 (6.3)	31.6 (6.3)	28.4 (6.9)	35.1 (5.5)	33.0 (7.4)	29.1 (5.0)	0.67	0.69
Protein energy%	15.0 (2.6)	16.4 (2.6)	16.1 (2.7)	13.8 (2.0)	15.0 (2.8)	15.7 (1.9)	0.89	0.96
Fibers, g/day	13.3 (3.4)	14.7 (3.7)	14.9 (3.9)	14.4 (3.4)	13.1 (2.7)**	15.2 (2.5)	0.02	0.10

[a] *P* values are based on time x group effect from repeated measures ANOVA taking into account baseline and 16 weeks.

[b] *P* values are based on time x group effect from repeated measures ANOVA taking into account baseline, 16 weeks and 12 months.

* Statistically significant increase compared to baseline ($p = 0.001$).

Between baseline and end of the treatment program, a statistically significant increase in the daily number of steps was found for the usual-care group. For the multidisciplinary intervention group, there was a trend towards a statistical significance increase (p = 0.09). There was no difference between the groups. With regard to the nutrition data, in both groups a decrease in energy intake was observed. Only the change in daily intake of fibers between baseline and 16 weeks showed a statistically significant difference between both groups, in favor of the multidisciplinary intervention group. Between baseline and 12 months after start of the treatment program, neither group demonstrated a significant change over time in the daily number of steps and energy intake, despite the expected trends in nutrient intake, such as a decrease in the intake of mono- and disaccharides, a small relative increase in energy percent in total fat intake (due to reduced saccharide intake) and an increase in fiber intake. There was neither a difference between the groups.

Discussion

The aim of this study was to evaluate the effects of a multidisciplinary intervention program in overweight and obese children aged 3-5 years, and their families. We show that this multidisciplinary treatment program for overweight and obese preschool children has better results on changes in anthropometry and body composition, than a usual-care treatment program. The positive effect of the multidisciplinary treatment program is present directly after the intervention has finished, and is still present 12 months after start of the treatment program. At the end of the intervention period, the children in the multidisciplinary treatment group showed a higher decrease in BMI, BMI-z and WC-z, compared with the children in the usual-care group. Twelve months after start of the intervention, a higher reduction in BMI, BMI-z, WC and WC-z was observed for the intervention group, compared with the usual-care group. The reduction in VF showed a trend towards statistical significance.

With the exception of the daily intake of fibers, no significant differences in daily number of steps and energy intake were found between both groups, neither at the end of the treatment period, nor 12 months after start of the intervention. It would be expected that these parameters had improved more in the multidisciplinary treatment group, compared with the usual-care group. Especially, as the changes in anthropometry showed better results for the multidisciplinary treatment group. It can be hypothesized that the documentation or measurement of diet and physical activity has not been sensitive enough to detect differences, as has been described in literature.[15,16]

A successful treatment program for reversing overweight and obesity in young children is important as tracking of obesity has been demonstrated.[7] Consequently, an elevated BMI in adolescence is a clear risk factor for obesity-related disorders in midlife.[17] Besides possible health risks at a later age, obese and overweight children may have health problems already at a young age. MS has been described in childhood,[18] and complications of obesity in obese prepubertal children have been demonstrated.[19]

Long-lasting positive effects of treatment programs for overweight and obese children are difficult to realize. It has been demonstrated that younger children generally achieve larger reductions in BMI SDS in weight management programs.[20] However, little is known about the effects of multidisciplinary intervention programs in overweight and obese preschool children.[21] A randomized, controlled trial in 18 obese children aged 2-5 years, showed a decrease in BMI-z in the intervention group, compared with an increase in the control group, at post-treatment and 12 months follow-up.[22] For children aged 5-12 years, the best results have been achieved in multidisciplinary programs aimed at changing lifestyle.[6] Hughes et al. demonstrated in 5- to 11-year-old overweight children that family-centered counselling and behavioral strategies to modify diet, physical activity and sedentary behavior, had modest benefits on physical activity and sedentary behavior, but did not have a significant effect on BMI-z, compared with a standard care program.[23] A 12-month randomized, controlled trial in 6-9 year old overweight children involving parenting-skills training, showed a reduction in BMI-z and WC-z, particularly in boys.[24] The present study clearly shows that a combined lifestyle intervention program can result in an important improvement in anthropometry and body composition, already in overweight and obese preschool children. Furthermore, the results of this multidisciplinary treatment program are more pronounced, compared with the usual-care program. Still, it has to be shown if this positive effect remains in the years after the treatment program has ended.

An important result of the present study is the positive effect on the reduction of abdominal fat mass in the intervention group, shown by a decrease in WC-z and VF. The reduction of WC-z is of importance, as this better demonstrates abdominal obesity than BMI.[25] One year after start of the treatment program, a reduction in WC-z and VF was shown for children in the intervention group, whereas children in the usual-care group only demonstrated a reduction in WC-z. Comparing both treatment modalities, the decrease in WC and WC-z was thereby more distinct in the group which received the multidisciplinary treatment program. VF showed a trend towards a higher decrease in the children who received the multidisciplinary treatment program. Reduction of abdominal fat mass is important as visceral adipocytes are responsible for the production of adipokines. Adipokines can induce a state of low-grade inflammation,[26] oxidative stress,[27] and MS.[28] Furthermore, visceral obesity is responsible for the development of insulin resistance (IR) and eventually type 2 diabetes.[29] Besides a reduction in VF, children in the multidisciplinary intervention group also had a reduction in abdominal SCF, 16 weeks and 12 months after start of the intervention. The importance of abdominal SCF in oxidative stress, IR and MS has been demonstrated.[30]

In conclusion, we show that a multidisciplinary intervention program for 3- to 5-year-old overweight and obese children has beneficial effects on anthropometry and body composition, compared with a usual-care program. The positive effects of the intervention program remain 12 months after start of the treatment. Especially the effect on parameters for abdominal adipose tissues is important, as this may imply a decreased risk for the development of insulin resistance and metabolic syndrome at a later age. However, additional studies in overweight and obese preschool children and long term follow-up are needed to further elucidate if the positive effects of multidisciplinary treatment programs remain over a longer period of time.

References

1. Van den Hurk K, van Dommelen P, van Buuren S, Verkerk PH, Hirasing RA. Prevalence of overweight and obesity in the Netherlands in 2003 compared to 1980 and 1997. Arch Dis Child 2007;92:992-995.
2. Netherlands Organization for Applied Scientific Research TNO, Leiden, The Netherlands. Factsheet results Fifth Dutch Growth Study. Http://www.tno.nl/. Accessed June 10, 2010.
3. Speiser PW, Rudolf MC, Anhalt H, Camacho-Hubner C, Chiarelli F, Eliakim A, et al. Consensus statement: Childhood obesity. J Clin Endocrinol Metab 2005;90:1871-1887.
4. Jago R, Baranowski T, Baranowski JC, Thompson D, Greaves KA. BMI from 3-6 y of age is predicted by TV viewing and physical activity, not diet. Int J Obes 2005;29:557-564.
5. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002;360:473-482.
6. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury V.A, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev 2009;CD001872.
7. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. Int J Pediatr Obes 2009;4:281-288.
8. Gordon-Larsen P, The NS, Adair LS. Longitudinal trends in obesity in the United States from adolescence to the third decade of life. Obesity (Silver Spring) 2010;18:1801-1804.
9. Jouret B, Ahluwalia N, Dupuy M, Cristini C, Nègre-Pages L, Grandjean H, et al. Prevention of overweight in preschool children: results of kindergarten-based interventions. Int J Obes 2009;33:1075-1083.
10. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-1243.
11. Fredriks AM, van Buuren S, Fekkes M, Verloove-Vanhorick SP, Wit JM. Are age references for waist circumference, hip circumference and waist-hip ratio in Dutch children useful in clinical practice? Eur J Pediatr 2005;164:216-222.
12. Horlick M, Arpadi SM, Bethel J, Wang J, Moye J Jr, Cuff P, et al. Bioelectrical impedance analysis models for prediction of total body water and fat-free mass in healthy and HIV-infected children and adolescents. Am J Clin Nutr 2002;76:991-999.
13. Stolk RP., Wink O, Zelissen PM, Meijer R, van Gils AP, Grobbee DE. Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. Int J Obes Relat Metab Disord 2001;25:1346-1351.
14. De Lucia Rolfe E, Sleigh A, Finucane FM, Brage S, Stolk RP, Cooper C, et al. Ultrasound measurements of visceral and subcutaneous abdominal thickness to predict abdominal adiposity among older men and women. Obesity (Silver Spring) 2010;18:625-631.
15. Maffeis C, Schutz Y, Zaffanello M, Piccoli R, Pinelli L. Elevated energy expenditure and reduced energy intake in obese prepubertal children: paradox of poor dietary reliability in obesity? J Pediatr 1994;124:348-354.
16. Sijtsma A, Sauer PJ, Stolk RP, Corpeleijn E. Is directly measured physical activity related to adiposity in preschool children? Int J Pediatr Obes 2011;6:389-400.
17. Tirosh A, Shai I, Afek A, Dubnov-Raz G, Ayalon N, Gordon B, et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. N Engl J Med 2011;364:1315-1325.
18. Calcaterra V, Klersy C, Muratori T, Telli S, Caramagna C, Scaglia F, et al. Prevalence of metabolic syndrome (MS) in children and adolescents with varying degrees of obesity. Clin Endocrinol (Oxf) 2008;68:868-872.
19. D'Adamo E, Impicciatore M, Capanna R, Marcovecchio ML, Masuccio FG, Chiarelli F, et al. Liver steatosis in obese prepubertal children: a possible role of insulin resistance. Obesity (Silver Spring) 2008;16:677-683.
20. Sabin MA, Ford A, Hunt L, Jamal R, Crowne EC, Shield JP. Which factors are associated with a successful outcome in a weight management programme for obese children? J Eval Clin Pract 2007;13:364-368.
21. Kuhl ES, Clifford LM, Stark LJ. Obesity in preschoolers: behavioral correlates and directions for treatment. Obesity (Silver Spring) 2012;20:3-29.
22. Stark LJ, Spear S, Boles R, Kuhl E, Ratcliff M, Scharf C, et al. A pilot randomized controlled trial of a clinic and home-based behavioral intervention to decrease obesity in preschoolers. Obesity (Silver Spring) 2011;19:134-141.
23. Hughes AR, Stewart L, Chapple J, McColl JH, Donaldson MD, Kelnar CJ, et al. Randomized, controlled trial of a best-practice individualized behavioral program for treatment of childhood overweight: Scottish Childhood Overweight Treatment Trial (SCOTT). Pediatrics 2008;121:e539-e546.
24. Golley RK, Magarey AM, Baur LA, Steinbeck KS, Daniels LA. Twelve-month effectiveness of a parent-led, family-focused weight-management program for pre-pubertal children: a randomized, controlled trial. Pediatrics 2007;119:517-525.

25. Daniels SR, Khoury PR, Morrison JA. Utility of different measures of body fat distribution in children and adolescents. Am J Epidemiol 2000;152:1179-1184.
26. Tamakoshi K, Yatsuya H, Kondo T, Hori Y, Ishikawa M, Zhang H, et al. The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. Int J Obes Relat Metab Disord 2003;27:443-449.
27. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol 2004;24:816-823.
28. Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 2008;28:629-636.
29. Weiss R, Caprio S. The metabolic consequences of childhood obesity. Best Pract Res Clin Endocrinol Metab 2005;19:405-419.
30. Kelly AS, Jacobs DR Jr, Sinaiko AR, Moran A, Steffen LM, Steinberger J. Relation of circulating oxidized LDL to obesity and insulin resistance in children. Pediatr Diabetes 2010;11:552-555.

4

Effect of Obesity Intervention Programs on Adipokines, Insulin Resistance, Lipid Profile and Low-Grade Inflammation in 3- to 5-Year-Old Children

Gianni Bocca[1]
Eva Corpeleijn[2]
Ronald P. Stolk[2]
Bruce H. Wolffenbuttel[3]
Pieter J.J. Sauer[1]

[1] Department of Pediatrics, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[2] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[3] Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Pediatric Research, accepted for publication

Abstract

Background: Childhood obesity can cause the development of cardiovascular risk factors. We assessed the effect of a multidisciplinary intervention program on cardiovascular risk factors and compared this effect with a usual-care program in 3- to 5-year-old overweight or obese children.

Methods: Seventy-five children were randomly assigned to a multidisciplinary intervention or a usual-care program. Anthropometry, body composition and abdominal adipose tissue were assessed at the start and end of a 16-week program. Concurrently, fasting concentrations of serum lipids, glucose, insulin, HbA1c, leptin, adiponectin, hsCRP, TNFα and IL-6 were determined.

Results: In both groups insulin sensitivity improved, demonstrated by decreased insulin concentrations and a decreased HOMA2-IR. In the multidisciplinary intervention group, there was also a decrease of HbA1c and TNFα. In the usual-care group, an increase in glucose concentrations was found. Comparing both groups, changes over time were not different, besides trends in the decrease in total cholesterol and TNFα, in favor of the multidisciplinary intervention group. Combining the results of both groups, a correlation was found between the decrease in body fat percentage (BF%), and both HOMA2-IR and triglyceride concentrations.

Conclusions: In 3- to 5-year-old children, both obesity intervention programs improved insulin sensitivity, in parallel with a reduced BF%.

Introduction

Recent data have shown that the prevalence of childhood overweight and obesity in the Netherlands is still increasing.[1] Childhood obesity is a risk factor for the development of insulin resistance (IR), dyslipidemia and hypertension at a later age, together described as metabolic syndrome (MS).[2] MS cannot be diagnosed in children under the age of 10 years.[3] However, increased concentrations of the separate components of MS have already been demonstrated in children 6 to 9 years old.[4]

Systemic low-grade inflammation may be an underlying cause of MS, induced by the release of inflammatory cytokines from adipose tissue, and even more so from visceral adipose tissue.[5,6] Increased concentrations of TNFα, high-sensitive c-reactive protein (hsCRP) and IL-6 have been found in obese children aged 9-13 years.[7,8] The adipose tissue hormone adiponectin has anti-inflammatory properties, demonstrated by the significant inverse correlation with markers of inflammation in obese children.[8] Whether these deleterious processes related to obesity are already present in overweight and obesity at a very young age is unknown, and no data on systemic low-grade inflammation are available in very young obese children.

Multidisciplinary lifestyle intervention programs for obese children have proven to be successful in reducing weight.[9] Recent studies demonstrated that weight loss in obese children aged 6-11 years also reduced low-grade inflammation and IR.[4,8] In obese children, 9-13 years old, weight loss over a 1-year period led to a significant decrease in triglyceride concentrations and an improvement of an indicator of insulin sensitivity (HOMA-IR).[7] This study did not show a significant correlation between changes in inflammatory parameters and changes in lipids and HOMA-IR. Significant weight loss can lead to increased concentrations of adiponectin, as has been demonstrated in obese children 6-15 years old.[10]

Little is known about the effects of a successful treatment program for obesity on markers of low-grade inflammation, lipid profile, IR and adipokines in preschool-aged children. We assessed the effects of a 16-week multidisciplinary intervention program, aimed at reducing BMI, on inflammatory parameters, lipid profile, IR and adipokines, in 3-year-old to 5-year-old overweight or obese children, and compared the results with a group of overweight or obese children receiving a usual-care program.

Methods

Children and parents participated in a randomized controlled clinical trial, called "Groningen Expert Center for Kids with Obesity (GECKO)-Outpatient Clinic". Details on this study have been described previously.[11] In brief, children aged 3-5 years were referred to the outpatient clinic by youth health care physicians, general practitioners or other physicians if they had a BMI z-score > 1.1. Children with medical conditions causing obesity, eating disorders, mental retardation or behavioral problems were excluded from the study. Enrollment took place from October 2006 to March 2008, and a total of 75 children were included.

Children and their parents were randomly assigned to a multidisciplinary intervention or a usual-care program. The outline of both programs is given in table 1.

Table 1. Schematic representation of weekly activities in the multidisciplinary intervention and usual-care groups.

Multidisciplinary intervention group	baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Measurements	v																v
Dietary advice by dietician		v	v		v				v			v			v		
Physical activity session by physiotherapist				v	v	v	v	v	v	v	v	v	v	v	v		
Parental behavioral therapy by psychologist						v		v		v		v		v		v	
Usual-care group	baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Measurements	v																v
Visit to resident in pediatrics			v					v					v				

Numbers indicate the weeks of the program.

The multidisciplinary intervention program consisted of dietary advice, physical activity sessions and psychological counselling for parents. Dietary advice, 6 sessions of 30 minutes each, was given by a dietician and focused on improving eating behavior by setting personal goals for parents and children. Feedback was given on these goals using food diaries. Physical activity, 12 sessions of 60 minutes each, were supervised by a physiotherapist and resembled elementary school exercise, including ball playing and dancing to music. An active lifestyle was propagated during these activity sessions. Psychological counselling for parents, 6 sessions of 120 minutes each, was given by a psychologist and aimed at teaching parents to be a healthy role model, thereby demonstrating a healthy lifestyle to their children. In the usual-care program, children and parents were seen by a resident in pediatrics (3 sessions of 30-60 minutes each) who advised on healthy eating and physical activity. In total, both programs lasted 16 weeks. Written informed consent was obtained from the parents or legal caretakers. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

At the start and at the end of the treatment period, anthropometry and assessment of body composition were performed. Height and weight were measured using standard calibrated stadiometers and scales and used to calculate BMI. Waist circumference (WC) was measured using a standard measuring tape, at the midpoint between the lateral iliac crest and the lowest rib. The web-based program Growth Analyser 3 (Growth Analyser B.V., Rotterdam, the Netherlands) was used to calculate age- and gender-specific z-scores for BMI (BMI-z) and WC (WC-z). Body composition, i.e. fat-free mass (FFM) and body fat percentage (BF%), was assessed by bio-impedance analysis (BIA) (BIA-101, Akern S.r.l./RJL Systems, Florence, Italy) and measurements of visceral fat (VF) and abdominal subcutaneous fat (SCF) were performed using ultrasound (SonoSite Titan, SonoSite, Inc., Bothell, WA).[12]

Blood was drawn after an overnight fast, at the start and end of the treatment period. An enzymatic colorimetric method (Roche Modular, Mannheim, Germany) was used to determine total cholesterol (T (C)), HDL (C), LDL (C) and triglycerides (TG). HbA1c was determined using a high-performance liquid chromatography method (Bio-Rad Variant, Bio-Rad Laboratories, Veenendaal, the Netherlands), insulin by radioimmunoassay (Diagnostic Systems Laboratories, Inc., Webster, TX) and glucose by an enzymatic method (hexokinase-mediated reaction, Roche Modular, Mannheim, Germany). The updated homeostasis model assessment of IR (HOMA2-IR) was used to calculate IR.[13] For markers of low-grade systemic inflammation, high-sensitive c-reactive protein (hsCRP) was determined by a nephelometric method (BN II system, Siemens Healthcare Diagnostics B.V., Breda, the Netherlands). Serum concentrations of leptin, IL-6 and TNFα were simultaneously measured by a combination ELISA (Milliplex Map Human Adipokine Panel B, Millipore, St. Charles, MN). Serum concentrations of adiponectin were quantified by ELISA (Millipore).

Statistical analysis was performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL). Distribution of normality was tested using the one-sample Kolmogorov-Smirnov test. For within-group differences, a paired sample Students T-test was used for normally distributed variables. For variables not normally distributed, a related-samples Wilcoxon Signed Rank test was used. For differences between groups, the independent Students T-test was used for variables with a normal distribution and the Mann-Whitney test for not normally distributed variables. To assess the association between changes over time of various variables, the difference over time was calculated as variable at baseline minus variable at 16 weeks. All differences over time were normally distributed. Then, Pearson correlation coefficients were calculated. The significance level of all tests was 0.05. To further explore the underlying structure of the correlation in changes in cardiovascular risk factors after the obesity intervention, we performed exploratory factor analysis. Factors were attributed to variables with correlation > 0.55, and variables with correlation > 0.3 are mentioned.

Results

During the treatment period 13 children were lost to follow-up, 7 children in the multidisciplinary intervention group and 6 children in the usual-care group. Children who were either lost to follow-up or stopped the study had a slightly lower BMI compared with children who continued the study. However, this difference was not statistically significant. At the end of the treatment period, children in the multidisciplinary intervention group showed a larger decrease in BMI (-1.2 (1.0) kg/m^2, mean (SD) vs. -0.6 (1.1)), BMI-z (-0.5 (0.4) vs. -0.3 (0.4)) and WC-z (-0.3 (0.5) vs. 0.0 (0.6)) compared with children in the usual-care group, as previously described.[11] Also, children in the multidisciplinary intervention group showed a statistically significant decrease in BF% (-1.5 (3.4)), in contrast to no statistically significant decrease observed in the usual-care group (-0.3 (4.0)). However, the mean difference in the change in BF% between both groups was not statistically significant.[11] Table 2 shows the details at baseline on serum lipids, parameters for glucose metabolism, markers for low-grade systemic inflammation and adipokines, for the multidisciplinary intervention group and usual-care group. At baseline, there were no significant differences for these parameters between the two groups.

Table 2. Descriptive and anthropometric characteristics, serum lipids, adipokines and markers for low-grade inflammation and insulin resistance of the study population at baseline.

	Multidisciplinary intervention group (n = 40)	**Usual care group (n = 35)**	***P*-value**
Age (years)	4.6 (0.8)	4.7 (0.8)	0.47
Boys / Girls (n)	12 (30.0%) / 28 (70.0%)	9 (25.7%) / 26 (74.3%)	
Adiposity [11]			
Body mass index z-score	2.7 (1.0)	2.7 (1.0)	0.77
Waist circumference z-score	2.7 (1.0)	2.7 (1.0)	0.95
Body fat percentage	29.0 (7.8)	28.6 (6.3)	0.80
Fat-free mass (kg)	19.7 (2.4)	19.7 (3.6)	0.97
Visceral fat (cm)	4.4 (1.4)	4.3 (0.8)	0.65
Subcutaneous fat (cm)	1.8 (0.7)	1.7 (0.7)	0.64
Lipids			
T (C) (mg/dL)	150.8 (23.1)	146.7 (23.9)	0.46
HDL (C) (mg/dL)	51.1 (8.9)	47.5 (11.8)	0.13
LDL (C) (mg/dL)	96.7 (21.6)	94.7 (20.2)	0.69
TG (mg/dL)	63.6 (23.4)	75.3 (41.3)	0.13
Glucose metabolism			
Glucose (mg/dL)	75.6 (5.1)	74.9 (7.5)	0.67
Insulin (mU/L)	8.1 (4.3)	7.6 (3.8)	0.67
HOMA2-IR	1.0 (0.5)	1.0 (0.5)	0.68
HbA1c (%)	5.3 (3.3 - 6.0)	5.3 (4.5 - 5.8)	0.78
Inflammation / adipokines			
Adiponectin (ng/mL)	18.9 (5.0)	17.6 (4.3)	0.26
Leptin (ng/mL)	5.7 (1.5 - 40.8)	8.4 (0.9 - 47.4)	0.43
hsCRP (mg/L)	1.0 (0.1 - 8.7)	0.9 (0.1 - 8.7)	0.54
TNFα (pg/mL)	3.0 (1.1 - 26.1)	2.8 (1.2 - 7.9)	0.60
IL-6 (pg/mL)	1.3 (0.3 - 4.3)	0.6 (0.3 - 7.1)	0.23

Normal distributed variables are expressed as mean (±SD); not normally distributed variables are expressed as median (minimum - maximum). For differences between groups, the independent Students T-test was used for variables with a normal distribution and the Mann-Whitney test for not normally distributed variables.

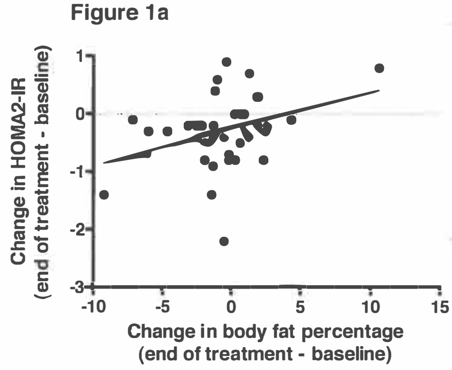
Table 3 shows the changes in parameters for glucose metabolism, markers for low-grade systemic inflammation, adipokines and serum lipids for both groups, between baseline and end of the 16-week treatment program, and the difference in the change in these parameters between the groups. In the multidisciplinary intervention group, a statistically significant decrease in insulin, HOMA2-IR, HbA1c and TNFα was found. IL-6 showed a trend towards a statistically significant decrease (p = 0.09). In the usual-care group, decreases were only found for insulin and HOMA2-IR, in parallel with a small but statistically significant increase in serum glucose (4.4 mg/dL). Comparing both groups, changes over time were not significantly different apart for trends in the decrease in T (C) (p = 0.07) and TNFα (p = 0.06) which almost reached statistical significance in favor of the multidisciplinary intervention group.

Table 3. Changes in lipids, adipokines and markers for low-grade inflammation and insulin resistance, between baseline and end of the 16-week treatment program.

	Multidisciplinary intervention group		Usual care group		Difference between groups	
	Mean difference (SD)	*P*-value	Mean difference (SD)	*P*-value	Mean (SD)	*P*-value
T (C) (mg/dL)	-2.5 (16.2)	0.38	6.4 (20.3)	0.11	8.9 (4.7)	0.07
HDL (C) (mg/dL)	-0.2 (9.6)	0.89	0.7 (9.5)	0.70	0.9 (2.5)	0.71
LDL (C) (mg/dL)	-3.6 (15.3)	0.19	3.0 (17.1)	0.36	6.7 (4.2)	0.12
TG (mg/dL)	-1.8 (19.5)	0.60	-4.8 (35.5)	0.48	3.0 (7.3)	0.68
Glucose (mg/dL)	1.9 (7.1)	0.21	4.4 (8.9)	0.03	2.5 (2.3)	0.29
Insulin (mU/L)	-2.2 (4.0)	0.01	-2.9 (4.8)	0.01	0.6 (1.3)	0.63
HOMA2-IR	-0.3 (0.5)	0.02	-0.4 (0.6)	0.01	0.1 (0.2)	0.65
HbA1c (%)	-0.3 (0.5)	0.01	-0.1 (0.5)	0.42	0.2 (0.1)	0.12
Adiponectin (ng/mL)	-0.9 (3.9)	0.22	-1.3 (4.0)	0.08	0.5 (1.0)	0.64
Leptin (ng/mL)	-1.4 (6.8)	0.25	-1.3 (9.6)	0.46	0.1 (2.1)	0.98
hsCRP (mg/L)	-0.2 (2.7)	0.73	-0.3 (3.0)	0.63	0.1 (0.8)	0.87
TNFα (pg/mL)	-2.5 (4.9)	0.01	-0.4 (3.1)	0.48	2.1 (1.1)	0.06
IL-6 (pg/mL)	-0.4 (1.3)	0.09	0.0 (1.0)	0.83	0.4 (0.3)	0.23

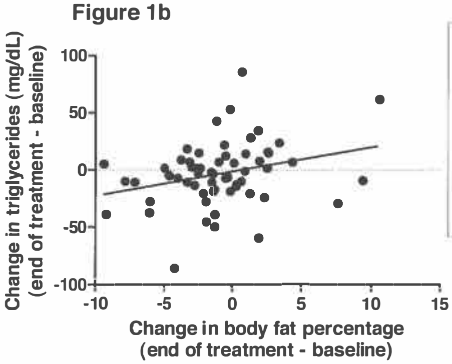
Positive numbers indicate an increase over time. For within-group differences, a paired sample Students T-test was used for normally distributed variables. For variables not normally distributed, a related-samples Wilcoxon Signed Rank test was used.

We investigated in an observational manner whether the changes over time in measures of adiposity were related to improvements in cardiovascular risk factors. These analyses were performed in children from both treatment groups together, since children lost weight in both programs. Moreover, there were no differences between these variables at baseline. Regarding parameters for glucose metabolism, statistically significant correlations were found between the decrease in BF% and decrease in insulin (r = 0.352; p = 0.02) and between the decrease in BF% and improvement in HOMA2-IR (r = 0.365; p = 0.02) (Figure 1a). There were no statistically significant correlations between changes in VF and changes in insulin concentrations (r = 0.011; p = 0.94) and HOMA2-IR (r = 0.026; p = 0.87).



Pearson correlation coefficient between the change in body fat percentage and the change in the updated HOMA-IR, between baseline and end of the treatment period. $P = 0.02$; $r^2 = 0.133$.

Concerning the lipid profile, a decrease in BF% correlated with a decrease in serum TG ($r = 0.290$; $p = 0.02$) (Figure 1b), mainly due to a correlation between changes in SCF and TG ($r = 0.273$; $p = 0.04$).



Pearson correlation coefficient between the change in body fat percentage and the change in serum triglycerides (mg/dL), between baseline and end of the treatment period. $P = 0.02$; $r^2 = 0.084$.

No statistically significant correlations were present between a decrease in VF and a decrease in T (C) ($r = 0.187$; $p = 0.15$) and TG ($r = 0.085$; $p = 0.52$). Statistically significant correlations were found between changes in leptin concentrations and changes in BMI-z ($r = 0.535$; $p < 0.001$), WC-z ($r = 0.323$; $p = 0.01$), VF and BF% (both $r = 0.345$; $p = 0.01$). No correlation was found between changes in BF% and changes in adiponectin concentrations ($r = -0.181$; $p = 0.16$).

Regarding associations between parameters for glucose metabolism and markers for inflammation and adipokines, statistically significant correlations were found between changes in leptin concentrations and changes in insulin concentrations ($r = 0.367$; $p = 0.01$)

and HOMA2-IR (r = 0.372; p = 0.01). Also, a decrease in hsCRP concentrations showed a correlation with a decrease in HOMA2-IR (r = 0.359; p = 0.03) and with a decrease in insulin concentrations (r = 0.360; p = 0.02). For associations between serum lipids and markers for low-grade systemic inflammation, an inverse correlation was found between changes in IL-6 and changes in serum HDL (C) (r = -0.311; p = 0.02) and between the change in IL-6 and change in T (C) (r = -0.346; p = 0.01).

In the factors analysis, we included changes in BMI-z, leptin, adiponectin, HOMA2-IR, HDL (C), T (C) and TG, TNFα, IL-6 and hsCRP. LDL (C) was excluded because it inhibited the elimination process. The factor analysis was performed several times with in- and excluding several factors, to check for stability of the analysis. The final model included all variables but LDL (C), and resulted in 4 factors with eigenvalue >1 that together explained 53% of the variance, i.e. a leptin/BMI factor (17%), a T (C) factor (13%) that also included HDL (C) and TNFα, a TG factor (13%) with HDL (C) and HOMA2-IR, and a IL-6/hsCRP factor (10%) that also included HOMA2-IR.

Discussion

This study shows that both obesity treatment programs in 3-year-old to 5-year-old children resulted in improved insulin sensitivity. In the children receiving the multidisciplinary intervention program TNFα, an indicator of low-grade systemic inflammation, decreased. When combining both groups, strong correlations were found between improvements in parameters for glucose metabolism and lipid profile, with improvements in body composition. Also, correlations were found between a decrease in inflammatory markers, and improvements in lipid profile and glucose metabolism.

The importance of reducing IR in lowering metabolic risk factors in children has been demonstrated in a previous study.[14] A decrease in HOMA-IR correlated with a decrease in TG, independently of changes in weight status, thereby emphasizing the role of IR in the development of cardiovascular risk factors. The association between reduced body fat and decreased insulin resistance was further illustrated by a prospective cohort study in obese children, 9 to 17 years old.[15] In obese Hispanic adolescents participating in an exercise program, a decrease in visceral fat also decreased IR.[16] Our data confirm these findings and show that this association is already present in very young children.

Obesity related dyslipidemia, already described in childhood, increases the risk on the development of atherosclerosis.[17] Lifestyle intervention programs are recommended to treat child and adolescent overweight and obesity.[18] To date, little is known about the effect of lifestyle intervention programs on lipid profiles in preschool-aged children. Recently, it was shown that a 13-week multicomponent wellness intervention program in, on average 16-year-olds, led to a 15% increase in HDL (C) concentrations, despite a lack of decrease in BMI.[19] In 9-year-old to 13-year-old obese children, weight loss over a one-year period was associated with a significant decrease of TG concentrations.[7] Our study in 3-year-old to 5-year-old overweight and obese children shows that a reduction in abdominal SCF and BF% is associated with a decrease in TG concentrations. These results may imply that treatment programs in preschool-aged overweight and obese children can prevent a cumulative lifetime exposure to increased risk factors for CVD.

The present study also shows that a multidisciplinary intervention program in preschool-aged overweight and obese children has positive effects on one of the markers of low-grade systemic inflammation, TNFα. Positive effects of a reduction in BMI on TNFα have been described in obese children with a mean age of 10.7 years.[8] In contrast, no effect on TNFα concentrations was observed in 9-year-old to 13-year-old obese children who experienced a decrease in BMI-SDS of ≥ 0.5 over a 1-year period.[7] For comparison, in the present study the decrease in the multidisciplinary treatment group was 0.5 SD over 16 weeks, and 0.3 SD in the usual-care group. A significant decrease in CRP and IL-6 concentrations was demonstrated in 24 obese children, 6 to 9 years old, who obtained a decrease in BMI-SDS of ≥ 0.5 over a period of 9 months.[4] This could not be confirmed by our data, although the decrease in IL-6 concentrations in the multidisciplinary intervention group showed a trend towards statistical significance.

Obesity can have effects on cardiovascular risk profile and IR through several mechanisms. The two most well-known pathways are adipocyte dysfunction/inflammation and lipotoxicity/ ectopic fat disposition.[20] Inflammatory factors have been shown to induce IR in several tissues by interacting with the insulin signaling pathway.[21,22] An obesity-related profile of inflammation and adipocyte dysfunction is often found in parallel with impairments in lipid metabolism.[23] Elevated FFA are thought to play an important role, since higher circulating fatty acids may induce intramyocellular lipid accumulation, directly inducing IR in skeletal muscle and impairing substrate utilization.[24] All of these processes are well-described in adults. It is surprising to see that even at a very young age these processes are ongoing.

Since it can be hypothesized that the pathophysiological pathways could still be different at this young age, we explored the data using factor analysis. The finding that 43% of the variance was explained by a factor dominated by changes in leptin/BMI, T (C) and TG suggests that changes in lipotoxicity concomitant with a reduction in leptin are the most important changes with weight loss in 3 to 5-year-olds. The remaining factor was dominated by changes in IL-6 and hsCRP (10%) suggesting that also inflammation plays a role, but to a lesser extent, and that it is not strongly intertwined with the lipotoxicity pathway. Of course, these factors are exploratory in nature and should only be interpreted as hypothesis-generating.

Strong points of this study are the young age of the children and the range in degree of obesity of the study participants. Until present time, no data were available on the effect of obesity intervention programs on cardiovascular risk factors in preschool-aged children. Our data may imply that children with overweight or obesity at this young age will benefit from obesity intervention programs with respect to reducing the risk of developing MS in adulthood. Furthermore, since children in our study were either overweight or obese, the results on adipokines, IR, lipid profile and low-grade inflammation can be generalized to a larger extent, in contrast to studies only reporting on children with extremes in obesity.

A weak point of the study was the limited power to detect more differences between baseline and the end of the treatment program. Due to low power for changes in leptin, adiponectin, HDL (C), IL-6 and hsCRP, the lack of significant effects should be interpreted with care. Nevertheless, we feel that our data clearly show beneficial effects of both obesity treatment programs in preschool-aged children. Also, the present study did not include a control group of non-overweight children to determine if the results of the parameters are different from a normal population or to evaluate if there is a change over time in children without overweight. It was our intention to evaluate the effect of an intervention program in overweight or obese children. Therefore we did not include children without overweight.

In addition, the use of BIA to estimate BF% and the use of ultrasound to measure abdominal fat have some limitations, although discriminatory power for repeated measurements is good. Moreover, it has been demonstrated in 6-year-old children that BIA is reliable in assessing fat mass.[25] Furthermore, the use of ultrasound to measure abdominal adiposity has been validated in adults,[12] and proven its reliability in assessing subcutaneous abdominal fat in 6-year-old to 7-year-old children.[26]

In conclusion, the present study shows that obesity treatment programs in 3-year-old to 5-year-old children have beneficial effects on insulin sensitivity and that, already in very young children, a reduction in body fat improves insulin sensitivity. In the multidisciplinary intervention group, next to improved insulin sensitivity, we also found a reduction in TNFα concentrations. It can be hypothesized that the improvement in these parameters may diminish the increased cumulative lifetime exposure to risk factors related to childhood obesity, thereby reducing MS and CVD risk in adulthood. Prospective studies are needed to further explore the effects of different treatment programs for overweight and obesity in preschool children, on parameters leading to MS later in life.

References

1. Schönbeck Y, Talma H, van Dommelen P, Bakker B, Buitendijk SE, Hirasing RA, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. PLoS One 2011;6:e27608.
2. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002;360:473-482.
3. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al; IDF Consensus Group. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007;8:299-306.
4. Martos R, Valle M, Morales RM, Cañete R, Gascón F, Urbano MM. Changes in body mass index are associated with changes in inflammatory and endothelial dysfunction markers in obese prepubertal children after 9 months of body mass index SD score loss. Metabolism 2009;58:1153-1160.
5. Roth CL, Reinehr T. Roles of gastrointestinal and adipose tissue peptides in childhood obesity and changes after weight loss due to lifestyle intervention. Arch Pediatr Adolesc Med 2010;164:131-138.
6. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes 2007;56:1010-1013.
7. Reinehr T, Stoffel-Wagner B, Roth CL, Andler W. High-sensitive C-reactive protein, tumor necrosis factor , and cardiovascular risk factors before and after weight loss in obese children. Metabolism 2005;54:1155-1161.
8. Roth CL, Kratz M, Ralston MM, Reinehr T. Changes in adipose-derived inflammatory cytokines and chemokines after successful lifestyle intervention in obese children. Metabolism 2011;60:445-452.
9. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev 2009;CD001872.
10. Reinehr T, Roth C, Menke T, Andler W. Adiponectin before and after weight loss in obese children. J Clin Endocrinol Metab 2004;89:3790-3794.
11. Bocca G, Corpeleijn E, Stolk RP, Sauer PJ. Results of a multidisciplinary treatment program in 3-year-old to 5-year-old overweight or obese children. A randomized controlled clinical trial. Arch Pediatr Adolesc Med 2012;166:1109-1115.
12. Stolk RP, Wink O, Zelissen PM, Meijer R, van Gils AP, Grobbee DE. Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. Int J Obes Relat Metab Disord 2001;25:1346-1351.,
13. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-1495.
14. Reinehr T, de Sousa G, Andler W. Longitudinal analyses among overweight, insulin resistance, and cardiovascular risk factors in children. Obes Res 2005;13:1824-1833.
15. Ford AL, Hunt LP, Cooper A, Shield JP. What reduction in BMI SDS is required in obese adolescents to improve body composition and cardiometabolic health? Arch Dis Child 2010;95:256-261.
16. Van der Heijden GJ, Wang ZJ, Chu ZD, Sauer PJ, Haymond MW, Rodriguez LM, et al. A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. Obesity (Silver Spring) 2010;18:384-390.
17. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338:1650-1656.
18. Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics 2007;120 Suppl 4:S164-192.
19. Hardy OT, Wiecha J, Kim A, Salas C, Briceno R, Moody K, et al. Effects of a multicomponent wellness intervention on dyslipidemia among overweight adolescents. J Pediatr Endocrinol Metab 2012;25:79-82.
20. Taubes G. Insulin resistance. Prosperity's plague. Science 2009;325:256-260.
21. Gustafson B, Hammarstedt A, Andersson CX, Smith U. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 2007;27:2276-2283.
22. Arner P. Insulin resistance in type 2 diabetes – role of the adipokines. Curr Mol Med 2005;5:333-339.
23. Weiss R, Kaufman FR. Metabolic complications of childhood obesity: identifying and mitigating the risk. Diabetes Care 2008;31 Suppl 2:S310-316.
24. Corpeleijn E, Saris WH, Blaak EE. Metabolic flexibility in the development of insulin resistance and type 2 diabetes: effects of lifestyle. Obes Rev 2009;10:178-193.
25. Pecoraro P, Guida B, Caroli M, Trio R, Falconi C, Principato S, et al. Body mass index and skinfold thickness versus bioimpedance analysis: fat mass prediction in children. Acta Diabetol 2003;40 Suppl 1:S278-281.
26. Liem ET, De Lucia Rolfe E, L'Abée C, Sauer PJ, Ong KK, Stolk RP. Measuring abdominal adiposity in 6 to 7-year-old children. Eur J Clin Nutr 2009;63:835-841.

5

Quality of Life in 3- to 5-Year-Old Overweight or Obese Children Participating in a Multidisciplinary Intervention Program

Gianni Bocca[1]
Mirije W.B. Kuitert[1]
Boudien C. Flapper[1]
Ronald P. Stolk[2]
Eva Corpeleijn[2]
Pieter J.J. Sauer[1]

[1] Department of Pediatrics, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[2] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Submitted

Abstract

Background: Childhood obesity is rising and may affect health-related quality of life (HRQoL). Effects of obesity treatment in preschool-aged children remain unknown.

Objective: To evaluate the effect of a multidisciplinary intervention program on HRQoL in 3- to 5-year-old overweight or obese children and to assess the association between changes in adiposity and changes in HRQoL.

Methods: Seventyfive children (28% boys, age 4.7±0.8 years, BMI z-score 2.7±1.0) were randomized to a multidisciplinary intervention or to a usual-care program, both lasting 16 weeks. The multidisciplinary intervention consisted of dietary advice (6 times), 12 exercise sessions and, for parents only, 6 psychological counseling sessions. Participants in the usual-care program visited a pediatrician 3 times, who advised on a healthy lifestyle. At baseline, after 16 weeks and 12 months, anthropometry was performed and parents completed DUX-25 and CHQ-PF50 questionnaires. Non-parametric statistical tests were used.

Results: At 12 months follow-up, children in the multidisciplinary intervention group showed a positive change in HRQoL, compared with the usual-care group (median 5.0 vs. -4.5, respectively, $p = 0.04$), especially for the physical domain (8.3 vs. -4.2, respectively, $p = 0.03$). For both groups combined, a decreased BMI z-score over 12 months was associated with increased "global health" ($r = -0.36$, $p = 0.03$). Reduced visceral fat was correlated with increased "global health" ($r = -0.37$, $p = 0.03$), "general behavior" ($r = -0.41$, $p = 0.01$), and "general health" ($r = -0.43$, $p = 0.01$).

Conclusions: A multidisciplinary intervention program in 3- to 5-year-old overweight or obese children had beneficial effects on HRQoL. A reduction in obesity parameters was associated with an increase in several HRQoL aspects.

Introduction

In the Netherlands, as is seen worldwide, childhood obesity is still becoming more prevalent.[1] At present, the prevalence of overweight in Dutch boys between the ages of 3 to 5 years is 7.8 to 12.8% and in Dutch girls 12.8 to 18.1%.[1] For obesity, the prevalence in Dutch boys and girls aged 3 to 5 years is 0.8-2.0% and 1.6-3.3%, respectively.[1] A high-fat diet and excess caloric intake contribute to the increase in childhood obesity.[2] Children with overweight or obesity are at risk to develop physical and psychological health problems.[3] Moreover, childhood obesity and its complications tend to persist into adolescence and adulthood,[4,5] demonstrating the urgent need to treat obesity at a young age.

Literature on the consequences of obesity or its treatment on the physical, emotional, and social well-being of obese children is emerging.[6,7] Lower general health scores have been reported in obese children 5-13 years old.[8] In obese children 8-11 years old, lower psychosocial health has been described compared with non-obese children.[9] Severely obese children aged 5-18 years were shown to report a lower health-related quality of life (HRQoL) compared with healthy children, and even as low as those in children diagnosed with cancer.[10] Data on HRQoL in preschool-aged obese children are, however, scarce.[11]

A Cochrane review showed that a multidisciplinary approach in the treatment of obese children 5-12 years old can result in an important weight reduction.[12] Although the association between obesity and quality of life is clearly recognized in children, the effect of obesity treatment on quality of life outcomes has not been extensively studied. Positive effects of a multidisciplinary cognitive behavioral treatment program on HRQoL were demonstrated by a randomized controlled study in 79 obese children with a mean age of 13 years.[13] After a 12-month follow-up period, an improved HRQoL was shown in the children receiving the multidisciplinary intervention program, while HRQoL remained unchanged in the control group.[13] Another study demonstrated positive effects of an outpatient training program on HRQoL in 74 overweight children with a mean (SD) age of 11.6 (1.7) years, during the 6-month treatment program as well as during a 12-month follow-up period.[14] However, consistent associations between weight reduction and improved HRQoL were not present in this study.[14] Focusing on a healthy lifestyle may also have negative psychological effects, as health programs in elementary school have been shown to increase anxieties about body weight.[15] At present, it remains largely unknown what the effects of a multidisciplinary obesity treatment program are on HRQoL in preschool-aged children.

The aim of our study was to assess the effect of a multidisciplinary intervention program in 3- to 5-year-old overweight or obese children on HRQoL and to compare the effect with a group of overweight or obese children receiving a usual-care treatment program. Furthermore, associations between changes in anthropometric parameters of obesity and changes in HRQoL were assessed. We hypothesized that children receiving the multidisciplinary program would demonstrate a greater improvement in HRQoL, compared with the children receiving the usual-care program. Also, we expected that a decrease in the anthropometric parameters of obesity would be associated with an increase in HRQoL. In addition, we compared the HRQoL in obese children with other populations, i.e. healthy Dutch children, children with asthma, and children with attention deficit hyperactivity disorder (ADHD).

Methods

Details of the study have been described previously.[16] In short, children and their parents were participating in a randomized controlled clinical trial studying the effect of a multidisciplinary lifestyle intervention program on anthropometry and body composition in overweight and obese children 3-5 years old. Children were included in the study if they had a body mass index (BMI) z-score > 1.1. Children with obesity caused by medical problems, and with mental retardation or behavioral problems, were excluded from the study.

In total, 75 children were enrolled in the study and they were randomly assigned to a multidisciplinary intervention or a usual-care program. Both programs lasted 16 weeks. In 6 sessions of 30 minutes, children and parents in the multidisciplinary intervention group received dietary advice by a dietician. Dietary advice consisted of education to improve eating behavior and setting personal goals for children and parents regarding the diet. Feedback was given on these goals on consecutive sessions. Physical activity group sessions (12 times 60 minutes), conducted by a physiotherapist, mimicked elementary school exercise and aimed at improving the child's well-being. Furthermore, parents in the multidisciplinary intervention group received psychological counseling in 6 sessions of 120 minutes each. These sessions were given by a psychologist and aimed at teaching the parents to be a healthy role model and to change family attitudes toward healthy eating and physical activity. Children and parents in the usual-care group were followed up by a resident in pediatrics who, in 3 sessions of 30-60 minutes each, advised on a healthy lifestyle. All measurements were performed at the start and the end of the treatment period, and 12 months after the study started. Anthropometry was performed, body composition was assessed, and parents completed the questionnaires. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen and informed consent was obtained from the parents or legal caretakers.

HRQoL was assessed using the Dutch-Child-AZL-TNO-Quality-of-Life (DUX-25) questionnaire and the Dutch edition of the Child Health Questionnaire-Parent Form (CHQ-PF50). The DUX-25 measures daily activities and contains 25 questions regarding physical, emotional, home, and social items. Possible responses on each question are expressed in 5 abstract faces from happy (score 5) to sad (score 1), thereby constructing a 5-point Likert scale. Domain scores were calculated by adding all single item scores. Then, the total score for that domain was transformed to a 0 to 100 scale, with a higher score indicating a higher quality of life. Originally, the DUX-25 questionnaire was developed to be filled out by parents and by children from the age of 5 years. As our study also contained children under the age of 5 years, all questionnaires were completed by one of the parents. It has been shown that both parent and child reports are valid in HRQoL questionnaires, although children generally report lower scores on physical and motor functioning than their parents do.[17] However, in obese children and adolescents, parents are reported to perceive worse HRQoL than children do about themselves.[18]

The Dutch CHQ-PF50 measures health perception and contains 50 items, divided over 11 multi-scales and 4 single-items questions and addresses the child's physical, emotional and social well-being.[19] Each CHQ scale has 3 to 6 items with 4 to 6 possible responses per item. Total scores for each scale were transformed into a score ranging from 0 to 100, a higher score indicating a higher quality of life.

In order to assess baseline HRQoL of the overweight or obese preschool-aged children in our study, we compared the results with outcomes on DUX-25 and CHQ-PF50 questionnaires in healthy Dutch children,[17,19] children with asthma,[19,20] and children with ADHD.[19,21]

Statistical analysis was performed using IBM SPSS Statistics version 20. Distribution of normality was tested using descriptive analyses and the 1-sample Kolmogorov-Smirnov test. The analysis showed non-normally distributed variables. Therefore non-parametric statistical tests were chosen. To determine within-group differences, the Friedman test was used. Wilcoxon Rank tests were used to follow-up significant main-effects. A Bonferroni correction was applied. To determine differences between groups over time, a Mann-Whitney test was used on the differences between baseline and 16 weeks and between baseline and 12 months. Associations between the changes in parameters of obesity and the changes in HRQoL domains over time were assessed calculating the Spearman's rank correlation coefficient. The level of significance for all main analyses was 0.05, for post-hoc analyses 0.025.

Results

A total of 75 children with a mean (SD) age of 4.7 (0.8) years were included in the study and 40 and 35 children were allocated to the multidisciplinary intervention and usual-care programs, respectively. Children in the multidisciplinary intervention group had a mean (SD) BMI z-score of 2.7 (1.0), a mean waist circumference (WC) z-score of 2.7 (1.0), and a mean body fat percentage (BF%) of 29.0 (7.8). For children in the usual-care group, mean (SD) BMI z-score, WC z-score and BF% were 2.7 (1.0), 2.7 (1.0), and 28.6 (6.3), respectively.[16]

During the intervention period, 7 children in the multidisciplinary intervention group and 6 children in the usual-care group were lost to follow-up. Drop-outs had lower total scores for the DUX-25 questionnaires than the children who continued the study (median (25^{th};75^{th} percentile) 70.0 (72.0;77.0) vs. 87.0 (79.0;94.3), respectively ($p < 0.01$)). Between the end of the treatment period and 12 months after starting both programs, another child in the multidisciplinary intervention group and 4 children in the usual-care group were either lost to follow-up or discontinued the study. The main results of both treatment programs on obesity and body composition have been described previously.[16] At the end of the treatment program and at 12 months from baseline, a statistically larger reduction in mean BMI z-score in the multidisciplinary intervention group, compared with the usual-care group, was demonstrated (0.5 ± 0.4 vs. 0.3 ± 0.4 and 0.6 ± 0.5 vs. 0.3 ± 0.5, at the end of the program and at 12 months follow-up, respectively).

Tables 1a (DUX-25) and 1b (CHQ-PF50) show HRQoL scores in different study populations. According to the DUX-25 scores, the overweight and obese children from our study did not show a lower HRQoL compared with healthy Dutch children, and even reported higher scores. Using the CHQ-PF50 questionnaires, different HRQoL scores between the children in our study and healthy Dutch children were not observed, except for lower "general behavior" and higher "family cohesion" in the overweight or obese children. Compared with children with asthma or behavioral problems, parents of the children in our study generally reported a higher HRQoL, both on the DUX-25 and CHQ-PF50 questionnaires. There were no statistically significant correlations between baseline anthropometric parameters of obesity and baseline HRQoL items in the children participating in our study.

Table 1a. Health-related quality of life in different study populations measured by DUX-25 questionnaires.

	Obese children (present study, n = 75)	Healthy Dutch children[17] (n = 86)	Children with asthma[20] (n = 71)	Children with ADHD[21] (n = 23)
Total	85 (10)	75 (15)	76 (11)	74 (9)
Physical	79 (16)	70 (18)	73 (16)	50 (16)
Home	89 (11)	80 (17)	86 (14)	67 (16)
Emotional	85 (11)	71 (17)	71 (14)	70 (12)
Social	86 (10)	78 (14)	75 (14)	75 (9)

For comparison, data of the present study are expressed as mean (SD).

ADHD, attention deficit hyperactivity disorder.

Table 1b. Health-related quality of life in different study populations measured by CHQ-PF50 questionnaires.

	Obese children (present study, n = 75)	Dutch schoolchildren[19] (n = 353)	Children with asthma[19] (n = 178)	Children with ADHD[19] (n = 83)
Global health	85 (60 ; 85)	n.a.	n.a.	n.a.
Physical functioning	100 (89 ; 100)	100 (100 ; 100)	89 (78 ; 94)	100 (100 ; 100)
Role functioning-				
emotional/behavior	100 (100 ; 100)	100 (100 ; 100)	100 (89 ; 100)	78 (44 ; 95)
physical	100 (100 ; 100)	100 (100 ; 100)	100 (67 ; 100)	100 (100 ; 100)
Bodily pain	90 (80 ; 100)	90 (80 ; 100)	80 (60 ; 100)	100 (70 ; 100)
General behavior	60 (60 ; 85)	80 (70 ; 90)	75 (65 ; 85)	56 (45 ; 65)
Behavior	77 (68 ; 85)	n.a.	n.a.	n.a.
Mental health	85 (75 ; 90)	85 (75 ; 90)	80 (75 ; 85)	65 (55 ; 80)
Self-esteem	79 (75 ; 93)	75 (75 ; 88)	83 (75 ; 96)	63 (50 ; 79)
General health	77 (64 ; 85)	85 (73 ; 93)	56 (44 ; 68)	84 (71 ; 100)
Change in health	50 (50 ; 50)	n.a.	n.a.	n.a.
Parental impact-				
emotional	92 (75 ; 100)	92 (83 ; 100)	75 (58 ; 88)	58 (42 ; 75)
time	100 (89 ; 100)	100 (89 ; 100)	78 (61 ; 92)	95 (90 ; 100)
Family activities	92 (79 ; 100)	95 (90 ; 100)	n.a.	67 (50 ; 80)
Family cohesion	85 (60 ; 100)	60 (60 ; 85)	n.a.	n.a.

Numbers are expressed as median (25^{th};75^{th} percentiles). ADHD, attention deficit hyperactivity disorder. N.a., not available.

Table 2 shows for both groups the baseline scores of the DUX-25 questionnaires and the changes in the scores from baseline to 12 months after the start of the treatment programs.

Table 2. Baseline DUX-25 scores and the changes from baseline to the end of the 16-week treatment program and to 12 months after the start of the intervention.

	Multidisciplinary intervention group			Usual-care group		
	Baseline (n = 37)	16 weeks[a] (n = 31)	12 months[a] (n = 20)	Baseline (n = 32)	16 weeks[a] (n = 28)	12 months[a] (n= 20)
Total	85.0 (74.0 ; 92.5)	-1.0 (-3.0 ; 10.0)	5.0 (-1.8 ; 6.5)[b]	84.5 (77.5 ; 97.0)	-1.0 (-8.5 ; 4.0)	-4.5 (-15.3 ; 4.0)
Physical	81.3 (62.5 ; 94.8)	4.2 (-6.3 ; 12.5)	8.3 (-6.3 ; 16.7)[c]	79.2 (66.7 ; 95.8)	-4.2 (-8.3 ; 8.3)	-4.2 (-12.5 ; 4.7)
Home	90.0 (80.0 ; 95.0)	0.0 (-5.0 ; 10.0)	0.0 (-5.0 ; 5.0)	85.0 (80.0 ; 100)	0.0 (-5.0 ; 0.0)	0.0 (-15.0 ; 10.0)
Emotional	85.7 (78.6 ; 92.9)	1.8 (-8.0 ; 8.0)	0.0 (-3.6 ; 3.6)	85.7 (75.0 ; 96.4)	0.0 (-10.7 ; 3.6)	-3.6 (-17.9 ; 10.7)
Social	87.5 (75.9 ; 92.9)	0.0(-7.1 ; 7.1)	1.8 (-9.8 ; 7.1)	87.5 (81.3 ; 97.3)	0.0 (-7.1 ; 3.6)	-8.9 (-14.3 ; 1.8)

Numbers are expressed as median (25^{th};75^{th} percentiles) at baseline, and as median change (25^{th};75^{th} percentiles) at 16 weeks and 12 months.

[a] Positive numbers indicate an increase over time.

[b] Statistically significant higher increase in the multidisciplinary intervention group compared with the usual-care group (p = 0.04).

[c] Statistically significant higher increase in the multidisciplinary intervention group compared with the usual-care group (p = 0.03).

At baseline, 16 weeks and 12 months, 69 (92.0% of the children), 59 (95.2%), and 40 (70.2%) questionnaires were available for evaluation. Compared with the children in the usual-care group, children in the multidisciplinary intervention group showed a statistically significant increase (medians 5.0 vs. -4.5, p = 0.04) in the total DUX-25 score at 12 months after the start of the treatment program, indicating an increase in HRQoL. This increase in overall HRQoL was expressed in the physical subscale (medians 8.3 vs. -4.2, p = 0.03, for the multidisciplinary intervention and usual-care groups, respectively). Changes over time for the other subscales of the DUX-25 did not differ between the groups.

Regarding the CHQ-PF50, 71 (94.7% of the children), 59 (95.2%), and 40 (70.2%) questionnaires were available for evaluation at the start and the end of the treatment programs, and after 12 months follow-up. Table 3 shows the baseline scores for the CHQ-PF50 questionnaires and the changes over time, for the multidisciplinary intervention and usual-care groups. At the end of the treatment period, a decrease (median -5.0) in the score for the scale "bodily pain" was found in the multidisciplinary intervention group indicating more pain or limitations because of pain, whereas in the usual-care group the score for "bodily pain" remained unchanged (median 0.0). This difference was statistically significant (p = 0.03). Also, between both groups a statistically significant (p = 0.02) change in the scale "mental health" was present at the end of the treatment programs. In the multidisciplinary intervention group, the score for "mental health" had decreased (median -5.0), whereas in the usual-care group the score had increased (median 5.0), indicating less feelings of anxiety and depression in the last group. There were no differences between the groups for changes over time in the other CHQ-PF50 scales between the start and the end of the treatment programs or at 12 months follow-up.

Table 3. Baseline CHQ-PF50 scores and the changes from baseline to the end of the 16-week treatment program and to 12 months after the start of the intervention.

	Multidisciplinary intervention group			Usual-care group		
	Baseline (n = 34)	16 weeks[a] (n = 31)	12 months[a] (n = 20)	Baseline (n = 37)	16 weeks[a] (n = 28)	12 months[a] (n = 20)
Global health	85.0 (60.0 ; 85.0)	0.0 (-3.8 ; 17.5)	0.0 (-12.5 ; 20.0)	85.0 (60.0 ; 85.0)	0.0 (-25.0 ; 0.0)	0.0 (-25.0 ; 0.0)
Physical functioning	100 (91.7 ; 100)	0.0 (-4.2 ; 4.2)	0.0 (-1.4 ; 12.5)	100 (88.9 ; 100)	0.0 (0.0 ; 9.7)	0.0 (0.0 ; 9.7)
Role functioning-						
emotional/behavior	100 (100 ; 100)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	100 (100 ; 100)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)
physical	100 (100 ; 100)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	100 (100 ; 100)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)
Bodily pain	100 (80.0 ; 100)	-5.0 (-20.0 ; 0.0)[b]	0.0 (-5.0 ; 20.0)	100 (70.0 ; 100)	0.0 (0.0 ; 20.0)	0.0 (-17.5 ; 27.5)
General behavior	60.0 (60.0 ; 85.0)	0.0 (0.0 ; 25.0)	0.0 (0.0 ; 25.0)	60.0 (60.0 ; 85.0)	0.0 (-11.3 ; 25.0)	0.0 (-22.5 ; 25.0)
Behavior	76.7 (66.3 ; 76.7)	0.0(-7.7 ; 16.7)	4.2 (-9.4 ; 18.3)	80.8 (67.3 ; 89.2)	5.4 (-7.3 ; 17.3)	-9.6 (-16.7 ; 6.3)
Mental health	85.0 (75.0 ; 91.3)	-5.0 (-5.0 ; 3.8)[c]	0.0(-5.0 ; 10.0)	85.0 (75.0 - 90.0)	5.0 (0.0 ; 15.0)	-5.0 (-15.0 ; 10.0)
Self-esteem	79.2 (72.9 ; 89.6)	8.3 (-8.3 ; 18.8)	12.5 (-5.2 ; 29.2)	79.2 (75.0 ; 91.7)	8.3 (-8.3 ; 16.7)	4.2 (-8.3 ; 12.5)
General health	76.7 (67.5 ; 85.0)	3.3 (-11.9 ; 12.5)	0.0 (-3.3 ; 15.4)	76.7 (60.0 ; 85.0)	0.0 (-16.7 ; 16.7)	4.2 (-16.0 ; 17.9)
Change in health	50.0 (50.0 ; 62.5)	0.0 (0.0 ; 25.0)	25.0 (0.0 ; 31.3)	50.0 (50.0 ; 50.0)	0.0 (0.0 ; 25.0)	12.5 (0.0 ; 25.0)
Parental impact-						
emotional	91.7 (75.0 ; 100)	0.0 (-8.3 ; 8.3)	0.0 (-8.3 ; 8.3)	91.7 (75.0 ; 91.7)	0.0 (-8.3 ; 16.7)	-4.2 (-14.6 ; 8.3)
time	100 (88.9 ; 100)	0.0 (0.0 ; 0.0)	0.0 (-11.1 ; 11.1)	100 (100 ; 100)	0.0 (-8.3 ; 0.0)	0.0 (-11.1 ; 0.0)
Family activities	95.8 (79.2 ; 100)	0.0 (-4.2 ; 8.3)	-4.2 (-13.5 ; 8.3)	89.6 (82.3 ; 100)	0.0 (-3.1 ; 8.3)	0.0 (-8.3 ; 12.5)
Family cohesion	85.0 (60.0 ; 92.5)	0.0 (-15.0 ; 15.0)	0.0 (-15.0 ; 25.0)	85.0 (60.0 ; 100)	0.0 (-5.0 ; 22.5)	0.0 (-25.0 ; 22.5)

Numbers are expressed as median (25^{th},75^{th} percentiles) at baseline, and as median change (25^{th};75^{th} percentiles) at 16 weeks and 12 months.

[a] Positive numbers indicate an increase over time.

[b] Statistically significant higher decrease in the multidisciplinary intervention group compared with the usual-care group ($p = 0.03$).

[c] Statistically significant higher decrease in the multidisciplinary intervention group compared with the usual-care group ($p = 0.02$).

Associations between the changes over time in the parameters of obesity and the changes in HRQoL were studied for both groups together. Statistically significant correlations were found between a decrease in BMI z-score and an increase in the physical quality of life from the DUX-25, at the end of the treatment period ($r = -0.38$, $p = 0.01$). At 12 months follow-up, the correlation between a decrease in BMI z-score and an increase in the physical quality of life almost reached statistical significance ($r = -0.31$, $p = 0.07$). Furthermore, correlations were found between a decrease in BF% and an increase in the total DUX-25 score, at the end of the treatment program ($r = -0.31$, $p = 0.03$), and between a decrease in visceral fat and an increase in the physical quality of life, at 12 months follow-up ($r = -0.33$, $p = 0.046$).

With respect to the CHQ-PF50 questionnaires for the total group of children, correlations were found between a decrease in BMI z-score and an increase in "global health" ($r = -0.36$, $p = 0.03$), between baseline and 12 months follow-up. Furthermore, statistically significant associations were present between a decrease in BF% and an increase in "physical functioning" ($r = -0.29$, $p = 0.03$) at the end of both treatment programs. At 12 months follow-up, strong associations were found between decreases in visceral fat and increases in "global health" ($r = -0.37$, $p = 0.03$), "general behavior" ($r = -0.41$, $p = 0.01$), and "general health" ($r = -0.43$, $p = 0.01$).

Discussion

The aim of this study was to assess whether a multidisciplinary intervention program, besides having positive effects on parameters of obesity, also had positive effects on HRQoL in 3- to 5-year-old overweight or obese children. We demonstrated that HRQoL, especially for the physical domain, had improved from baseline to 12 months follow-up in the children in the multidisciplinary intervention group. Surprisingly, significant differences between the groups in the scales for "bodily pain" and "mental health" were found at the end of the treatment period, in favor of the children from the usual-care group. For both groups together, a decrease in various parameters of obesity was associated with an increase in several HRQoL domains.

The baseline data on HRQoL in the total group of overweight and obese children from our study did not confirm previous reports that overweight and obese children generally have a lower HRQoL compared with healthy or non-obese children.[8-10] This difference could be explained by the younger age of the children in our study. The effects of overweight and obesity on the different aspects of HRQoL may not have been fully present yet. Also, parents of 4- to 5-year-old children living in the same region of the Netherlands from which the children in our study were included, generally considered their overweight children to have a normal weight and even their obese children having either a normal weight or being a little too heavy.[22] As the parents completed the questionnaires, this might be an explanation for the absence of a decreased HRQoL in our preschool-aged overweight and obese children.

Childhood obesity treatment programs should, besides losing weight, also focus on improving HRQoL as obese children have been shown to report significant reductions in quality of life.[6] Impaired HRQoL in preschool-aged children has been reported especially in those children in who parents seek treatment.[11] In our study, children in the multidisciplinary intervention group received physical activity sessions aimed at teaching motor skills and having fun during exercise, thereby improving the child's well-being. Indeed, our study demonstrated that children receiving the multidisciplinary intervention program, perceived a greater improvement of HRQoL at 12 months follow-up, compared with the children in the usual-care group. Improvements were seen despite relatively normal HRQoL scores at the start of the study. The improvement in HRQoL was found for the physical subscale, emphasizing the positive effect of the multidisciplinary treatment program on the physical well-being of these children. Also, the associations between improvements over time in various parameters of obesity and several aspects of HRQoL demonstrate the beneficial effects of obesity treatment programs on the children's well-being. Positive effects of multidisciplinary obesity intervention programs on HRQoL at 12 months follow-up have been described previously in overweight and obese adolescents.[13,14] However, data on the effect of obesity treatment programs on HRQoL in preschool-aged children are still scarce.

Surprisingly, during the treatment period there was a statistically significant difference in the changes for the CHQ-PF50 scales "bodily pain" and "mental health", in favor of the children in the usual-care group. In the children in the multidisciplinary intervention group, HRQoL on these scales had decreased, in contrast to an unchanged score in "bodily pain" and an increased score in "mental health" observed in the usual-care group. However, at 12 months follow-up, these differences were no longer present, nor for any other scale of the CHQ-PF50 questionnaire. We expected the children in the multidisciplinary intervention group to have increased scores in the different HRQoL scales at the end of the treatment program, as the physical activity sessions focused on improving the child's well-being. However, it could be hypothesized that the intensive multidisciplinary treatment program had emphasized the physical and psychological consequences of the children's overweight or obesity too much.[23]

Strong points of our study are the young age of the children and the presence of both overweight and obese children participating in the study. Behavioral treatment in obese children 6-9 years old has proven to be successful in contrast to almost no effect in adolescents.[24] Until now, data on the effects of lifestyle intervention programs on HRQoL in preschool-aged children were scarce. This study further demonstrates that, besides improving anthropometry and body composition, a multidisciplinary intervention program in 3- to 5-year-old overweight or obese children also has positive effects on HRQoL. It has been suggested that discussion of impaired HRQoL in preschool-aged children with obesity might be a more effective strategy for health care professionals in broaching the topic of weight with parents.[11] Indeed, it has been demonstrated that parents underestimate the degree of overweight or obesity in their preschool-aged children.[22]

A weak point of our study was the use of HRQoL questionnaires which have not been specifically developed for children with overweight or obesity. The DUX-25 questionnaire has been used mostly to assess HRQoL in children with various chronic diseases.[21,25] In 2009, the development and initial validation of an obesity-specific quality of life measure for children aged 5-13 years was described.[26] The reliability and validity of this questionnaire still has to be determined.[27] The DUX-25 is a more general questionnaire and aims to assess HRQoL in children 5 years or older. The children in our study were 3-5 years old and too young to self-report. Therefore, parents completed the DUX-25 questionnaires. As mentioned above, parent reports are described to be valid in HRQoL questionnaires.[17] For future studies in preschool-aged overweight or obese children, the use of a HRQoL questionnaire for 1- to 5-year-olds could be considered.[28]

In conclusion, we showed that a multidisciplinary intervention program in 3- to 5-year-old overweight or obese children had beneficial effects on HRQoL, 12 months after the start of the intervention, compared with a usual-care program. Associations were present between a reduction in parameters of obesity and an increase in various aspects of HRQoL. At present time, it remains unclear whether the improvement in HRQoL remains over a longer period of time. Additional studies in preschool-aged overweight or obese children are needed to further investigate the effects of multidisciplinary intervention programs on HRQoL.

References

1. Schönbeck Y, Talma H, van Dommelen P, Bakker B, Buitendijk SE, Hirasing RA, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. PLoS One 2011;6:e27608.
2. Speiser PW, Rudolf MC, Anhalt H, Camacho-Hubner C, Chiarelli F, Eliakim A, et al. Consensus statement: Childhood obesity. J Clin Endocrinol Metab 2005;90:1871-1887.
3. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002;360:473-482.
4. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. Int J Pediatr Obes 2009;4:281-288.
5. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. J Pediatr 2008;152:201-206.
6. Griffiths LJ, Parsons TJ, Hill AJ. Self-esteem and quality of life in obese children and adolescents: a systematic review. Int J Pediatr Obes 2010;5:282-304.
7. Russell-Mayhew S, McVey G, Bardick A, Ireland A. Mental health, wellness, and childhood overweight/obesity. J Obes 2012;2012:281801.
8. Wake M, Salmon L, Waters E, Wright M, Hesketh K. Parent-reported health status of overweight and obese Australian primary school children: a cross-sectional population survey. Int J Obes Relat Metab Disord 2002;26:717-724.
9. Friedlander SL, Larkin EK, Rosen CL, Palermo TM, Redline S. Decreased quality of life associated with obesity in school-aged children. Arch Pediatr Adolesc Med 2003;157:1206-1211.
10. Schwimmer JB, Burwinkle TM, Varni JW. Health-related quality of life of severely obese children and adolescents. JAMA 2003;289:1813-1819.
11. Kuhl ES, Rausch JR, Varni JW, Stark LJ. Impaired health-related quality of life in preschoolers with obesity. J Pediatr Psychol 2012;37:1148-1156.
12. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev 2009;CD001872.
13. Vos RC, Huisman SD, Houdijk EC, Pijl H, Wit JM. The effect of family-based multidisciplinary cognitive behavioral treatment on health-related quality of life in childhood obesity. Qual Life Res 2012;21:1587-1594.
14. Finne E, Reinehr T, Schaefer A, Winkel K, Kolip P. Changes in self-reported and parent-reported health-related quality of life in overweight children and adolescents participating in an outpatient training: findings from a 12-month follow-up study. Health Qual Life Outcomes 2013;11:1.
15. Larkin J, Rice C. Beyond "healthy eating" and "healthy weights": harassment and the health curriculum in middle schools. Body Image 2005;2:219-232.
16. Bocca G, Corpeleijn E, Stolk RP, Sauer PJ. Results of a multidisciplinary treatment program in 3-year-old to 5-year-old overweight or obese children. A randomized controlled clinical trial. Arch Pediatr Adolesc Med 2012;166:1109-1115.
17. Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, et al. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res 1998;7:387-397.
18. Tsiros MD, Olds T, Buckley JD, Grimshaw P, Brennan L, Walkley J, et al. Health-related quality of life in obese children and adolescents. Int J Obes (Lond) 2009;33:387-400.
19. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index. J Clin Epidemiol 2002;55:67-76.
20. Van Doorn RK, Winkler LM, Zwinderman KH, Mearin ML, Koopman HM. CDDUX: a disease-specific health-related quality-of-life questionnaire for children with celiac disease. J Pediatr Gastroenterol Nutr 2008;47:147-152.
21. Flapper BC, Schoemaker MM. Effects of methylfenidate on quality of life in children with both developmental coordination disorder and ADHD. Dev Med Child Neurol 2008;50:294-299.
22. Oude Luttikhuis HG, Stolk RP, Sauer PJ. How do parents of 4- to 5-year-old children perceive the weight of their children? Acta Paediatr 2010;99:263-267.
23. Davison KK, Birch LL. Weight status, parent reaction, and self-concept in five-year-old girls. Pediatrics 2001;107:46-53.
24. Danielsson P, Kowalski J, Ekblom Ö, Marcus C. Response of severely obese children and adolescents to behavioral treatment. Arch Pediatr Adolesc Med 2012;166:1103-1108.
25. Kolsteren MM, Koopman HM, Schalekamp G, Mearin ML. Health-related quality of life in children with celiac disease. J Pediatr 2001;138:593-595.
26. Zeller MH, Modi AC. Development and initial validation of an obesity-specific quality-of-life measure for children: Sizing Me Up. Obesity (Silver Spring) 2009;17:1171-1177.
27. Cushing CC, Steele RG. Psychometric properties of sizing me up in a community sample of 4th and 5th grade students with overweight and obesity. J Pediatr Psychol 2012;37:1012-1022.
28. Fekkes M, Theunissen NC, Brugman E, Veen S, Verrips EG, Koopman HM, et al. Development and psychometric evaluation of the TAPQOL: a health-related quality of life instrument for 1-5-year-old children. Qual Life Res 2000;9:961-972.

6

Three-Year Follow-Up of 3- to 5-Year-Old Children after Participation in a Multidisciplinary or a Usual-Care Obesity Treatment Program

Gianni Bocca[1]
Eva Corpeleijn[2]
Ronald P. Stolk[2]
Pieter J.J. Sauer[1]

[1] Department of Pediatrics, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[2] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Clinical Nutrition, provisionally accepted for publication

Abstract

Background: Little is known on the long-term effects of obesity intervention programs in preschool-aged children. We compared the long-term effects of a multidisciplinary treatment program with a usual-care program in seventy-five 3- to 5-year-old overweight or obese children who had participated in a randomized controlled clinical trial.

Methods: A follow-up study collecting data at 18 and 36 months after starting both programs. The multidisciplinary program consisted of diet counseling, supervised exercise and psycho-education for parents. Outcome measures were changes in anthropometry and body composition, determined by bioelectrical impedance analysis and ultrasound.

Results: At the end of the 16-week treatment program, the multidisciplinary intervention showed a greater decrease in body mass index (BMI), BMI z-score (BMI-z), and waist circumference z-score (WC-z) than usual-care. At 18 months follow-up, BMI-z, WC-z and hip circumference z-score (HC-z) had decreased and fat-free mass (FFM) had increased in both groups. The decrease in WC-z was more pronounced in the multidisciplinary treatment program compared with the usual-care program. In the multidisciplinary intervention group BMI and body fat percentage had decreased. In both groups, at 36 months follow-up, BMI-z had decreased and FFM had increased. There were no differences over time between the groups.

Conclusions: Both programs in 3- to 5-year-old overweight or obese children show sustained beneficial effects on BMI-z and FFM. Although absolute differences were maintained, it cannot be concluded if a multidisciplinary lifestyle intervention program has additional long-term benefits on top of a usual-care program due to the small number of children.

Introduction

In the Netherlands, it has been recently demonstrated that the prevalence of childhood obesity is increasing.[1] In obese children, a decreased insulin sensitivity and dyslipidemia have been described at a young age.[2,3] Childhood obesity may persist into adulthood,[4] potentially leading to the development of cardiovascular disease (CVD) and type 2 diabetes (T2D).[5,6]

Prevention of childhood obesity should have a high priority.[7] When despite prevention efforts obesity develops at a young age, it is important to intervene. Systematic reviews have shown that family-based, multidisciplinary lifestyle intervention programs for children under the age of 12 years with overweight or obesity can be successful in reducing weight.[8] Literature reporting on long-term effects of lifestyle intervention programs is limited. These long-term effects are important since maintenance of beneficial effects of obesity intervention programs would indicate persistence of a reduced life-time risk on CVD and T2D.

At present, the longest follow-up period of obesity treatment programs was published in 1994.[9] Epstein and colleagues reported 10-year outcomes of 4 randomized studies in 185 children aged 6 to 12 years.[9] The authors concluded that the results obtained in the first 5 years of treatment were predictive for the outcome at 10 years. The importance of positive results during the intervention period on maintaining these effects on the long-term was also emphasized by an obesity intervention study in 663 children with a mean age of 10.6 years.[10]

Little is known about the long-term outcome of obesity intervention programs in preschool-aged children. The aim of this study was to evaluate the long-term effects of a multidisciplinary intervention program in overweight or obese children aged 3 to 5 years and in children receiving usual-care. Primary outcome measures were the actual weight reduction, changes in body mass index (BMI) and BMI z-score (BMI-z), and changes in body fat percentage (BF%) and visceral fat (VF) at 18 and 36 months after the start of the intervention. Secondary outcome measures were changes in waist circumference (WC) and WC z-score (WC-z), hip circumference (HC) and HC z-score (HC-z), upper arm circumference (UAC), fat-free mass (FFM) and abdominal subcutaneous fat (SCF).

Methods

Details of the programs and effects until 12 months after the start of both programs have been described previously.[11] In short, children and parents participated in a randomized, controlled clinical trial at the "Groningen Expert Center for Kids with Obesity (GECKO)-Outpatient Clinic". Children aged 3 to 5 years were referred to the outpatient clinic if they had a BMI-z > 1.1. After exclusion of medical causes for obesity, eating disorders, mental retardation and behavioral problems, children were randomly assigned to the multidisciplinary lifestyle intervention or usual-care programs. Enrollment took place from October 2006 to March 2008. A total of 75 children started with the study. They all were Dutch, except for five children from former Dutch colonies (two Suriname and three Dutch Antillean children) and one child from Morocco. Children lived in rural as well as in urban regions.

The multidisciplinary lifestyle intervention program included dietary advice for children and parents (6 sessions of 30 minutes each), physical activity sessions for children (12 sessions of 60 minutes each) and psychological counselling for parents only (6 sessions of 120 minutes each). Dietary advice, given by a dietician, aimed at improving eating behavior using personal goals. Physical activity sessions under guidance by a physiotherapist mimicked elementary school exercise. Psychological counselling was given by a psychologist teaching parents to be a healthy role model for their children. In the usual-care group, children and parents were followed up by a pediatrician (3 sessions of 30-60 minutes each) who advised on healthy eating and an active lifestyle. Both programs lasted 16 weeks. Written informed consent was obtained from the parents or legal caretakers. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

Between the anthropometric measurements and assessment of body composition at 12 months after the start of the intervention and visits at 18 and 36 months from baseline, no follow-up visits or interventions were done. Height and weight were measured *in duplo* using standard calibrated stadiometers and scales. BMI was calculated and age- and gender-specific z-scores were determined using the web-based program Growth Analyser 3 (http://www.growthanalyser.org/). WC, HC and UAC were measured *in duplo* using a standard measuring tape. WC-z and HC-z were calculated as described for BMI. Bio-impedance analysis (BIA-101, Akern S.r.l./RJL Systems) was used to assess BF% and FFM,[12] and ultrasound (SonoSite Titan, SonoSite, Inc) to measure VF and SCF.[13]

Pedometers (Yamax Digi-Walker SW-200, Yamax USA, Inc) were used to assess the children's physical activity and were worn, at a minimum, three weekdays and one weekend-day. The average number of steps was calculated. During two weekdays and two weekend-days, specially developed diaries were used to document the type and amount of food consumed. The diaries were analyzed by a dietician using a validated computer program (Vodisys Medical Software, IP Health Solutions) containing the 2006 Dutch food composition database, and the intake of nutrients was calculated.

Statistical analysis was done using PASW Statistics version 18.0. Distribution of normality was tested using the 1-sample Kolmogorov-Smirnov test. A paired sample *t* test was used for within-group differences and the independent *t* test for differences between groups. Repeated-measures analysis of variance, including baseline, 16 weeks, 12, 18 and 36 months was used to determine the difference between groups at 18 and 36 months, respectively. The significance level of all tests was $p < 0.05$.

Due to loss to follow-up, data on anthropometry and body composition from 48 (64.0%) children were analyzed 18 months after the start of the intervention, 25 of 40 (62.5%) children from the multidisciplinary intervention group and 23 of 35 (65.7%) children from the usual-care group. At 36 months after starting the intervention, anthropometric data and data on body composition from 29 (38.7%) children were analyzed, 17 of 40 (42.5%) children from the multidisciplinary intervention group and 12 of 35 (34.3%) children from the usual-care group. Not all children and parents used the pedometers and diaries to assess physical activity and food consumption. At 18 and 36 months from baseline respectively, in children from the multidisciplinary intervention group, data from 12 and 12 pedometers and 16 and 14 diaries were analyzed respectively. In children from the usual-care group, this was 10 and 5 and 8 and 6, at 18 and 36 months from baseline. Because of the low number of data collected from pedometers and diaries at 36 months after the intervention started, we analyzed these data for both groups together.

Results

Table 1 shows the descriptive and anthropometric characteristics of the study population at baseline.

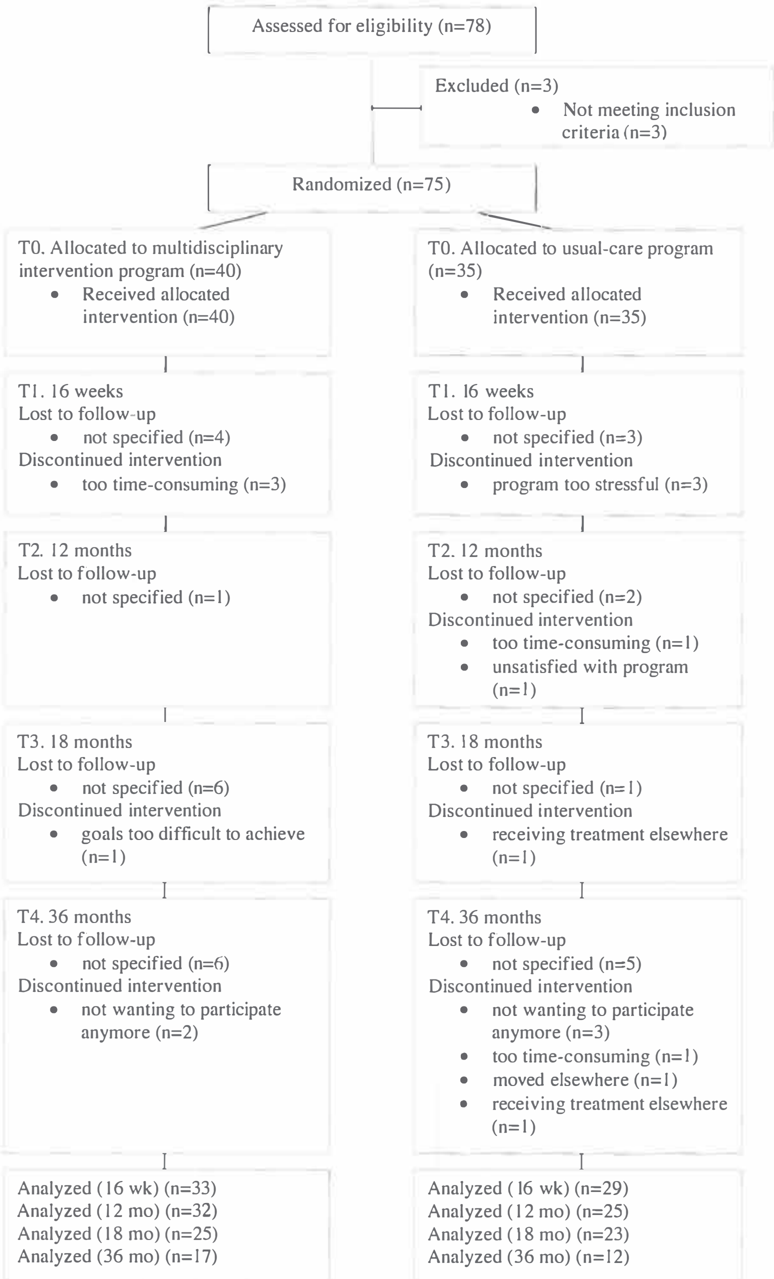
Table 1. Descriptive and anthropometric characteristics of the study population at baseline. Mean (SD).[11]

	Multidisciplinary Intervention Group n = 40	Usual-Care Group n = 35
Boys, No. (%)	12 (30.0)	9 (25.7)
Girls, No. (%)	28 (70.0)	26 (74.3)
Age, y	4.6 (0.8)	4.7 (0.8)
Overweight, No. (%)	14 (35.0)	15 (42.9)
Obese, No. (%)	26 (65.0)	20 (57.1)
Weight, kg	28.4 (6.3)	28.1 (6.8)
Body mass index, kg/m^2	21.2 (2.9)	21.0 (2.7)
Body mass index z-score	2.7 (1.0)	2.7 (1.0)
Waist circumference, cm	64.6 (7.1)	65.2 (8.0)
Waist circumference z-score	2.7 (1.0)	2.7 (1.0)
Hip circumference, cm	69.0 (7.9)	68.6 (7.2)
Hip circumference z-score	2.5 (1.3)	2.4 (1.1)
Upper arm circumference, cm	22.6 (2.3)	22.4 (2.4)
Body fat %	29.0 (7.8)	28.6 (6.3)
Fat-free mass, kg	19.7 (2.4)	19.7 (3.6)
Visceral fat, cm	4.4 (1.4)	4.3 (0.8)
Subcutaneous fat, cm	1.8 (0.7)	1.7 (0.7)
Steps, n/d	11998 (3031)	9862 (2729)[a]
Energy intake, kcal/d	1434 (252)	1504 (316)

[a] Statistically significant lower number of steps compared with the multidisciplinary intervention group (independent *t* test, $p < 0.01$).

Figure 1 provides details about inclusion and dropout from the study.

Figure 1. Flow diagram of study group assignment and follow-up.



In the multidisciplinary intervention group, 7 children were not available for follow-up between 12 and 18 months after the start of the intervention. In the same period, 2 children in the usual-care group were not available for follow-up. Between 18 and 36 months, 8 children in the multidisciplinary intervention group were unavailable for follow-up. During the same period, the number of children in the usual-care group unavailable for follow-up was 11. Mean (SD) age of the children in the multidisciplinary intervention group 18 months after the start of the intervention was 6.0 (0.8) years and 7.3 (1.1) years at 36 months. In the usual-care group, mean (SD) ages at 18 and 36 months from baseline were 6.2 (0.9) years and 7.4 (1.3) years, respectively.

Table 2 shows, for both groups, the changes in anthropometry and body composition from baseline to 18 and 36 months after the start of the intervention.

Table 2. Changes in anthropometry and body composition from baseline to 18 and 36 months after the start of the intervention.

	Multidisciplinary Intervention Group		Usual-Care Group		Group x Time	
	18 months	36 months	18 months	36 months	*p*-value[a]	*p*-value[b]
	n = 25	n = 17	n = 23	n = 12		
Weight, kg	3.4 (3.3)	11.9 (6.3)	4.3 (2.6)	13.5 (5.5)	0.47	0.59
Body mass index, kg/m²	-1.1 (1.7)	0.4 (2.5)	-0.5 (1.7)	1.2 (2.1)	0.28	0.47
Body mass index z-score	-0.8 (0.6)	-0.9 (0.8)	-0.6 (0.6)	-0.6(0.8)	0.21	0.24
Waist circumference, cm	0.1 (4.4)	7.4 (7.1)	0.5 (4.7)	7.2 (5.5)	0.06	0.28
Waist circumference z-score	-0.6(0.6)	0.4(0.8)	-0.5 (0.6)	-0.5 (0.6)	0.05	0.17
Hip circumference, cm	3.3 (7.6)	6.2 (9.3)	2.6 (4.6)	9.5 (6.0)	0.51	0.24
Hip circumference z-score	-0.4 (1.0)	-1.1 (1.2)	-0.5 (0.8)	-0.4 (1.0)	0.45	0.22
Upper arm circumference, cm	-0.1 (1.7)	2.6 (2.4)	0.7 (1.5)	3.6 (1.8)	0.22	0.48
Body fat %	-2.7 (5.4)	2.6 (5.9)	0.1 (5.7)	4.8 (4.8)	0.38	0.78
Fat-free mass, kg	3.1 (2.1)	7.0 (2.4)	3.0 (1.4)	7.1 (2.2)	0.97	0.97
Visceral fat, cm	-0.8 (1.8)	0.6 (1.8)	-0.3 (1.3)	1.7 (1.0)	0.28	0.59
Subcutaneous fat, cm	-0.1 (0.5)	0.4 (0.7)	-0.1 (0.6)	1.0 (0.6)	0.82	0.17

Numbers are presented as mean differences (SD), negative numbers reflect a decrease over time.

[a] *p*-values are based on time x group effect from repeated-measures analysis of variance, including baseline, 16 weeks, 12 and 18 months.

[b] *p*-values are based on time x group effect from repeated-measures analysis of variance, including baseline, 16 weeks, 12, 18 and 36 months.

At 18 months from baseline, a significant decrease for BMI ($p < 0.01$), BMI-z ($p < 0.001$), WC-z ($p < 0.001$), HC-z ($p = 0.046$), BF% ($p = 0.02$) and VF ($p = 0.05$) was found in the multidisciplinary intervention group. FFM ($p < 0.001$) had increased significantly. In the usual-care group, only BMI-z ($p < 0.001$), WC-z ($p = 0.001$) and HC-z ($p = 0.01$) had decreased significantly, whereas FFM ($p < 0.001$) had increased. Comparing both groups over time, the decrease in WC-z ($p = 0.05$) was more pronounced in the multidisciplinary intervention group than in the usual-care group. The difference between both groups over time in WC ($p = 0.06$) reached borderline significance, in favor of the multidisciplinary intervention group.

Concerning the changes in anthropometry and body composition from baseline to 36 months after the start of the intervention, children in the multidisciplinary intervention group showed a statistically significant decrease in BMI-z ($p < 0.001$) and HC-z ($p < 0.01$), whereas the decrease in WC-z ($p = 0.07$) reached borderline significance. There was a significant increase in FFM ($p < 0.001$). In the usual-care group, BMI-z ($p = 0.02$) and WC-z ($p = 0.03$) had decreased significantly, and FFM ($p < 0.001$) had increased significantly. Over time, there were no differences between the groups (Figure 2). Body fatness tended to increase in both groups 18 months after the start of the intervention. There were no differences between the groups.

Figure 2. Body mass index (BMI) z-score and waist circumference (WC) z-score in the multidisciplinary intervention group (open dots) and usual-care group (closed dots) from baseline to 36 months after the start of the intervention.

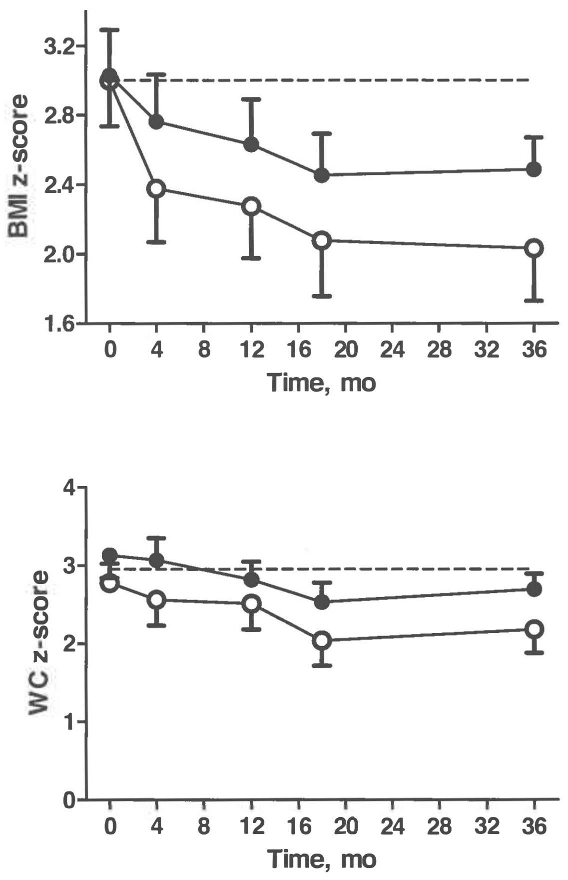


Table 3 shows the changes in physical activity and energy intake from baseline to 18 and 36 months after the start of the intervention. A statistically significant decrease in mono-/disaccharide intake was found in the multidisciplinary intervention group at 18 months (-3.3 [5.1] (mean [SD]) energy %; 95% CI, -6.0 to -0.6; p = 0.02). This decrease was no longer present at 36 months. In the usual-care group, at 18 months, a statistically significant increase in the average number of steps per day was found (3381 [2043] steps per day; 95% CI, 1919 to 4842; $p < 0.01$). At 36 months, this increase was no longer present. However, at 36 months there was a statistically significant decrease in carbohydrate intake (-5.2 [3.6] energy %; 95% CI, -9.0 to -1.4; p = 0.02) and mono-/disaccharide intake (-10.2 [6.7] energy %; 95% CI -17.2 to -3.1; p = 0.01) in the usual-care group. In contrast, fat intake had increased significantly (4.3 [3.4] energy %; 95% CI, 0.8 to 7.8; p = 0.03). There were no statistical significant differences over time between the two treatment groups. Therefore, for further analysis data from both groups were combined. When total energy intake, and energy intake for fat, carbohydrates and proteins, was calculated per kg body weight, a significant decrease in carbohydrate intake (p = 0.02) was found at 18 months. Significant decreases in total energy, fat, carbohydrate (all p's < 0.001) and protein intake ($p < 0.01$) were observed at 36 months after the start of the intervention. There was no significant increase over time for the number of steps (p = 0.10).

Table 3. Changes in physical activity and energy intake from baseline to 18 and 36 months after the start of the intervention.

	Multidisciplinary Intervention Group			Usual-Care Group			Group x Time	
	Baseline	18 months	36 months	Baseline	18 months	36 months	p-value[a]	p-value[b]
Pedometers	n = 33	n = 12	n = 12	n = 32	n = 10	n = 5		
Steps, n/d	11998 (3031)	14541 (2721)	12745 (2199)	9862 (2729)	12622 (2226)	11652 (2019)	0.26	0.41
Food diaries	n = 38	n = 16	n = 14	n = 32	n = 8	n = 6		
Energy intake, kCal/d	1434 (252)	1460 (213)	1438 (263)	1504 (316)	1330 (331)	1445 (443)	0.29	0.87
Fat energy %	27.7 (3.9)	29.6 (5.1)	28.2 (5.8)	27.7 (3.8)	29.4 (3.8)	31.2 (3.1)	0.68	0.10
Saturated fat energy %	11.0 (2.2)	11.3 (1.8)	11.0 (2.8)	10.6 (1.7)	11.7 (2.3)	11.6 (1.1)	0.62	0.58
Unsaturated fat energy %	13.8 (2.0)	15.2 (3.5)	14.3 (3.0)	14.4 (2.5)	14.8 (2.7)	16.3 (2.3)	0.74	0.38
Carbohydrate energy %	57.3 (4.7)	54.8 (4.9)	56.7 (6.9)	58.6 (4.3)	55.1 (2.4)	55.0 (4.3)	0.91	0.33
Mono-/disaccharide energy %	32.8 (6.3)	30.4 (6.1)	30.7 (8.2)	35.1 (5.5)	29.5 (2.2)	27.7 (6.8)	0.77	0.19
Protein energy %	15.0 (2.6)	15.6 (2.9)	15.2 (1.9)	13.8 (2.0)	15.5 (2.2)	13.8 (2.2)	0.91	0.06
Fiber intake, g/d	13.3 (3.4)	14.1 (2.7)	13.5 (2.9)	14.4 (3.4)	14.0 (3.3)	12.2 (3.3)	0.45	0.79

Numbers are presented as mean (SD).

[a] p-values are based on time x group effect from repeated-measures analysis of variance, including baseline, 16 weeks, 12 and 18 months.

[b] p-values are based on time x group effect from repeated-measures analysis of variance, including baseline, 16 weeks, 12, 18 and 36 months.

Discussion

The aim of this study was to assess the 3-year outcome in a multidisciplinary and a usual-care obesity intervention program in 3-year-old to 5-year-old children. At 12 months after the start of both programs, children in the multidisciplinary intervention group showed greater decreases in BMI, BMI-z, WC and WC-z compared with children in the usual-care group.[11] At 36 months from baseline, a significant decrease in BMI-z and HC-z and increase in FFM was present in the multidisciplinary intervention group. The decrease in WC-z reached borderline significance. In the usual-care group a decrease in BMI-z and an increase in FFM were also found. However, in contrast to the multidisciplinary intervention group, there was no decrease in HC-z. The decrease in WC-z at 36 months from baseline was statistically significant in the usual-care group. Despite a stable BMI-z, body fatness tended to increase again 18 months after the start of the intervention. This may be due to a natural increase in body fatness at ages 5 to 6 years. However, it may also indicate that measures of adiposity may provide useful information on when to intensify the caloric restriction to sustain progressive normalization of BMI-z.

Regarding energy intake and physical activity at 36 months, no significant changes from baseline were found in the multidisciplinary intervention group. In the usual-care group a significant decrease in carbohydrate and mono-/disaccharide intake was found, with a significant increase in fat intake. However, it should be noted that the total number of food diaries analysed was small. Combining the dietary data from both groups and expressed per kg body weight, there was a significant decrease in total energy intake and intake of fat, carbohydrates and proteins at 36 months after the start of the intervention.

Maintenance of weight reducing effects of childhood obesity intervention programs is important as this may imply persistence of a decreased risk on the development of adult CVD.[6] Indeed, sustained beneficial effects of obesity treatment programs on lipid profile and markers for insulin sensitivity have been demonstrated in obese 8- to 16-year-old children.[14] Literature on the long-term outcome of lifestyle intervention programs for childhood obesity is scarce and different long-term results have been reported. A 5-year follow-up study in 31 obese children with a mean age of 8.4 years, in which eight follow-up visits were included, showed a persistent decrease in BMI-SDS and WC, together with improved family habits towards a healthy lifestyle and decreased total energy intake.[15] The 2-year outcome of a family-based group program in 27 obese children 7 to 13 years old demonstrated a mean change in BMI-z of -0.23, however, without an improvement in WC-z.[16] The decrease in BMI-z reported by Robertson and colleagues[16] is lower than in our study in which at 36 months from baseline a mean decrease in BMI-z of 0.9 and 0.6 was found in the multidisciplinary intervention and usual-care groups, respectively.

Multidisciplinary lifestyle intervention programs for overweight and obese children aim at sustaining the positive effects of improved eating habits and increased physical activity. No study evaluated if a multidisciplinary program is more beneficial on the long term than only advices given by a paediatrician, what is considered usual-care in our country. In our study, at 3 years after the start of the intervention, there were no statistically significant differences over time between both groups regarding the number of steps and energy intake. However, for both groups together, there was a sustained decrease over time in energy intake per kg body weight. Positive long-term effects of lifestyle intervention programs in obese children have been described in studies with older children. Dietary data of overweight 5- to 9-year-old children who participated in an intervention program showed a sustained decrease of the consumption of energy-dense, nutrient-poor foods and an increased consumption of core foods at 2 years follow-up.[17] Persistent reductions of exposure to unhealthy foods with an improved eating style and reduction in sedentary behavior at 2-year follow-up have also been reported in 7- to 13-year-old obese children.[16]

Mechanisms leading to weight regain after obesity intervention programs are important to understand, as this may give the opportunity to prevent their occurrence. Children may show the tendency to relapse into unhealthy behavior, as was shown in a prospective, randomized study comparing two weight-reducing diets in obese 11- to 16-year-olds.[18] In this study, energy intake increased and physical activity decreased between the first and second year after treatment, together with a regain in weight. The importance of maintaining a healthy lifestyle in preventing weight regain was also shown in a study in adolescents who during follow-up had lower total energy intake, more energy at breakfast and less snacking and television watching.[19] These adolescents were more successful in weight maintenance after an obesity treatment program than children who had a higher energy intake, specifically at 2-year follow-up.

The addition of maintenance interventions to prevent weight regain after the end of obesity treatment programs has been studied by Wilfley and colleagues.[20] This randomized controlled trial studied the 2-year outcome of 2 different maintenance interventions after a 5-month weight loss program in 204 obese children, 7 to 12 years old. The authors conclude that maintenance-targeted programs improve short-term results of weight loss treatment but question whether this effect is caused by the content of the maintenance program, or by the increased frequency and duration of contact with parents and children. Unfortunately, this study also demonstrated that the positive effects wane off during follow-up. Our study did not provide maintenance sessions after the intervention period, nor were there contacts with parents and children between the follow-up moments. Nevertheless, a sustained decrease in BMI-z was observed for both treatment groups.

In conclusion, our study shows that, at 36 months after the start of the intervention, the usual-care and multidisciplinary treatment programs demonstrate a sustained decrease in BMI-z and an increase in FFM. Because of the small number of children at 36 months of follow-up, it cannot be concluded if a multidisciplinary obesity treatment program in 3- to 5-year-old children has additional effects on improving weight and body composition, compared with a usual-care program. However, the results show a clear trend that the multidisciplinary intervention program has a persistent greater effect than the usual-care program. If maintenance programs might have additional effects to prevent the relapse of positive lifestyle changes and regain in weight has to be studied further.

References

1. Schönbeck Y, Talma H, van Dommelen P, Bakker B, Buitendijk SE, Hirasing RA, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. PLoS One 2011;6:e27608.
2. Martos R, Valle M, Morales RM, Cañete R, Gascón F, Urbano MM. Changes in body mass index are associated with changes in inflammatory and endothelial dysfunction markers in obese prepubertal children after 9 months of body mass index SD score loss. Metabolism 2009;58:1153-1160.
3. Breslin WL, Johnston CA, Strohacker K, Carpenter KC, Davidson TR, Moreno JP, et al. Obese Mexican American children have elevated MCP-1, TNF-α, monocyte concentration, and dyslipidemia. Pediatrics 2012;129:e1180-1186.
4. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. Int J Pediatr Obes 2009;4:281-288.
5. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002;360:473-482.
6. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. Pediatrics 2007;120:340-345.
7. Baidal JA, Taveras EM. Childhood obesity: shifting the focus to early prevention. Arch Pediatr Adolesc Med 2012;166:1179-1181.
8. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev 2009;CD001872.
9. Epstein LH, Valoski A, Wing RR, McCurley J. Ten-year outcomes of behavioral family-based treatment for childhood obesity. Health Psychol 1994;13:373-383.
10. Reinehr T, Kleber M, Lass N, Toschke AM. Body mass index patterns over 5 y in obese children motivated to participate in a 1-y lifestyle intervention: age as a predictor of long-term success. Am J Clin Nutr 2010;91:1165-1171.
11. Bocca G, Corpeleijn E, Stolk RP, Sauer PJ. Results of a multidisciplinary treatment program in 3-year-old to 5-year-old overweight or obese children. A randomized controlled clinical trial. Arch Pediatr Adolesc Med 2012;166:1109-1115.
12. Horlick M, Arpadi SM, Bethel J, Wang J, Moye J Jr, Cuff P, et al. Bioelectrical impedance analysis models for prediction of total body water and fat-free mass in healthy and HIV-infected children and adolescents. Am J Clin Nutr 2002;76:991-999.
13. Stolk RP, Wink O, Zelissen PM, Meijer R, van Gils AP, Grobbee DE. Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. Int J Obes Relat Metab Disord 2001;25:1346-1351.
14. Savoye M, Nowicka P, Shaw M, Yu S, Dziura J, Chavent G, et al. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics 2011;127:402-410.
15. Vignolo M, Rossi F, Bardazza G, Pistorio A, Parodi A, Spigno S, et al. Five-year follow-up of a cognitive-behavioural lifestyle multidisciplinary programme for childhood obesity outpatient treatment. Eur J Clin Nutr 2008;62:1047-1057.
16. Robertson W, Thorogood M, Inglis N, Grainger C, Stewart-Brown S. Two-year follow-up of the 'Families for Health' programme for the treatment of childhood obesity. Child Care Health Dev 2012;38:229-236.
17. Burrows T, Janet WM, Collins CE. Long-term changes in food consumption trends in overweight children in the HIKCUPS intervention. J Pediatr Gastroenterol Nutr 2011;53:543-547.
18. Rolland-Cachera MF, Thibault H, Souberbielle JC, Soulié D, Carbonel P, Deheeger M, et al. Massive obesity in adolescents: dietary interventions and behaviours associated with weight regain at 2y follow-up. Int J Obes (Lond) 2004;28:514-519.
19. Péneau S, Thibault H, Meless D, Soulié D, Carbonel P, Roinsol D, et al. Anthropometric and behavioral patterns associated with weight maintenance after an obesity treatment in adolescents. J Pediatr 2008;152:678-684.
20. Wilfley DE, Stein RI, Saelens BE, Mockus DS, Matt GE, Hayden-Wade HA, et al. Efficacy of maintenance treatment approaches for childhood overweight. A randomized controlled trial. JAMA 2007;298:1661-1673.

7

Summary, General Discussion, and Future Perspectives

Summary

As childhood obesity is worldwide becoming increasingly prevalent, effective strategies to treat overweight and obese children are needed. Multidisciplinary lifestyle intervention programs in obese children aged 5-12 years, including a behavioral component, have been shown to be effective in reducing weight.[1] However, obesity starts already before the age of 5 years. Obesity treatment programs must therefore focus on even younger children as young obese children are at high risk to remain obese into adolescence and adulthood.[2-4] Childhood obesity has extensive health risks, both physical and psychological. To assess the effects of a multidisciplinary lifestyle intervention program in 3- to 5-year-old overweight or obese children, a randomized controlled clinical trial was performed at the Groningen Expert Center for Kids with Obesity (GECKO). Overweight and obesity were defined according to international cut-off values, as a body mass index (BMI) > 1.1 SDS and > 2.3 SDS, respectively.[5] Between October 2006 and March 2008, 75 children were allocated to a multidisciplinary intervention program or to a usual-care program. Both treatment programs lasted 16 weeks. The multidisciplinary intervention program for children and their parents contained 6 sessions of dietary advice by a dietician (30 minutes each), 12 physical activity group sessions of 60 minutes each supervised by a physiotherapist and, for parents only, 6 group sessions (120 minutes each) with behavioral therapy and guided by a psychologist. Children and parents in the usual-care group received advice on a healthy lifestyle by a resident in pediatrics, 3 sessions of 30-60 minutes each.

Height and weight of the children were measured using standard calibrated scales and stadiometers. BMI was calculated and standardized using age- and sex-specific data from the Fourth Dutch Growth Study.[6] Waist circumference (WC) was measured using a standard measuring tape at the midpoint between the lateral iliac crest and the lowest rib, and standardized as described above. Body composition was assessed by bio-impedance analysis (BIA-101, Akern S.r.l./RJL Systems, Florence, Italy) and body fat percentage (BF%) and fat-free mass (FFM) were calculated as previously described.[7] Abdominal subcutaneous fat (SCF) and visceral fat (VF) were measured by ultrasound (SonoSite Titan, SonoSite, Inc., Bothell, WA, USA).[8] Systolic (SBP) and diastolic (DBP) blood pressure were measured with a Dinamap Critikon 1846SX digital sphygmomanometer (Critikon Inc., Tampa, Florida, USA). The children's blood pressure was classified according to sex, height, and age.[9]

After an overnight fast, blood was drawn for determination of serum lipids (total cholesterol (T-C), HDL- and LDL-cholesterol (HDL-C and LDL-C), and triglycerides (TG)) and parameters of glucose metabolism (HbA1c, insulin, and glucose). Insulin sensitivity was assessed by the updated Homeostasis Model Assessment of Insulin Resistance (HOMA2-IR).[10] Furthermore, markers of low-grade systemic inflammation (high-sensitive c-reactive protein (hsCRP), tumor necrosis factor α (TNFα), and interleukin-6 (IL-6)), and the adipokines leptin and adiponectin were determined.

During both treatment programs, the eating pattern of the children was documented using specially developed diaries in which the type and amount of food consumed was written down by the parents. The diaries were used during 4 consecutive days: 2 weekdays and 2 weekend days. The food diaries were evaluated by a dietician and the intake of nutrients was calculated with a validated computer program (Vodisys Medical Software, IP Health Solutions, Groningen, the Netherlands), using the Dutch food composition database (NEVO 2006). Physical activity of the children was measured using a pedometer (Yamax Digi-Walker SW-200, Yamax USA, Inc., San Antonio, TX, USA). The pedometer was worn at least 3 weekdays and 1 weekend day. Parents documented the amount of steps in a diary, each day the pedometer was worn. The average number of steps per day was calculated.

Health-related quality of life (HRQoL) was assessed using two questionnaires, which were completed by one of the parents. The Dutch-Child-AZL-TNO-Quality-of-Life (DUX-25) questionnaire measures daily activities and contains 25 questions regarding physical, emotional, home, and social items. Possible responses on each question are expressed in 5 abstract faces from happy (score 5) to sad (score 1), thereby constructing a 5-point Likert scale. The Dutch edition of the Child Health Questionnaire-Parent Form (CHQ-PF50) measures health perception and contains 50 items, divided over 11 multi-scales and 4 single-items questions and addresses the child's physical, emotional and social well being. A higher score on each of the questionnaires indicated a higher quality of life.

In **chapter 2**, we describe the prevalence of insulin resistance and cardiovascular risk factors in the overweight and obese children at the start of both treatment programs. Of the 75 children, 29 children were overweight and 46 were obese. The presence of cardiovascular risk factors was confirmed if one or more of the following criteria were present: (1) TG $\geq$ 1.24 mmol/L; (2) HDL-C $\leq$ 1.03 mmol/L; (3) hypertension (SBP and/or DBP $\geq 90^{th}$ percentile for age, sex and height); (4) impaired glucose tolerance (HOMA2-IR $\geq 97.5^{th}$ percentile).

We found that cardiovascular risk factors were present in 6.9% (elevated triglycerides) to 74.3% (hypertension) of the children. In 5 of 65 children (7.7%), a HOMA2-IR above the upper limit of the normal range was found. This included one overweight child (4.0%) and 4 (10.0%) obese children. HOMA2-IR and fasting insulin were significantly higher in the obese children than in the overweight children (both $p < 0.01$), as was fasting glucose ($p = 0.01$). HOMA2-IR was strongly correlated with BMI ($r = 0.63$), WC ($r = 0.62$), and BF% ($r = 0.58$) (all $p < 0.001$).

In **chapter 3**, we present the results of the multidisciplinary intervention program in our 3- to 5-year-old overweight or obese children on anthropometric parameters of obesity and body composition, at the end of the treatment period and at 1 year of follow-up. We compared the results with a group of overweight and obese children receiving the usual-care program.

During the 16-week treatment period, 7 children in the multidisciplinary intervention group either discontinued the study or were lost to follow-up. In 3 of these children, parents commented that the study was too time-consuming. In the other children, no specific reason was given by the parents. In the usual-care group, 6 children were lost to follow-up. For 3 children, parents mentioned that the program was too stressful, in the other 3 children no reason was given. Between the end of both treatment programs and 1 year follow-up, another child in the multidisciplinary intervention group and another 4 children in the usual-care group were lost to follow-up. At the end of the intervention period, data on 62 children (82.7%) were analyzed and data on 57 children (76.0%) were analyzed at 1 year of follow-up.

Comparing the effect of both treatment programs between baseline and the end of the 16-week programs, we demonstrated in the multidisciplinary intervention group a statistically significant greater decrease in BMI (mean (standard deviation (SD)) difference 0.5 (0.3) kg/m², $p = 0.05$), BMI z-score (mean (SD) difference 0.2 (0.1), $p = 0.03$), and WC z-score (mean (SD) difference 0.3 (0.1), $p = 0.02$), compared with the children in the usual-care group. At 1 year of follow-up, the multidisciplinary treatment program obtained significantly greater decreases in BMI ($p = 0.03$), BMI z-score ($p = 0.02$), WC ($p = 0.02$) and WC z-score ($p = 0.01$), compared with the usual-care program. The decrease in VF reached borderline significance, in favor of the multidisciplinary intervention group ($p = 0.08$).

With regard to physical activity and nutrient intake, only the daily intake of fiber between baseline and 16 weeks showed a statistically significant difference between both groups, in favor of the multidisciplinary intervention group ($p = 0.02$). Between baseline and 12 months follow-up, no statistically significant differences were present between the groups.

In **chapter 4**, the effect of both treatment programs on adipokines, insulin resistance, lipid profile, and low-grade systemic inflammation is described. In both groups, insulin sensitivity had improved at the end of the 16-week treatment period, as shown by decreased insulin concentrations and a decreased HOMA2-IR. Furthermore, in the multidisciplinary intervention group, HbA1c and TNFα had significantly decreased (both $p = 0.01$). Comparing both groups over time, no statistically significant differences were present between the groups. However, the decrease in T-C ($p = 0.07$) and TNFα ($p = 0.06$) concentrations reached borderline statistical significance, in favor of the multidisciplinary intervention group. Combining the results of both groups, we demonstrated a statistically significant correlation between the decrease in BF% and decreases in HOMA2-IR ($r = 0.37$, $p = 0.02$) and TG concentrations ($r = 0.29$, $p = 0.02$).

In **chapter 5**, the effect of the multidisciplinary intervention program on HRQoL is described. The results are compared with the effects observed in the usual-care group. HRQoL was measured at the start, at the end, and 12 months after the start of both treatment programs. At baseline, 16 weeks and 12 months, 69 (92.0% of the children), 59 (95.2%), and 40 (70.2%) DUX-25 questionnaires were available for evaluation. For the CHQ-PF50, these were 71 (94.7% of the children), 59 (95.2%), and 40 (70.2%) questionnaires, respectively. The baseline data from the DUX-25 questionnaires of both treatment groups together did not demonstrate a lower HRQoL, compared with healthy Dutch children. Even higher scores were reported. In general, this difference in HRQoL could not be concluded from the CHQ-PF50 questionnaires. Compared with children with asthma or behavioral problems, parents of our overweight or obese 3- to 5-year-olds generally reported a higher HRQoL, both on the DUX-25 and CHQ-PF50 questionnaires.

At 12 months follow-up, children in the multidisciplinary intervention group demonstrated a statistically significant increase in the total DUX-25 score, compared with the children in the usual-care group (medians 5.0 vs. -4.5, $p = 0.04$). This increase in HRQoL in the children from the multidisciplinary intervention group was also demonstrated for the physical subscale of the DUX-25 questionnaire (medians 8.3 vs. -4.2, $p = 0.03$). Regarding the CHQ-PF50 questionnaires, at the end of the treatment period the score for the scale "bodily pain" had decreased in the multidisciplinary intervention group indicating more pain or limitations because of pain, whereas in the usual-care group the score for "bodily pain" remained unchanged (medians -5.0 vs. 0.0, $p = 0.03$). For the scale "mental health", children in the multidisciplinary intervention group demonstrated increased feelings of anxiety and depression at the end of the 16-week program, compared with the children in the usual-care group who reported less feelings of anxiety and depression (medians -5.0 vs. 5.0, $p = 0.02$). At 12 months follow-up, no statistically significant different changes between the groups were present.

For both groups combined, a decrease in BMI z-score between baseline and 12 months of follow-up was associated with increased "global health" ($r = -0.36$, $p = 0.03$). At 12 months from baseline, a decrease in VF was correlated with increases in the CHQ-PF50 scales "global health" ($r = -0.37$, $p = 0.03$), "general behavior" ($r = -0.41$, $p = 0.01$), and "general health" ($r = -0.43$, $p = 0.01$).

In **chapter 6**, we describe the long-term effects of the multidisciplinary intervention program on anthropometric parameters of obesity and body composition, compared with the results in the children in the usual-care group. Data were collected at 1.5 and 3 years after the start of the treatment program. At 1.5 years from baseline, data from 48 children (64.0%) were available for evaluation. Mean (SD) age of the children in the multidisciplinary intervention group was 6.0 (0.8) years and 6.2 (0.9) years in the usual-care group. At 3 years from baseline, data from 29 children (38.7%) were available for evaluation. Mean (SD) ages of the children in the multidisciplinary intervention and usual-care groups were 7.3 (1.1) and 7.4 (1.3) years, respectively.

At 18 months of follow-up, children in the multidisciplinary intervention group still demonstrated significant decreases in BMI z-score (mean (SD) -0.8 (0.6), $p < 0.001$), WC z-score (mean (SD) -0.6 (0.6), $p < 0.001$), BF% (mean (SD) -2.7 (5.4), $p = 0.02$), and VF (mean (SD) -0.8 (1.8) cm, $p = 0.05$). FFM had increased significantly (mean (SD) 3.1 (2.1) kg, $p < 0.001$). Also, in the usual-care group, BMI z-score (mean (SD) -0.6 (0.6), $p < 0.001$) and WC z-score (mean (SD) -0.5 (0.6), $p = 0.001$) had decreased, and FFM had increased (mean (SD)

3.0 (1.4) kg, $p < 0.001$). Comparing the changes in both groups, from baseline to 18 months after the start of the intervention, the decrease in WC z-score was more pronounced in the multidisciplinary intervention group, compared with the usual-care group ($p = 0.05$).

At 36 months of follow-up, children in the multidisciplinary intervention group demonstrated a sustained decrease in BMI z-score (mean (SD) -0.9 (0.8), $p < 0.001$), and an increase in FFM (mean (SD) 7.0 (2.4) kg, $p < 0.001$). The decrease in WC z-score reached borderline statistical significance (mean (SD) -0.4 (0.8), $p = 0.07$). In the usual-care group, the decrease in BMI z-score was also still present (mean (SD) -0.6 (0.8), $p = 0.02$), as was the decrease in WC z-score (mean (SD) -0.5 (0.6), $p = 0.03$). An increase in FFM could also still be demonstrated (mean (SD) 7.1 (2.2) kg, $p < 0.001$). Comparing the results in both groups, from the start to 3 years after the start of the treatment, no different changes in anthropometry or body composition were present. Concerning physical activity and energy intake, there were no statistically significant differences over time between the two treatment groups.

Because both programs showed sustained beneficial effects on BMI z-score and FFM, it cannot be concluded whether a multidisciplinary intervention program had additional long-term effects over a usual-care program, due to the small number of children available for evaluation.

General discussion

The first objective of this thesis was to determine the effect of a multidisciplinary intervention program in 3- to 5-year-old overweight or obese children on anthropometry and body composition. We showed that, at the end of the treatment program, children in the multidisciplinary intervention group achieved greater decreases in BMI, BMI z-score, and WC z-score, compared to children receiving the usual-care program and that this difference was still present at 12 months follow-up. Eighteen months after the start of the treatment program, the greater decrease in WC z-score in the children from the multidisciplinary intervention group had persisted. At 3 years from baseline, no significant differences were present between the groups, although both groups demonstrated sustained positive effects over time on BMI z-score and FFM.

Positive effects of multidisciplinary lifestyle intervention programs on reducing weight have been demonstrated in obese children 5-12 years old.[1] However, little is known on the effect of obesity intervention programs in preschool-aged children. An effective treatment of childhood obesity at a young age is important, as tracking of obesity has been demonstrated.[4] This implies that young children with overweight or obesity are at high risk to remain so into adolescence and adulthood, unless treatment is offered. Furthermore, obesity intervention programs in young children have been shown to be more effective than in older children.[11] Our study shows that a multidisciplinary treatment program is already effective in preschool-aged overweight or obese children, and emphasizes that treatment programs for childhood obesity should aim at early intervention.[3] The positive results from our study are supported by a pilot study in 18 obese children aged 2-5 years, in which the children in the intervention group showed a decrease in BMI z-score, in contrast to an increase in BMI z-score in the children from the control group.[12]

Due to the small number of children participating at long-term follow-up, it could not be concluded if the multidisciplinary treatment program had additional benefits compared to a usual-care program. However, both programs did show sustained positive effects on parameters of obesity over time. Literature reporting on the long-term effects of childhood obesity programs is limited, but do show that the effects obtained during the intervention period are predictive for the long-term outcome.[13] The presence of positive long-term effects could imply a reduced risk on the tracking of obesity and the development of obesity related disorders later in life. It is of importance for the development of future childhood obesity treatment programs to study what content and what frequency of lifestyle interventions in children with overweight or obesity show the best long-term results.

In that perspective, it is important to identify the factors that lead to the persistence of the positive effects of obesity treatment programs, achieved at short-term follow-up, as this could further improve treatment programs for childhood obesity. Preventing a regain in weight by maintenance of a healthy lifestyle during follow-up has been demonstrated in obese adolescents.[14] However, obese children aged 11-16 years may relapse into unhealthy behavior, characterized by increased energy intake and decreased physical activity, after participating in a dietary intervention program.[15] Literature on the long-term effects of lifestyle intervention programs in overweight and obese preschool-aged children is scarce, and data on interventions aimed at sustaining the positive results achieved during the intervention period are lacking. In obese children 7 to 12 years old, maintenance interventions after a weight loss treatment program have been shown to improve short-term results.[16] However, it remains unclear if this positive effect is caused by the content of the program or by the more frequent contact with the children and their parents.

The second objective of this thesis was to determine the prevalence of insulin resistance and cardiovascular risk factors in overweight or obese children 3-5 years old and to determine the effect of a multidisciplinary intervention program on insulin resistance, lipid profile, low-grade systemic inflammation, and adipokines. We demonstrated that insulin resistance and cardiovascular risk factors were already evident in many overweight or obese preschool-aged children and that insulin resistance was strongly related to body composition. Furthermore, a multidisciplinary intervention program, as well as a usual-care program, improved insulin sensitivity in 3- to 5-year-old overweight or obese children, in parallel with a reduction in BF%.

Although it still has to be determined whether the presence of insulin resistance and cardiovascular risk factors in preschool-aged overweight or obese children is related to an increased risk on cardiovascular disease or metabolic syndrome at a later age, the results of our study are alarming. Since, the tracking from childhood to adolescence of cardiovascular risk factors associated with obesity has been demonstrated.[17] According to international guidelines, metabolic syndrome cannot be diagnosed in children under the age of 10 years.[18] Therefore, it is not possible to compare the results of our study with other studies describing the prevalence of metabolic syndrome in overweight or obese children aged 10 years or older. For example, in moderately obese 13-year-olds, metabolic syndrome was found in 38.7% of the children, compared to 49.7% in severely obese 11-year-olds.[19]

We chose to describe the cardiovascular risk factors separately and defined the presence of each risk factor according to the best available cut-off levels in literature. With the exception of reference values for blood pressure,[9] it should be noted that normal values for the separate cardiovascular risk factors in children aged 3-5 years do not exist. Therefore, reference bias may have played a role in the prevalence of insulin resistance and cardiovascular risk factors in our overweight and obese preschool-aged children. However, the results from our study are supported by a study in 7- to 9-year-old overweight or obese Portuguese children, which showed approximately the same prevalence of the different cardiovascular risk factors as we have reported.[20]

Our study also demonstrated that insulin sensitivity was strongly related to anthropometric parameters of obesity in overweight or obese 3- to 5-year-old children. Significant higher HOMA2-IR values were found in the obese children than in the overweight children, and a reduction in BF% induced by the obesity treatment programs led to an improvement in insulin sensitivity. Also, an improvement in body composition induced improvements in lipid profile.

The role of body fat mass involved in the pathogenesis of insulin resistance in obese children has been demonstrated in other studies.[19,21] Improving insulin sensitivity by reducing fat mass should therefore be one of the objectives in obesity treatment programs. Decreasing body fat has been shown to decrease insulin resistance in obese children, 9 to 17 years old.[22] With our study we show that an improvement in insulin sensitivity by reducing BF% can already be achieved in preschool-aged children. Furthermore, the decrease in TG concentrations associated with improvements in body composition (decreased BF% and abdominal SCF) in our overweight and obese preschool-aged children are important observations, as obesity related dyslipidemia increases the risk of atherosclerosis.[23] Previously, it was demonstrated in 9- to 13-year-old obese children that weight loss over a one-year period was associated with decreased TG concentrations.[24] The results of our study may imply that obesity treatment programs in preschool-aged children diminish the cumulative lifetime exposure to increased cardiovascular risk factors later in life.

The third objective of this thesis was to determine the effect of a multidisciplinary intervention program on HRQoL in 3- to 5-year-old overweight and obese children. Also, we studied whether improvements in body weight and body composition in these children had led to improvements in HRQoL. At baseline, the preschool-aged children in our study did not show a lower HRQoL compared with healthy Dutch children. Compared with children with asthma or behavioral problems, HRQoL was generally reported to be higher. We demonstrated at 12 months of follow-up that a multidisciplinary intervention program induced a greater increase in HRQoL, compared with a usual-care program. The improvement in HRQoL was especially present for the physical domain. When we combined the results from both treatment programs, a decrease in BMI z-score and VF was associated with improvements in several HRQoL domains.

In contrast to other studies, the overweight or obese children in our study did not show a decreased HRQoL, compared with healthy or non-obese children.[25,26] This might be explained by the younger age of the children in our study or by the fact that parents filled in the questionnaires. Due to the children's young age, the negative effects on HRQoL of being overweight or obese may not be present yet. However, in preschool-aged obese children HRQoL has been shown to be impaired, especially in those children in who parents seek treatment.[27] A possible explanation for this discrepancy may be the fact that parents of 4- to 5-year-old children living in the northern parts of the Netherlands, generally consider their overweight and obese children to have a normal weight.[28] The children in our study lived in the same region of the Netherlands and, as parents completed the HRQoL questionnaires, a possible decreased HRQoL could therefore not have been detected.

Data on the effects of obesity treatment programs on HRQoL in preschool-aged overweight and obese children are lacking. Positive effects of multidisciplinary obesity intervention programs on HRQoL at 12 months follow-up have been described previously in overweight and obese adolescents.[29,30] Our study shows that a multidisciplinary treatment program containing physical activity sessions aimed at improving the child's well being, can lead to an improvement in HRQoL in 3- to 5-year-old overweight or obese children, especially on the physical domain. Furthermore, the strong associations between improvements over time in various parameters of obesity and several aspects of HRQoL demonstrate the beneficial effects of obesity treatment programs on HRQoL in preschool-aged children. This is an important finding concerning treatment strategies for overweight or obese preschool-aged children. Since, it has been suggested that focusing on HRQoL in preschool-aged children with obesity might be a more effective strategy for health care professionals in broaching the topic of weight with parents.[27]

Our study does have some limitations. At first, during the intervention period and three-year follow-up, several children and parents were lost to follow-up. It could be hypothesized that loss to follow-up was present in the children and parents who were less motivated to participate in the study. Therefore, it can be assumed that while mainly the motivated families continued the treatment programs, the outcome of our study has been positively influenced. In general, participation in obesity treatment programs requires a high level of motivation, especially in children and parents receiving an intensive multidisciplinary intervention program. However, we showed in our study that during both 16-week treatment programs, loss to follow-up was almost equal in the multidisciplinary intervention and usual-care groups (17.5% and 17.1%, respectively).

At the end of the 16-week treatment period, 82.7% of the children who were initially enrolled in the study were still participating. At 1 year, 1.5 and 3 years after the start of the study, 76.0%, 64.0% and 38.7% of the children were available for evaluation, respectively. As a result of this loss to follow-up, the power to detect statistical significant differences between both treatment groups had become low. Therefore, especially after a 3-year follow-up period, no statistically significant differences in anthropometry and body composition could be detected between the groups. However, both treatment programs did show sustained beneficial effects over time on anthropometric parameters of obesity.

It should be noted that a large loss to follow-up is frequently observed in treatment programs for childhood obesity. In a randomized controlled trial in 209 obese children aged 8-16 years studying the effect of a lifestyle intervention program, 36.4% of the children were still participating in the study after 2 years of follow-up.[31] A longitudinal observational study in 643 obese children 6-16 years old reported an overall loss to follow-up of 56% after a 3-year follow-up period.[32] For the age group of 6-9 years in this study, approximately 32% of the children were reported to be lost to follow-up, in contrast to a loss to follow-up percentage of 78 for the age group 14-16 years.[32]

The lack of a maintenance program in our study after the active intervention period could be the main reason for the large number of loss to follow-up we encountered and therefore be considered as a further limitation of our study. The importance of maintaining a healthy lifestyle in preventing a regain in weight has been demonstrated in obese adolescents.[14] In obese children 7-12 years old, the efficacy of a maintenance program after a 5-month weight loss treatment period was studied in a randomized controlled trial.[16] It was shown that maintenance programs improved the short-term results of the initial treatment program. However, it was unclear if this positive effect was achieved by the content of the maintenance program or by the increased frequency and duration of the contact with the children and their parents. Unfortunately, this study did also show that the positive effects wane off during follow-up. To our knowledge, no data exist on the efficacy of maintenance programs after multidisciplinary treatment programs in overweight or obese preschool-aged children and this research subject should have a high priority in future studies.

As a final limitation of our study, the results on HRQoL may be considered to be influenced by the parental point of view regarding the physical and psychological consequences of the child's overweight or obesity. Since, due to the young age of the children in our study, parents filled in the DUX-25 and CHQ-PF50 questionnaires. Literature reports contrasting results on the influence of the parental perception in assessing HRQoL in young children with a chronic disease. In general, children report lower scores on physical and motor functioning than their parents do.[33] In obese children and adolescents, the parents are reported to perceive a worse HRQoL than the children do about themselves.[34] Similar changes in self-reported and parent-reported HRQoL have been described in overweight children participating in a 6-month obesity treatment program, until 12 months after the start of the intervention.[29] This should imply that the results on the changes in HRQoL obtained in our study are valid. For future research on HRQoL in preschool-aged obese children, the use of a HRQoL questionnaire for 1- to 5-year-olds could be considered.[35]

Future perspectives

Several research questions should be addressed in future studies. In the first place, it should be studied how to improve the short-term effects of multidisciplinary intervention programs for children with overweight or obesity. Factors that lead to a better adherence to lifestyle intervention programs should be identified. In this way, the frequently observed high numbers of loss to follow-up during the intervention period may be diminished. Also, factors that lead to the maintenance of the positive effects achieved during the intervention period should be clarified, thereby potentially improving the long-term outcome of obesity intervention programs. It will be of interest for the development of future treatment programs to elucidate whether the content and/or the frequency of maintenance programs can lead to improvements in multidisciplinary intervention programs for children with overweight or obesity. For example, it should be studied what type of lifestyle intervention program will be most effective in obtaining the best long-term results: an intensive intervention period succeeded by less frequent follow-up sessions, or a less intensive intervention program followed by frequent follow-up moments. Improvement of the positive long-term results of intervention programs for young children with overweight or obesity may further diminish the increased cumulative lifetime exposure to cardiovascular risk factors related to obesity, thereby decreasing the risk of the development of cardiovascular disease and type 2 diabetes at a later age.

Secondly, reference values for lipid profile and markers for insulin sensitivity should be developed for preschool-aged children. At present, no reference values are present for children in this age category, hindering the interpretation of the measured values for lipid profile and insulin sensitivity in preschool-aged overweight or obese children. Also, it should be investigated whether elevated cardiovascular risk factors in preschool-aged overweight or obese children may already predict the development of metabolic syndrome at a later age. In the future, results from these studies will render it possible to diagnose metabolic syndrome even in children under the age of 10 years, which is not possible at present time according to international guidelines.

Thirdly, discussion on the future development of national intervention programs targeting children with overweight or obesity should also regard whether to focus on treating children in the youngest age categories. Multidisciplinary intervention programs in young children are more effective in decreasing weight and show better long-term results, compared to treatment programs for adolescents with overweight or obesity. However, preventing the development of overweight and obesity in children should have the highest priority.

References

1. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev 2009;CD001872.
2. Liem ET, van Buuren S, Sauer PJ, Jaspers M, Stolk RP, Reijneveld SA. Growth during infancy and childhood, and adiposity at age 16 years: ages 2 to 7 years are pivotal. J Pediatr 2013;162:287-292.
3. Baidal JA, Taveras EM. Childhood obesity: shifting the focus to early prevention. Arch Pediatr Adolesc Med 2012;166:1179-1181.
4. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. Int J Pediatr Obes 2009;4:281-288.
5. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-1243.
6. Fredriks AM, van Buuren S, Fekkes M, Verloove-Vanhorick SP, Wit JM. Are age references for waist circumference, hip circumference and waist-hip ratio in Dutch children useful in clinical practice? Eur J Pediatr 2005;164:216-222.
7. Horlick M, Arpadi SM, Bethel J, Wang J, Moye J Jr, Cuff P, et al. Bioelectrical impedance analysis models for prediction of total body water and fat-free mass in healthy and HIV-infected children and adolescents. Am J Clin Nutr 2002;76:991-999.
8. Stolk RP, Wink O, Zelissen PM, Meijer R, van Gils AP, Grobbee DE. Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. Int J Obes Relat Metab Disord 2001;25:1346-1351.
9. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114:555-576.
10. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-1495.
11. Sabin MA, Ford A, Hunt L, Jamal R, Crowne EC, Shield JP. Which factors are associated with a successful outcome in a weight management programme for obese children? J Eval Clin Pract 2007;13:364-368.
12. Stark LJ, Spear S, Boles R, Kuhl E, Ratcliff M, Scharf C, et al. A pilot randomized controlled trial of a clinic and home-based behavioral intervention to decrease obesity in preschoolers. Obesity (Silver Spring) 2011;19:134-141.
13. Reinehr T, Kleber M, Lass N, Toschke AM. Body mass index patterns over 5 y in obese children motivated to participate in a 1-y lifestyle intervention: age as a predictor of long-term success. Am J Clin Nutr 2010;91:1165-1171.
14. Péneau S, Thibault H, Meless D, Soulié D, Carbonel P, Roinsol D, et al. Anthropometric and behavioral patterns associated with weight maintenance after an obesity treatment in adolescents. J Pediatr 2008;152:678-684.
15. Rolland-Cachera MF, Thibault H, Souberbielle JC, Soulié D, Carbonel P, Deheeger M, et al. Massive obesity in adolescents: dietary interventions and behaviours associated with weight regain at 2y follow-up. Int J Obes (Lond) 2004;28:514-519.
16. Wilfley DE, Stein RI, Saelens BE, Mockus DS, Matt GE, Hayden-Wade HA, et al. Efficacy of maintenance treatment approaches for childhood overweight. A randomized controlled trial. JAMA 2007;298:1661-1673.
17. Bugge A, El-Naaman B, McMurray RG, Froberg K, Andersen LB. Tracking of clustered cardiovascular disease risk factors from childhood to adolescence. Pediatr Res 2013;73:245-249.
18. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al; IDF Consensus Group. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007;8:299-306.
19. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 2004;350:2362-2374.
20. Pedrosa C, Oliveira BM, Albuquerque I, Simões-Pereira C, Vaz-de-Almeida MD, Correia F. Obesity and metabolic syndrome in 7-9 years-old Portuguese schoolchildren. Diabetol Metab Syndr 2010;2:40.
21. Calcaterra V, Klersy C, Muratori T, Telli S, Caramagna C, Scaglia F, et al. Prevalence of metabolic syndrome (MS) in children and adolescents with varying degrees of obesity. Clin Endocrinol (Oxf) 2008;68:868-872.
22. Ford AL, Hunt LP, Cooper A, Shield JP. What reduction in BMI SDS is required in obese adolescents to improve body composition and cardiometabolic health? Arch Dis Child 2010;95:256-261.
23. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338:1650-1656.
24. Reinehr T, Stoffel-Wagner B, Roth CL, Andler W. High-sensitive C-reactive protein, tumor necrosis factor , and cardiovascular risk factors before and after weight loss in obese children. Metabolism 2005;54:1155-1161.
25. Wake M, Salmon L, Waters E, Wright M, Hesketh K. Parent-reported health status of overweight and obese Australian primary school children: a cross-sectional population survey. Int J Obes Relat Metab Disord 2002;26:717-724.

26. Friedlander SL, Larkin EK, Rosen CL, Palermo TM, Redline S. Decreased quality of life associated with obesity in school-aged children. Arch Pediatr Adolesc Med 2003;157:1206-1211.
27. Kuhl ES, Rausch JR, Varni JW, Stark LJ. Impaired health-related quality of life in preschoolers with obesity. J Pediatr Psychol 2012;37:1148-1156.
28. Oude Luttikhuis HG, Stolk RP, Sauer PJ. How do parents of 4- to 5-year-old children perceive the weight of their children? Acta Paediatr 2010;99:263-267.
29. Finne E, Reinehr T, Schaefer A, Winkel K, Kolip P.. Changes in self-reported and parent-reported health-related quality of life in overweight children and adolescents participating in an outpatient training: findings from a 12-month follow-up study. Health Qual Life Outcomes 2013;11:1.
30. Vos RC, Huisman SD, Houdijk EC, Pijl H, Wit JM. The effect of family-based multidisciplinary cognitive behavioral treatment on health-related quality of life in childhood obesity. Qual Life Res 2012;21:1587-1594.
31. Savoye M, Nowicka P, Shaw M, Yu S, Dziura J, Chavent G, et al. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics 2011;127:402-410.
32. Danielsson P, Kowalski J, Ekblom Ö, Marcus C. Response of severely obese children and adolescents to behavioral treatment. Arch Pediatr Adolesc Med 2012;166:1103-1108.
33. Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP., et al. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res 1998;7:387-397.
34. Tsiros MD, Olds T, Buckley JD, Grimshaw P, Brennan L, Walkley J, et al. Health-related quality of life in obese children and adolescents. Int J Obes (Lond) 2009;33:387-400.
35. Fekkes M, Theunissen NC, Brugman E, Veen S, Verrips EG, Koopman HM, et al. Development and psychometric evaluation of the TAPQOL: a health-related quality of life instrument for 1-5-year-old children. Qual Life Res 2000;9:961-972.

Nederlandse Samenvatting

Omdat obesitas bij kinderen over de hele wereld nog steeds toeneemt, zijn effectieve strategieën voor de behandeling van overgewicht en obesitas bij kinderen noodzakelijk. Gebleken is dat programma's met multidisciplinaire interventies gericht op de leefstijl in de leeftijd van 5-12 jaar, met inbegrip van een gedragscomponent, effectief zijn voor gewichtsvermindering. Obesitas begint echter al voor het vijfde levensjaar. Daarom moeten programma's voor het behandelen van obesitas gericht zijn op jongere kinderen, omdat jonge kinderen met obesitas een groot risico hebben om tijdens de puberteit en het volwassen leven obees te blijven. Obesitas tijdens de kinderjaren brengt aanzienlijke gezondheidsrisico's met zich mee, zowel lichamelijk als geestelijk. Om de effecten van een multidisciplinair leefstijl interventieprogramma bij 3- tot en met 5-jarige kinderen met overgewicht of obesitas te onderzoeken werd een gerandomiseerde, gecontroleerde klinische trial uitgevoerd door het Groningen Expertise Centrum voor Kinderen met Overgewicht (GECKO). Overgewicht en obesitas werden gedefinieerd volgens internationale afkapwaarden, als een BMI (Body Mass Index) van respectievelijk > 1,1 standaarddeviatiescore (SDS) en > 2,3 SDS. Tussen oktober 2006 en maart 2008 werden 75 kinderen ingedeeld bij een multidisciplinair interventieprogramma of bij een programma met conventionele zorg. Beide behandelprogramma's duurden 16 weken. Het multidisciplinaire interventieprogramma voor kinderen en hun ouders bestond uit 6 sessies met voedingsadvies van een diëtist (30 minuten elk), 12 groepssessies van elk 60 minuten onder begeleiding van een fysiotherapeut en, alleen voor de ouders, 6 groepssessies (van elk 120 minuten) met gedragstherapie onder begeleiding van een psycholoog. Kinderen en ouders uit de groep met conventionele zorg kregen advies over een gezonde leefstijl door een kinderarts in opleiding, 3 sessies van elk 30-60 minuten.

De lengte en het gewicht van de kinderen werden gemeten met een standaard geijkte weegschaal en een stadiometer. De BMI werd berekend en gecorrigeerd voor leeftijds- en geslachtsspecifieke gegevens uit het Vierde Nederlandse Groeionderzoek. De middelomtrek werd gemeten met een standaard meetlint midden tussen de laterale crista iliaca en de onderste rib en gestandaardiseerd zoals hierboven is beschreven. De lichaamssamenstelling werd bepaald via bio-impedantie-analyse (BIA-101, Akern S.r.l./RJL Systems, Florence, Italië) en het percentage lichaamsvet (BF%, body fat) en de vetvrije massa (FFM, fat-free mass) werden berekend zoals eerder is beschreven. Subcutaan buikvet werd via echografie bepaald (SonoSite Titan, SonoSite, Inc., Bothell, WA, USA). De systolische en diastolische bloeddruk werden bepaald met een digitale sfygmomanometer Dinamap Critikon 1846SX (Critikon Inc., Tampa, Florida, USA). De bloeddruk van de kinderen werd geclassificeerd aan de hand van geslacht, lengte en leeftijd.

Na een vastenperiode van een nacht werd bloed afgenomen voor de bepaling van serumlipiden (totaal cholesterol (TC), HDL- en LDL-cholesterol (HDL-C en LDL-C) en triglyceriden (TG)) en van parameters voor het glucosemetabolisme (HbA1c, insuline, en glucose). De insulinegevoeligheid werd bepaald via het geactualiseerde Homeostasis Model Assessment of Insulin Resistance (homeostase model voor de insuline resistentie (HOMA2-IR)). Bovendien werden markers voor systemische lagegraadontsteking (high-sensitive c-reactive protein (hsCRP), tumornecrosefactor α (TNFα), en interleukine-6 (IL-6)), en werden de adipokinen leptine en adiponectine bepaald.

Tijdens beide behandelprogramma's werd het eetpatroon van de kinderen gedocumenteerd met behulp van speciaal ontwikkelde dagboeken, waarin het soort en de hoeveelheid genuttigd voedsel door de ouders werden genoteerd. De dagboeken werden tijdens 4 achtereenvolgende dagen gebruikt: 2 weekdagen en 2 weekenddagen. De voedseldagboeken werden door een diëtist geëvalueerd en de inname van nutriënten werd met een gevalideerd computerprogramma berekend (Vodisys Medical Software, IP Health Solutions, Groningen, Nederland), aan de hand van het Nederlands voedingsstoffenbestand (NEVO 2006). De lichamelijke activiteit van de kinderen werd met een pedometer bepaald (Yamax Digi-Walker SW-200, Yamax USA, Inc., San Antonio, TX, USA). De pedometer werd gedurende ten minste 3 weekdagen en 1 weekenddag gedragen. Voor elke dag waarop de pedometer werd gedragen, noteerden de ouders het aantal stappen in een dagboekje. Het gemiddelde aantal stappen per dag werd berekend.

De gezondheidsgerelateerde kwaliteit van leven (HRQoL, Health-related Quality of Life) werd bepaald met behulp van twee vragenlijsten die door één van de ouders werden ingevuld. De vragenlijst Dutch-Child-AZL-TNO-Quality-of-Life (DUX-25) meet de dagelijkse activiteiten en omvat 25 vragen met betrekking tot aspecten van de lichamelijke en de emotionele situatie, de thuissituatie en sociale onderwerpen. Antwoorden die bij elke vraag kunnen worden gegeven, worden uitgedrukt in 5 abstracte gezichten vanaf gelukkig (score 5) tot bedroefd (score 1), zodat een Likert-schaal van 5 punten ontstaat. De Nederlandse uitgave van de Child Health Questionnaire-Parent Form (CHQ-PF50) meet de perceptie van de gezondheid en omvat 50 vragen, verdeeld over 11 meervoudige schalen en 4 vragen met enkelvoudig onderwerp en richten zich op het lichamelijke, emotionele en sociale welzijn van het kind. Op beide schalen duidt een hogere score op een betere kwaliteit van leven.

In **hoofdstuk 2** beschrijven we de prevalentie van insulineresistentie en cardiovasculaire risicofactoren bij de kinderen met overgewicht en obesitas aan het begin van beide behandelprogramma's. Van de 75 kinderen hadden 29 kinderen overgewicht en 46 obesitas. Er werd bepaald dat sprake was van cardiovasculaire risicofactoren wanneer van één of meer van de volgende criteria sprake was (1) TG $\geq$ 1,24 mmol/l; (2) HDL-C $\leq$ 1,03 mmol/l; (3) hypertensie (systolische en/of diastolische bloeddruk $\geq$ 90^{ste} percentiel voor leeftijd, geslacht en lengte); (4) gestoorde glucosetolerantie (HOMA2-IR $\geq$ $97,5^{ste}$ percentiel).

We vonden dat bij 6,9% (verhoogde triglyceridenspiegel) tot 74,3% (hypertensie) van de kinderen cardiovasculaire risicofactoren aanwezig waren. Bij 5 van de 65 kinderen (7,7%) werd een HOMA2-IR boven de bovengrens van de normale spreiding aangetroffen. Dit betrof één kind met overgewicht (4,0%) en 4 kinderen met obesitas (10,0%). HOMA2-IR en nuchtere insuline waren significant hoger bij de kinderen met obesitas dan bij de kinderen met overgewicht (beide $p < 0,01$); hetzelfde gold voor de nuchtere glucosewaarde ($p = 0,01$).

HOMA2-IR vertoonde een sterke correlatie met de BMI ($r = 0{,}63$), middelomtrek ($r = 0{,}62$), en % lichaamsvet ($r = 0{,}58$) ($p < 0{,}001$ in alle gevallen).

In **hoofdstuk 3** presenteren we de resultaten van het multidisciplinaire interventie-programma bij onze 3- tot en met 5-jarige kinderen met overgewicht of obesitas voor de antropometrische parameters voor obesitas en voor de lichaamssamenstelling, aan het einde van de behandelperiode en na 1 jaar follow-up. We vergeleken de resultaten met een groep kinderen met overgewicht en obesitas in het programma met conventionele zorg.

Tijdens de behandelperiode van 16 weken stopten 7 kinderen uit de multidisciplinaire interventiegroep met het onderzoek of deden niet mee aan de follow-up. Bij 3 van deze kinderen gaven de ouders als verklaring dat het onderzoek te tijdrovend was. Bij de andere kinderen gaven de ouders geen specifieke reden. Bij de groep met conventionele zorg deden 6 kinderen niet aan de follow-up mee. Bij 3 kinderen merkten de ouders op dat het programma te veel stress opleverde, bij de andere 3 kinderen werd geen reden opgegeven. Tussen het einde van beide behandelprogramma's en de follow-up na 1 jaar, ging nog een kind uit de multidisciplinaire interventiegroep en nog eens 4 kinderen uit de groep met conventionele zorg voor de follow-up verloren. Aan het einde van de interventieperiode werden gegevens van 62 kinderen (82,7%) geanalyseerd en op het moment van de follow-up na een jaar werden gegevens van 57 kinderen (76,0%) geanalyseerd.

Bij vergelijking van het effect van beide behandelprogramma's tussen het begin en het einde van de interventie van 16 weken, toonden we bij de multidisciplinaire interventiegroep een statistisch grotere afname van de BMI aan (gemiddeld verschil 0,5 kg/m^2 met standaarddeviatie (SD) 0,3, $p = 0{,}05$); bij de z-score voor de BMI (gemiddeld verschil (SD) 0,2 (0,1), $p = 0{,}03$), en bij de z-score van de middelomtrek (gemiddeld verschil (SD) 0,3 (0,1), $p = 0{,}02$), in vergelijking met de kinderen uit de groep met conventionele zorg. Na 1 jaar follow-up hadden de kinderen in de multidisciplinaire interventiegroep een statistisch significante grotere afname van de BMI ($p = 0{,}03$), z-score voor de BMI ($p = 0{,}02$), middelomtrek ($p = 0{,}02$), en voor de z-score voor de middelomtrek ($p = 0{,}01$), vergeleken met de kinderen uit de groep met conventionele zorg. De afname van het viscerale vet was bijna statistisch significant ten gunste van de multidisciplinaire interventiegroep ($p = 0{,}08$).

Met betrekking tot lichamelijke activiteit en inname van nutriënten vertoonde alleen de dagelijkse inname van vezels tussen het begin en 16 weken een statistisch significant verschil tussen beide groepen, ten gunste van de multidisciplinaire interventiegroep ($p = 0{,}02$). Tussen het begin en de follow-up na 12 maanden waren er geen statistisch significante verschillen tussen beide groepen aantoonbaar.

In **hoofdstuk 4** wordt het effect van beide behandelprogramma's op adipokinen, insulineresistentie, lipidenprofiel en systemische lagegraadontsteking beschreven. In beide groepen was de insulinegevoeligheid aan het einde van de behandelperiode verbeterd, zoals bleek uit een daling van de insulineconcentratie en een afname van HOMA2-IR. Bovendien waren bij de multidisciplinaire interventiegroep HbA_{1c} en TNFα significant afgenomen (beide

p = 0,01). Bij vergelijking van beide groepen in de loop van de tijd bleken er geen statistisch significante verschillen tussen de groepen te bestaan. De afname van de concentraties van T-C (p = 0,07) en TNFα (p = 0,06) was bijna statistisch significant ten gunste van de multidisciplinaire interventiegroep. Wanneer het resultaat van beide groepen werd samen genomen, werd een statistisch significante correlatie aangetoond tussen de afname van het percentage lichaamsvet en een afname van de concentraties van HOMA2-IR (r = 0,37, p = 0,02) en van TG (r = 0,29, p = 0,02).

In **hoofdstuk 5** worden de effecten van het multidisciplinaire interventieprogramma op de gezondheidsgerelateerde kwaliteit van leven beschreven. De resultaten worden vergeleken met de effecten die in de groep met conventionele zorg zijn waargenomen. De gezondheidsgerelateerde kwaliteit van leven werd bij het begin en het einde van beide behandelprogramma's gemeten en na 12 maanden opnieuw. Bij het begin, na 16 weken en na 12 maanden waren 69 (92,0% van de kinderen), 59 (95,2%) en 40 (70,2%) van de DUX-25 vragenlijsten beschikbaar voor evaluatie. Voor de CHQ-PF50 waren dit respectievelijk 71 (94,7%), 59 (95,2%) en 40 (70,2%) vragenlijsten. Uit de gegevens bij het begin van de DUX-25 vragenlijsten van beide behandelgroepen bleek dat de gezondheidsgerelateerde kwaliteit van leven niet lager was dan die van gezonde Nederlandse kinderen. Zelfs hogere scores werden gemeld. In het algemeen kon dit verschil in gezondheidsgerelateerde kwaliteit van leven niet uit de CHQ-PF50 vragenlijsten worden geconcludeerd. In vergelijking met kinderen met astma of gedragsproblemen meldden ouders van onze 3- tot en met 5-jarigen met overgewicht of obesitas meestal een hogere gezondheidsgerelateerde kwaliteit van leven zowel op de DUX-25 als op de CHQ-PF50 vragenlijst.

Bij de follow-up na 12 maanden vertoonden kinderen uit de multidisciplinaire interventiegroep een statistisch significante toename van de totale DUX-25 score ten opzichte van de kinderen uit de groep met conventionele zorg (mediaan 5,0 vs. -4,5, p = 0,04). Deze toename van de gezondheidsgerelateerde kwaliteit van leven bij de kinderen uit de multidisciplinaire interventiegroep werd ook aangetoond voor de subschaal lichamelijke gezondheid van de DUX-25 vragenlijst (mediaan 8,3 vs. -4,2, p = 0,03). Met betrekking tot de CHQ-PF50 vragenlijsten was de score voor de schaal 'lichamelijke pijn' uit de multidisciplinaire interventiegroep afgenomen; deze score wees op meer pijn of meer beperkingen als gevolg van pijn, terwijl de score in de groep met conventionele zorg voor 'lichamelijke pijn' onveranderd was gebleven (mediaan -5,0 vs. 0,0, p = 0,03). Voor de schaal 'geestelijke gezondheid' gaven kinderen uit de multidisciplinaire interventiegroep meer blijk van gevoelens van angst en depressie aan het einde van het programma van 16 weken in vergelijking met de kinderen uit de groep met conventionele zorg die minder melding maakten van gevoelens van angst en depressie (mediaan -5,0 vs. 5,0, p = 0,02). Bij de follow-up na 12 maanden waren tussen de groepen geen statistisch significante veranderingen aantoonbaar.

Voor beide groepen gezamenlijk ging een afname van de z-score van de BMI tussen het begin en 12 maanden follow-up gepaard met een toegenomen 'globale gezondheid' (r

= -0,36, p = 0,03). Bij 12 maanden na het begin was een afname van het visceraal vet op de CHQ-PF50 gecorreleerd met een toename van de schalen 'globale gezondheid' (r = -0,37, p = 0,03), 'algemeen gedrag' (r = -0,41, p = 0,01), en 'algemene gezondheid' (r = -0,43, p = 0,01).

In **hoofdstuk 6** beschrijven we de effecten op lange termijn van het multidisciplinaire interventieprogramma op antropometrische parameters voor obesitas en voor lichaamssamenstelling in vergelijking met de resultaten van de kinderen uit de groep met conventionele zorg. De gegevens werden 1,5 en 3 jaar na het begin van het behandelprogramma verzameld. Na 1,5 jaar na het begin waren gegevens van 48 kinderen (64,0%) beschikbaar voor evaluatie. De gemiddelde (SD) leeftijd van de kinderen uit de multidisciplinaire interventiegroep was 6,0 (0,8) jaar; in de groep met conventionele zorg was dit 6,2 (0,9) jaar. Na 3 jaar na het begin waren gegevens van 29 kinderen (38,7%) beschikbaar voor evaluatie. De gemiddelde (SD) leeftijd van de kinderen uit de multidisciplinaire interventiegroep en de groep met conventionele zorg was respectievelijk 7,3 (1,1) en 7,4 (1,3) jaar.

Bij de follow-up na 18 maanden vertoonden de kinderen uit de multidisciplinaire interventiegroep nog altijd een significante afname van de z-score van de BMI (gemiddelde (SD) -0,8 (0,6), p < 0,001); van de z-score van de middelomtrek (gemiddelde (SD) -0,6 (0,6), p < 0,001), van het % lichaamsvet (gemiddelde (SD) -2,7 (5,4), p = 0,02), en van het visceraal vet (gemiddelde (SD) -0,8 (1,8) cm, p = 0,05). De vetvrije massa was significant toegenomen (gemiddelde (SD) 3,1 (2,1) kg, p < 0,001). Daarnaast was ook de z-score van de BMI in de groep met conventionele zorg afgenomen (gemiddelde (SD) -0,6 (0,6), p < 0,001) evenals de z-score voor middelomtrek (gemiddelde (SD) -0,5 (0,6), p = 0,001) en was de vetvrije massa toegenomen (gemiddelde (SD) 3,0 (1,4) kg, p < 0,001). Als we de veranderingen in beide groepen vanaf baseline tot 18 maanden na het begin van de interventie vergelijken, was de afname van de z-score van de middelomtrek in de multidisciplinaire groep meer uitgesproken in vergelijking met de groep met conventionele zorg (p = 0,05).

Bij de follow-up na 36 maanden vertoonden de kinderen uit de multidisciplinaire interventiegroep een blijvende afname van de z-score van de BMI (gemiddelde (SD) -0,9 (0,8), p < 0,001), en een toename van de vetvrije massa (gemiddelde (SD) 7,0 (2,4) kg, p < 0,001). De afname van de z-score van de middelomtrek was bijna statistisch significant (gemiddelde (SD) -0,4 (0,8), p = 0,07). In de groep met conventionele zorg was de afname van de z-score van de BMI eveneens nog steeds aantoonbaar (gemiddelde (SD) -0,6 (0,8), p = 0,02), evenals de afname van de z-score van de middelomtrek (gemiddelde (SD) -0,5 (0,6), p = 0,03). Ook kon nog steeds een toename van de vetvrije massa worden aangetoond (gemiddelde (SD) 7,1 (2,2) kg, p < 0,001). Als we de resultaten van beide groepen vanaf het begin tot 3 jaar na het begin van de behandeling vergelijken, waren er geen verschillende veranderingen van antropometrie of lichaamssamenstelling. Wat betreft de lichamelijke activiteit en de energie-inname waren er geen statistisch significante verschillen tussen de twee behandelgroepen in de loop van de tijd.

Omdat beide programma's langdurige gunstige effecten op de z-score van de BMI en de vetvrije massa bleken te hebben, kon niet worden geconcludeerd of een multidisciplinair interventieprogramma aanvullende positieve langetermijneffecten had ten opzichte van een programma voor conventionele zorg, mede doordat slechts een klein aantal kinderen voor evaluatie beschikbaar was.

Dankwoord

Misschien wel het belangrijkste hoofdstuk van dit proefschrift! Eindelijk de gelegenheid om iedereen in woord te bedanken voor hun bijdrage, op welke manier dan ook, aan mijn promotieonderzoek.

Allereerst de kinderen en ouders die aan het onderzoek hebben meegedaan. Fantastisch dat jullie bereid waren om deel te nemen aan alle behandelsessies, metingen, bloed afnamen en invullen van vragenlijsten en dagboekjes. Mede dankzij jullie hebben we meer gegevens om te komen tot een betere behandeling van kinderen met overgewicht.

Prof. dr. P.J.J. Sauer, beste Pieter. Allereerst heel veel dank voor de mogelijkheid die je me hebt geboden om dit onderzoek te kunnen doen binnen het Groningen Expertise Centrum voor Kinderen met Overgewicht, uiteindelijk resulterend in deze promotie. De manier waarop je me begeleid hebt, altijd beschikbaar, je immer positieve blik en enthousiasme, zijn voor mij een enorme stimulans geweest om dit onderzoek tot een mooi resultaat te brengen. Ik vond het altijd erg plezierig om naar je toe te komen, om te praten over het onderzoek, maar ook over andere dingen die binnen en buiten het Beatrix Kinderziekenhuis speelden. En dan te bedenken dat ik bijna niet naar Groningen was gekomen! Gelukkig heb je me destijds een tweede kans geboden. Ik hoop dat ik ook de komende tijd af en toe nog eens van je enthousiasme voor het onderzoek gebruik mag maken.
Prof. dr. R.P. Stolk, beste Ronald. Ook jij heel veel dank voor de kans die je me hebt geboden om dit onderzoek te kunnen doen. Het begon destijds met je uitnodiging om een overzichtsartikel te schrijven over niet-alcoholische leververvetting bij kinderen met overgewicht, gepubliceerd in het Nederlands Tijdschrift voor Geneeskunde. In de loop van het onderzoek heb je de dagelijkse begeleiding over gedaan aan Eva Corpeleijn, maar je was altijd zeer geïnteresseerd in mijn vorderingen in het onderzoek. Dank je voor je altijd kritische blik op de resultaten en de manuscripten. De stukken werden er altijd weer beter van. Ik hoop dat we ook in de toekomst kunnen blijven samenwerken binnen het onderzoek op het gebied van kinderen met overgewicht.

Dr. ir. E. Corpeleijn, beste Eva. Jij nam vanuit de afdeling epidemiologie de dagelijkse begeleiding van mijn promotieonderzoek van Ronald over. Ik ben je zeer erkentelijk voor je kritische blik op de getallen (waren deze kinderen echt wel nuchter toen ze geprikt werden?), hulp bij de analyses (dichotome uitkomsten bestaan niet!) en je wijze lessen over epidemiologie en statistiek. Er ging voor mij regelmatig een nieuwe wereld open. Fijn dat we de komende tijd contact blijven houden binnen het GECKO.

Prof. dr. H.A. Delemarre-van de Waal (beste Henriette), prof. dr. S.A. Reijneveld (beste Menno), en prof. dr. B.H.R. Wolffenbuttel (beste Bruce), heel veel dank voor jullie bereidheid en tijd om mijn manuscript te lezen en te beoordelen. Het is bijzonder voor mij dat juist jullie in de beoordelingscommissie zitten. Henriette, als mijn opleider tot kinderarts-endocrinoloog; Menno, als promotor van Inger; en Bruce, als hoofd van de afdeling Endocrinologie van het UMCG, waarmee de kinderendocrinologie een zeer prettige samenwerking heeft.

Karin Kremer-Veldman, in het begin van mijn promotieonderzoek heb jij me geholpen met mijn eerste stappen in de wereld van de statistiek. Heel erg bedankt voor het doen van de eerste analyses en de geduldige uitleg waarom je juist weer voor die statistische test koos. Fijn dat ik altijd bij je terecht kon als ik weer een statistisch probleem had.

Eefje Ongering, je was de eerste student geneeskunde die mij heeft geholpen met het onderzoek. Je deed dat binnen je wetenschapsstage en je analyseerde de data over het voorkomen van cardiovasculaire risicofactoren bij kinderen met overgewicht en obesitas. We hadden elkaar al eerder ontmoet in een tutorgroep waarbij ik onder de indruk was van je kennis en inzet. Toen je me enige tijd later mailde dat je graag onderzoek wilde doen, wist ik dat je hiervoor zeer geschikt zou zijn. Je hebt dat zeker bewezen! Je nauwkeurigheid en snelheid van werken hebben geresulteerd in het mede-auteurschap van het artikel dat in Hormone Research in Paediatrics is gepubliceerd. Eefje, nogmaals veel dank voor je hulp en ik wens je veel succes in je verdere loopbaan, nu in Amsterdam.

Mirije Kuitert, jij hebt mij binnen je wetenschapsstage geholpen met het analyseren van de vragenlijsten over de kwaliteit van leven bij kinderen met overgewicht en obesitas. Dat was een flink karwei. Ik was altijd erg onder de indruk van je kennis over statistiek en hoe snel je weer gegevens had geanalyseerd en uitgewerkt (zijn de data nu wel of niet normaal verdeeld?). Ook het uitzoeken van relevante medische literatuur kon ik goed aan jou overlaten. Inmiddels moet je een expert zijn op het gebied van kwaliteit van leven! Ik weet zeker dat het stuk waarvan je mede-auteur bent, gepubliceerd gaat worden. Mirije, ook jij veel dank voor je hulp en veel succes met je verdere loopbaan.

Alma Linde van Ommen, Marije Seves, Annelies Zwerver, Annette Velthuis, Saskia Muller en Jannie Postma. Vanuit de opleiding Voeding en Diëtetiek van de Hanzehogeschool Groningen hebben jullie je afstudeerspecialisatie binnen dit promotieonderzoek gedaan. Jullie hebben met veel inzet geholpen bij de planning van de polibezoeken en het analyseren van de dieet- en beweegdagboeken. Jullie inbreng is zeer waardevol geweest. Heel veel dank hiervoor.

Dr. B.T.C. Flapper, beste Boudien. Je hulp bij het interpreteren van de uitkomsten van de vragenlijsten over de kwaliteit van leven was onmisbaar. Ook wil ik je hierbij bedanken voor je inbreng bij het schrijven van het manuscript over de kwaliteit van leven bij de kinderen die aan het onderzoek meededen. Mede dankzij jou heeft het stuk meer focus gekregen.
Alle mensen van het lab, en Henk Breukelman in het bijzonder. Heel veel dank voor jullie hulp

bij de afname en verwerking van de bloedmonsters. Jullie waren altijd bereid mee te denken en mee te helpen als er praktische problemen waren. Ik kon altijd bij jullie terecht, heel veel dank hiervoor.

Bettine Haandrikman, veel dank voor het verrichten van de ELISA analyse van de adipokines en obesitas gerelateerde ontstekingsparameters. Mede dankzij jouw hulp is hieruit een mooie publicatie gekomen.

Mijn paranimfen Nynke Doornebal-Pietersen en Bas Zegers. Fantastisch dat jullie me willen bijstaan tijdens de verdediging van mijn proefschrift. Nynke (dokter Zaakje), onze gezamenlijke diensten vroeger waren altijd erg gezellig, wat hebben we veel gelachen! Fijn dat we inmiddels zulke goede vrienden en elkaars (bijna) buren zijn. Bas (Zegers, wat mot je?), we kennen elkaar al sinds de opleiding tot kinderarts. Ondanks het feit dat we ver van elkaar wonen en elkaar niet zo vaak zien, blijft onze vriendschap sterk. En, binnenkort is het jouw feestje!

Dr. Bart Rottier, beste Bart. Dank je voor je steun en grappen over Italianen tijdens mijn promotieonderzoek. Het was altijd erg prettig om mijn hart bij je te luchten als het onderzoek even tegen zat. Je relativeringsvermogen en humor gaven me altijd weer de nodige energie om verder te gaan. Ik hoop de komende tijd weer veel te kunnen lachen met je!
Mijn collega's kinderartsen van de sectie kinderendocrinologie, dr. Willie Bakker-van Waarde, dr. Annemieke Boot en dr. Mirjam van Albada. Wat hebben we een leuke club samen. Mede dankzij jullie kon dit onderzoek worden afgerond tot een promotie. Ik hoop dat onze endo-club zo nog lang blijft bestaan.

Alle collega's van het kinderdiabetesteam en endo-team: Annette Geluk, Liesbeth Breedland, Esther Gerrits, Nathalie Vandeursen, Gineke Venema, Jet van der Hulst, Kim van der Schoot, Janet Cuperus, Elsbeth Noordbeek, Peter Koster en Renée Staal. Dank voor jullie interesse, ondersteuning, inspringen als ik het weer te druk had, en luisterend oor tijdens mijn promotieonderzoek.

Michel Verstraelen, beste Michel. We kennen elkaar sinds onze studententijd in Nijmegen. Ondanks dat we ver van elkaar wonen en elkaar daardoor niet zo veel zien, blijft onze vriendschap sterk. Dank je voor de lange gesprekken over voetbal en over "het leven". Het was voor mij erg fijn om het zo nu en dan eens niet over wetenschap te hebben. Nu deze promotie is afgerond, hoop ik dat we elkaar de komende tijd vaker zullen zien!

Linda en Michiel, Elke en Joris, dank voor jullie belangstelling en steun tijdens mijn promotieonderzoek, maar vooral ook voor de altijd gezellige momenten samen!

Cara tante Lu, Paolo e Giorgio. Per me significa molto la vostra presenza oggi alla cerimonia del mio dottorato. Vi ringrazio per tutti i bei ricordi delle vacanze e dei bei momenti passati insieme. Un grande abbraccio!

Els en Bert Tjeertes, mijn lieve schoonouders. Op de eerste plaats heel veel dank voor jullie mooie dochter! Ook veel dank voor jullie hulp (nog steeds) bij het opvangen van zieke kinderen, oppassen tijdens congressen en al die dingen meer. Mede dankzij jullie kon het dagelijkse leven "gewoon" doorgaan en konden Inger en ik onze ambities waarmaken.

Lieve pap en mam, lief zusje, ik voel me een gelukkig mens dat ik in zo'n warm nest heb mogen opgroeien! Door jullie is ooit de basis gelegd om tot dit proefschrift te komen. Ik hoop jullie nog heel lang bij me te hebben.

Lieve Anne, Meinke en Isabelle. Het is een voorrecht om jullie pappa te mogen zijn. Wat maken jullie me gelukkig! Na een dag in het ziekenhuis is het altijd weer een feest om thuis te komen en jullie te knuffelen. Wordt alsjeblieft niet te snel groot.

Lieve Inger, lieve schat. Ik kan het niet vaak genoeg zeggen: je bent de liefde van mijn leven! Wat bijzonder dat we vandaag allebei ons proefschrift mogen verdedigen en wat ben ik trots op je. Dankzij jou heb ik mijn ambities in Groningen kunnen waarmaken. Je hebt daar destijds zelfs je opleiding tot kinderarts voor afgebroken. Nu, na het afronden van mijn promotie, kan ik hier eindelijk iets voor terug doen. Dank je voor wie je bent. Ti amo!

Publications

Articles

Bocca G, Corpeleijn E, Stolk RP, Wolffenbuttel BH, Sauer PJ. Effect of obesity intervention programs on adipokines, insulin resistance, lipid profile, and low-grade inflammation in 3-year-old to 5-year-old children. Pediatr Res, accepted for publication.

Bocca G, Ongering EC, Stolk RP, Sauer PJ. Insulin resistance and cardiovascular risk factors in 3- to 5-year-old overweight or obese children. Horm Res Paediatr 2013;80:201-206.

Bakker NE, Kuppens RJ, Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Bindels-de Heus GC, **Bocca G**, Haring DA, Hoorweg-Nijman JJ, Houdijk EC, Jira PE, Lunshof L, Odink RJ, Oostdijk W, Rotteveel J, Schroor EJ, van Alfen AA, van Leeuwen M, van Pinxteren-Nagler E, van Wieringen H, Vreuls RC, Zwaveling-Soonawala N, de Ridder MA, Hokken-Koelega AC. Eight years of growth hormone treatment in children with Prader-Willi syndrome: maintaining the positive effects. J Clin Endocrinol Metab 2013;98:4013-4022.

Sijtsma A, **Bocca G**, L'Abée C, Liem E, Sauer PJ, Corpeleijn E. Waist-to-height ratio, waist circumference and BMI as indicators of percentage fat mass and cardiometabolic risk factors in children aged 3 to 7 years. Clin Nutr 2013, doi: 10.1016/j.clnu.2013.05.010

De Lange AH, **Bocca G**. Vaginal bleeding in a four-month-old preterm girl: extreme mini-puberty mimicking central precocious puberty. J Pediatr Endocrinol Metab 2013;26:595-597.

De Vetten L, **Bocca G**. Systemic effects of hypothermia due to hypothalamic dysfunction after resection of a craniopharyngioma: case report and review of literature. Neuropediatrics 2013;44:159-162.

Bocca G, Corpeleijn E, Stolk RP, Sauer PJ. Results of a multidisciplinary treatment program in 3-year-old to 5-year-old overweight or obese children. A randomized controlled clinical trial. Arch Pediatr Adolesc Med 2012;166:1109-1115.

Heijsman SM, Koers AF, **Bocca G**, van der Veen BS, Appelhof M, Kamps AW. Non-invasive measurement of adrenal response after standardized exercise tests in prepubertal children. J Pediatr Endocrinol Metab 2012;25:471-478.

Siemensma EP, de Lind van Wijngaarden RF, Festen DA, Troeman ZC, van Alfen-van der Velden AA, Otten BJ, Rotteveel J, Odink RJ, Bindels-de Heus GC, van Leeuwen M, Haring DA, Oostdijk W, **Bocca G**, Houdijk EC, Hoorweg-Nijman JJ, van Wieringen H, Vreuls RC, Jira PE, van Trotsenburg AS, Schroor EJ, Pilon JW, van Pinxteren-Nagler E, Lunshof L, Hokken-Koelega

AC. Beneficial effects of growth hormone treatment on cognition in children with Prader-Willi syndrome: A randomized controlled trial and longitudinal study. J Clin Endocrinol Metab 2012;97:2307-2314.

Bergman JE, de Ronde W, Jongmans MC, Wolffenbuttel BH, Drop SL, Hermus A, **Bocca G**, Hoefsloot LH, van Ravenswaaij-Arts CM. The results of CHD7 analysis in clinically well-characterized patients with Kallmann syndrome. J Clin Endocrinol Metab 2012;97:E858-E862.

Swelheim HT, Westerlaken C, van Pinxteren-Nagler E, **Bocca G**. Lipoatrophy in a girl with type 1 diabetes. Beneficial effects of treatment with a glucocorticoid added to an insulin analog. Diabetes Care 2012;35:e22.

Bergman JE, **Bocca G**, Hoefsloot LH, Meiners LC, van Ravenswaaij-Arts CM. Anosmia predicts hypogonadotropic hypogonadism in CHARGE syndrome. J Pediatr 2011;158:474-479.

Van der Zee T, de Vries MJ, Vodegel RM, **Bocca G**, Kamps AW. Vitiligo bij kinderen: soms meer dan alleen de huidaandoening. Tijdschr Kindergeneeskd 2010;78:243-246.

De Lind van Wijngaarden RF, Siemensma EP, Festen DA, Otten BJ, van Mil EG, Rotteveel J, Odink RJ, Bindels-de Heus GC, van Leeuwen M, Haring DA, **Bocca G**, Houdijk EC, Hoorweg-Nijman JJ, Vreuls RC, Jira PE, van Trotsenburg AS, Bakker B, Schroor EJ, Pilon JW, Wit JM, Drop SL, Hokken-Koelega AC. Efficacy and safety of long-term continuous growth hormone treatment in children with Prader-Willi syndrome. J Clin Endocrinol Metab 2009;94:4205-4215.

De Lind van Wijngaarden RF, Festen DA, Otten BJ, van Mil EG, Rotteveel J, Odink RJ, van Leeuwen M, Haring DA, **Bocca G**, Houdijk EC, Hokken-Koelega AC. Bone mineral density and effects of growth hormone treatment in prepubertal children with Prader-Willi syndrome: A randomized controlled trial. J Clin Endocrinol Metab 2009;94:3763-3771.

De Vries HA, Brouwer OF, Goorhuis JF, **Bocca G**. Hashimoto-encefalopathie: gemakkelijk te missen, goed te behandelen. Tijdschr Kindergeneeskd 2009;77:71-73.

Bocca G, van Beek AP, de Bont ES. Growth hormone deficiency in children following radiotherapy for a brain tumour. Implement substitution promptly [Dutch]. Ned Tijdschr Geneeskd 2009;153:A342.

Bocca G, Stolk RP, Scheenstra R, Sauer PJ. Non-alcoholic fatty liver disease in children: a new complication of obesity [Dutch]. Ned Tijdschr Geneeskd 2008;152:2443-2447.

Donker AE, **Bocca G**. Chance finding of foetal and neonatal ovarian cysts on echography [Dutch]. Ned Tijdschr Geneeskd 2006;150:2577-2581.

Bocca G, van Mil EG, Voorhoeve PG, Wijnaendts LC, Delemarre-van de Waal HA. A girl with Cushing's syndrome due to primary pigmented nodular adrenocortical disease [Dutch]. Ned Tijdschr Geneeskd 2006;150:2390-2393.

Bocca G, Voorhoeve PG, Delemarre-van de Waal HA. Cushing's syndrome in children [Dutch]. Ned Tijdschr Geneeskd 2006;150:2345-2349.

Bocca G, Bruin N, Delemarre-van de Waal HA. Gonadotropin releasing hormone analogue therapy in children with isolated growth hormone deficiency – final height benefit from postponing puberty? J Pediatr Endocrinol Metab 2005;18:535-539.

Bocca G, Weemaes CM, van der Burgt I, Otten BJ. Growth hormone treatment in cartilage-hair hypoplasia: effects on growth and the immune system. J Pediatr Endocrinol Metab 2004;17:47-54.

Bocca G, Monnens LA. Defective proximal tubular function in a patient with I-cell disease. Pediatr Nephrol 2003;18:830-832.

Bocca G, van Moorselaar JA, Feitz WF, van der Staak FH, Monnens LA. Compartment syndrome, rhabdomyolysis and risk of acute renal failure as complications of the lithotomy position. J Nephrol 2002;15:183-185.

Van der Meer W, Jakobs BS, **Bocca G**, Smeitink JA, Schuurmans Steckhoven JH, de Keijzer MH. Peripheral blood lymphocyte appearance in a case of I cell disease. J Clin Pathol 2001;54:724-726.

Bocca G, Noordam C, Wevers RA, de Jong JG, van der Meer W, de Keijzer MH, Korver CR, Smeitink JA. I-cell disease presenting with severe hypophosphatemia and cardiomyopathy. Neuropediatrics 2000;31:49-50.

Bocca G, de Vries J, Cruysberg JR, Boers GH, Monnens LA. Optic neuropathy in McCune-Albright syndrome: an indication for aggressive treatment. Acta Paediatr 1998;87:599-600.

Chapters in Books

Werkboek Kinderendocrinologie. C. Noordam, J. Rotteveel, E.J. Schroor (red.). VU University Press, Amsterdam, 2010.

Leerboek intensive-care-verpleegkunde kinderen. Derde druk. Van den Brink GTWJ, Tol TNC, van Vught EM (red.). Elsevier Gezondheidszorg, Maarssen, 2008.

Delemarre-van de Waal HA, Bocca G, Cohen-Kettenis PT, Haasnoot K, Hack WWM, Rotteveel J, van Trotsenburg ASP. Praktische Kindergeneeskunde. Kinderendocrinologie. Bohn Stafleu van Loghum, Houten, 2006.

Curriculum Vitae

Gianlorenzo (Gianni) Bocca was born in Goirle on May 31st, 1969. He attended the Cobbenhagen College in Tilburg and graduated from VWO in 1987. Between 1987 and 1989 he studied biology and health sciences at the Catholic University Nijmegen. In 1989, Gianni started in medical school, also at the Catholic University Nijmegen (at present, Radboud University Medical Center Nijmegen), and graduated as a medical doctor in 1996.

After working as a resident in pediatrics, Gianni was trained in pediatrics between 1997 and 2002 at the Radboud University Medical Center Nijmegen (head: prof. dr. R.C.A. Sengers) and the St. Joseph Hospital Veldhoven (at present, Máxima Medical Center, Veldhoven, dr. W.E. Tjon A Ten). In 2002, he started with his clinical fellowship in pediatric endocrinology at the VU University Medical Center Amsterdam, under supervision of prof. dr. H.A. Delemarre-van de Waal, and qualified as a consultant in pediatric endocrinology in 2005. Between 2005 and 2006, Gianni worked as a pediatric endocrinologist at the Máxima Medical Center, Veldhoven. From 2006 onwards, he is working at the Beatrix Children's Hospital of the University Medical Center Groningen, at which he is head of the department of pediatric endocrinology. Gianni is married to Inger Tjeertes. Together they have three beautiful daughters: Anne (2007), Meinke (2008), and Isabelle (2011).