Intensive Inpatient Treatment for Severely Obese Children and Adolescents: Costs and Effects

Sabine Makkes
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Intensive Inpatient Treatment for Severely Obese Children and Adolescents: Costs and Effects

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GENERAL INTRODUCTION
Chapter 1

Childhood Obesity

Over the past thirty years, childhood obesity has become a major global health challenge. The prevalence of overweight and obesity has increased substantially in children and adolescents between 1980 and 2013 in both developed and developing countries.¹

In the Netherlands, the prevalence of obesity in native Dutch children and adolescents (2-21 years) has increased four to six times from 1980 to 2009 to 1.8% among boys and 2.2% among girls.² These percentages were even higher in children and adolescents in the same age group from Turkish (8.4% and 8.0% among boys and girls respectively) and Moroccan (6.0% and 7.5% among boys and girls respectively) descent.³

However, in recent years the rapid increase in prevalence of childhood obesity seems to have been leveling off in several countries.⁴-⁹ Despite this leveling off in the prevalence of childhood obesity, there is a worrisome increase in the prevalence of severe childhood obesity.¹⁰ The prevalence of severe obesity appears to be the fastest growing subcategory of obesity in children and adolescents in the United States.⁴,¹⁰-¹¹ In the United States, the prevalence has increased more than 300% in the last 25 years,¹⁰ and now afflicts between 4% and 6% of all youth (2-19 years).¹⁰-¹³ The prevalence of severe childhood obesity is still increasing.¹⁴-¹⁵ In the Netherlands the prevalence of severe obesity in native Dutch children and adolescents was 0.6% in boys and 0.5% in girls in 2009, which is a seven fold increase as compared with 1980.¹⁶ Again, these percentages are higher for children and adolescents from Turkish (2.5% and 1.7% among boys and girls respectively) and Moroccan (1.1% and 1.7% boys and girls respectively) descent.¹⁶ Although the prevalence of severe obesity in the Netherlands is low in comparison with other countries, there are already 18,500 children and adolescents with severe obesity in the Netherlands.¹⁶

Defining Severe Childhood Obesity

To define childhood obesity, the most widely used criteria are based on body mass index (BMI) metrics, because this is most feasible for usage in daily clinical practice. BMI is defined as the weight in kilograms divided by the square of the height in meters (kg/m²). For adults,
the World Health Organization (WHO) has defined overweight as a BMI ≥ 25 and BMI <30 kg/m² and obesity as a BMI ≥ 30 kg/m². Because children are still growing and there are differences between boys and girls, age and sex have to be taken into account when defining BMI cut-offs in children. In 2000, Cole determined age and sex adjusted BMI cut-offs to define overweight and obesity in children and adolescents based on BMI percentile curves that pass through the adult cut-offs of a BMI of 25 kg/m² for overweight and 30 kg/m² for obesity at the age of 18 years. The degree of overweight is quantified using Cole’s least mean square method, which normalizes the BMI’s skewed distribution and expresses BMI as SDS-BMI. SDS-BMI indicates how many standard deviations (SDS) a BMI measurement is above or below the median of the BMI distribution at a certain age in a reference population. In the integrated healthcare standard for obesity management in the Netherlands, it is recommended to use Cole’s cut-offs. Only recently, in 2012, extended international (IOTF) cut-offs for childhood obesity classes II and III (severe obesity) were presented. At the time we began our study (2009), these cut-offs were not yet available. Therefore, it was decided to define severe obesity in children and adolescents as a SDS-BMI ≥ 3.0 (99.9th age- and sex-specific percentile of BMI), or a SDS-BMI ≥ 2.3 (99th age- and sex-specific percentile of BMI) in combination with obesity-related comorbidity (e.g. obstructive sleep apnea syndrome, raised insulin, diabetes mellitus type 2, liver function disorders, dyslipidemia, worn out joints).

Physical and psychosocial health consequences of severe childhood obesity

Severe childhood obesity can have severe negative consequences on both the child’s physical and psychosocial health. Figure 1 shows an overview of these negative consequences of childhood obesity.

Physical health consequences
Children and adolescents with severe obesity have increased levels of risk factors such as dyslipidemia, hypertension, oxidative stress, and inflammation, which increases their risk of cardiovascular disease relatively early in life. It is suggested by clinical and population-based studies that both the number and severity of risk factors for cardiovascular disease increase with the degree of obesity in both childhood and adolescence. In
addition, severe obesity can lead to hyperinsulinemia, insulin resistance, prediabetes (impaired glucose tolerance) and even diabetes mellitus type 2.\textsuperscript{21, 29-33} Musculoskeletal problems associated with obesity include arthritis of the hip and knee joints, impairment in mobility and higher rates of fractures.\textsuperscript{34} Blount’s disease is less common than the musculoskeletal problems mentioned before, but a clear relationship exists between the severity of obesity and the risk of Blount’s disease.\textsuperscript{35} Other comorbidities often seen in severely obese children and adolescents are obstructive sleep apnea syndrome, gallstone disease, and non-alcoholic fatty liver disease.\textsuperscript{34, 36-38}
Besides the serious health effects related to obesity early in life, a direct link between obesity in childhood and adolescence and adult cardiovascular disease and mortality has been suggested, mainly because childhood obesity often tracks into adulthood. The degree of obesity in childhood and adolescence increases the risk of adult cardiovascular disease and mortality in an almost linear fashion. Risks of heart disease, stroke and diabetes mellitus type 2 increase steadily with increasing severity of obesity in childhood and are associated with premature death. Strong evidence exists for the association between obesity and several types of cancer such as esophageal adenocarcinoma, endometrial, colorectal, postmenopausal breast, prostate, and renal cancer.

**Psychosocial health consequences**

In addition to these physical consequences, childhood obesity has a negative impact on psychosocial health in children and adolescents. Psychosocial health results from the interactions between social influences, psychological health and behavior. Obesity is associated with a negative self-evaluation, bullying, psychological problems, social stigma, symptoms of depression and anxiety. Low self-esteem and behavioral problems are commonly seen in childhood obesity. Severely obese children and adolescents also report an impaired quality of life (QoL), with QoL-scores similar to individuals diagnosed with cancer.

**Economic consequences of severe obesity for society**

Besides having a negative impact on physical and psychosocial health, childhood obesity also results in a heavy financial burden for society. The presence of severe obesity in childhood is also associated with increased direct costs due to increased utilization of healthcare services. Healthcare services include for example the prescription of drugs, emergency room visits, outpatient visits, and inpatient treatment. This is possibly caused by the adverse effects of severe obesity on physical and psychological health. Childhood obesity is also associated with high indirect costs due to absence from school, probably due to comorbidity associated with childhood obesity or as the result of bullying. The 2002–2005 Medical Expenditure Panel Survey (MEPS) in the United States,
showed that children who were obese had $14.1 billion higher expenditures on prescription drug use, emergency room visits, and outpatient visit costs annually compared with normal/underweight children. Research on the cost implications of childhood obesity, mostly cross-sectional studies, provides a mixed picture of the excess costs, indicating that results are not generalizable beyond the population under study. More detailed and more precise data on short- and long-term costs of childhood obesity are required in order to determine cost-effective treatments.

Severe childhood obesity often tracks into adulthood and is associated with comorbidities. Obesity in adulthood is associated with increased healthcare costs. In the Netherlands alone, direct costs are estimated at half a billion euro per year. Indirect costs such as absenteeism and presenteeism increase as well with increasing BMI in adults. In the Netherlands, these costs account for €2 billion per year. Childhood obesity is thus expected to lead to severe economic consequences later in life.

Treatment of severely obese children and adolescents

To counteract the negative physical-, psychosocial health, and economic consequences, interventions to treat childhood obesity are of the utmost importance. Although many treatments for childhood obesity exist, results on the effectiveness of these interventions have not been very promising, especially regarding their long-term effectiveness. Moreover, studies evaluating the effectiveness of treatment aimed at children with severe obesity are relatively rare.

In principle, two treatment options are available for severely obese children; bariatric surgery or intensive lifestyle treatment. Bariatric surgery is considered the most effective treatment for severely obese adolescents. It is associated with long-term weight-loss and decreased overall mortality. Other beneficial effects of bariatric surgery include improvements in lifestyle, and reduced prevalences of diabetes mellitus type 2, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, hypertension, and hyperuricemia compared with a control group. Therefore, countries like the United States, Chili, Sweden, and Italy perform bariatric surgery in some adolescents.
However, bariatric surgery also has serious negative effects; it is irreversible, surgery itself is risky and the child will have to live with the consequences of the surgery for the rest of its life. For example, gastric banding may involve dilation of the esophagus. This means patients need to stick to a strict diet for the rest of their lives and have regular postoperative follow-up visits. Gastric bypass procedures can lead to long-term vitamin and mineral deficiencies, and patients must use lifelong supplementation as a result. Therefore, bariatric surgery is currently not considered a suitable treatment option for severely obese children in the Netherlands. For severely obese adolescents, bariatric surgery is not indicated either, apart from exceptional cases in combination with intensive lifestyle treatment, e.g. when no other treatments have demonstrated long-term effectiveness. Moreover, in the Netherlands bariatric surgery is not permitted, except for research purposes.66 Thus, intensive lifestyle treatment is the only viable treatment option for the majority of children and adolescents with severe obesity in the Netherlands.

This intensive lifestyle treatment should incorporate a combination of dietary, physical activity, and behavioral counseling. It is important that the family is involved in the treatment, as the most successful obesity treatments are family-based.18, 60, 67-69 This seems logical as the child lives with its family and family members can support the child in continuing the learned behavior at home. If they are unaware of what the learned behavior is exactly, they will be unable to support the child. In order to support the child, knowing how to stimulate and coach the child is equally important as practical knowledge.

The aim of treatment should be a sustainable improvement in lifestyle that not only leads to a decrease in SDS-BMI during treatment, but which also prevents a relapse in SDS-BMI during follow-up on the longer term.66 Intensive lifestyle treatment for severely obese children and adolescents is often delivered in the form of ambulatory treatment. However, research shows that obesity treatment for severely obese children and adolescents in ambulatory form is insufficiently effective in the long-term.70-71 Therefore long-term inpatient treatment is suggested as the most effective nonsurgical treatment for severely obese children and adolescents.59 Severely obese children and adolescents should preferably be referred to experienced, specialized childhood obesity centers where such intensive lifestyle treatment with an inpatient period can be provided.
Inpatient treatment at Heideheuvel

Currently in the Netherlands, Heideheuvel is the only specialized childhood obesity center offering intensive lifestyle treatment with an inpatient period for severely obese children and adolescents. The intensive one-year lifestyle treatment that is provided at Heideheuvel was modeled after the treatment developed by Braet et al\textsuperscript{72} and originally included a six-month inpatient period. However, an inpatient period of six months is very long and expensive, and poses a considerable burden on both the participants and their families.

This study, the Health Effects of Lifestyle Interventions in Obese children and adolescents Study (HELIOS), compared the original one-year treatment with a six-month inpatient period with a modified one-year treatment with a two-month inpatient period, followed by biweekly return visits during the next four months. The second half year of both treatments consisted of monthly return visits.
Study objectives

The overall objective of this thesis was to evaluate the cost-effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods (two or six months) for severely obese children and adolescents from a societal perspective over a period of two years (Chapter 5). The specific objectives of this thesis were:

- To describe the design of HELIOS and the intensive one-year lifestyle treatment in detail (Chapter 2).
- To describe the demographic characteristics and cardiometabolic risk factors of the study population of severely obese children and adolescents included in HELIOS (Chapter 3).
- To evaluate the effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and cardiometabolic risk factors (Chapter 4).
- To evaluate the cost-effectiveness comparing two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and quality-adjusted life-years (QALYs) (Chapter 5).
- To examine changes in health-related quality of life (HRQoL) in severely obese children and adolescents participating in an intensive one-year lifestyle treatment with an inpatient period (Chapter 6).

Outline of this thesis

In order to address the above mentioned objectives, Chapter 2 provides information on the design of HELIOS and the intensive one-year lifestyle treatment with either an inpatient period during weekdays of two months (short-stay group) or six months (long-stay group). Chapter 3 describes the demographic characteristics and the prevalence of cardiometabolic risk factors and quality of life at baseline in severely obese children and adolescents participating in the study. Chapter 4 evaluates the effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and...
adolescents with regard to SDS-BMI and cardiometabolic risk factors directly after one year of treatment. The cost-effectiveness comparing two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and quality-adjusted life-years (QALYs) after two years of follow-up is evaluated in Chapter 5. Chapter 6 examines changes in health-related quality of life (HRQoL) using both generic and weight-related questionnaires in severely obese children and adolescents participating in an intensive one-year lifestyle treatment with an inpatient period, directly after treatment and at follow-up one year later. Finally, in the general discussion in Chapter 7, the results are summarized and a reflection of the main outcomes of the work presented in Chapters 2-6 is provided. Furthermore, implications for practice and recommendations for future research and policy are addressed.
References

Vitamin D

**Synthesis of the active vitamin D metabolite - 1,25(OH)2D**

Figure 1: Synthesis of the active vitamin D metabolite - 1,25(OH)2D throughout the body.

The inactive vitamin D is converted into 25-hydroxyvitamin D (25(OH)D), which is the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed in the liver to hydroxylate 25(OH)D, resulting in 25(OH)D, the active form.

Vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is produced by the skin and is also derived from animal food sources, while vitamin D3 – the more common form of vitamin D in nature – is produced by the skin when exposed to sunlight.

In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert the inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D), which is then circulated throughout the body.

This process mainly occurs in the kidney and 1,25(OH)2D is circulated through the bloodstream. The active vitamin D metabolite has a half-life of 15-20 days, and it is inactivated by the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed in the liver to hydroxylate 25(OH)D, resulting in 25(OH)D, the active form.

Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is produced by the skin and is also derived from animal food sources, while vitamin D3 – the more common form of vitamin D in nature – is produced by the skin when exposed to sunlight.

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53. Trasande L, Chatterjee S. The impact of obesity on health service utilization and costs in childhood. Obesity (Silver Spring, Md. 2009 Sep;17(9):1749-54.
exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production.

Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Vitamin D₂ is the plant and yeast-derived form of vitamin D. Vitamin D₃ – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources.

In humans, both vitamin D₂ and vitamin D₃ are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)₂D (Figure 1). This process mainly occurs in the kidney and 1,25(OH)₂D is circulated throughout the body.

Figure 1: Synthesis of the active vitamin D metabolite - 1,25(OH)₂D
COST-EFFECTIVENESS OF INTENSIVE INPATIENT TREATMENTS FOR SEVERELY OBESE CHILDREN AND ADOLESCENTS IN THE NETHERLANDS; A RANDOMIZED CONTROLLED TRIAL (HELIOS)

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CHAPTER 2

Abstract

Background
Intensive combined lifestyle interventions are the recommended treatment for severely obese children and adolescents, but there is a lack of studies and their cost-effectiveness. The objective of this study is to compare the cost-effectiveness of two intensive one-year inpatient treatments and usual care for severely obese children and adolescents.

Methods/Design
Participants are 40 children aged 8-13 and 40 adolescents aged 13-18 with severe obesity (SDS-BMI ≥ 3.0 or SDS-BMI ≥ 2.3 with obesity related comorbidity). They will be randomized into two groups that will receive a comprehensive treatment program of 12 months that focuses on nutrition, physical activity and behavior change of the participant and their parents. The two programs are the same in total duration (12 months), but differ in inpatient treatment duration. Group A will participate in a six-month intensive inpatient treatment program during weekdays, followed by six monthly return visits of two days. Group B will participate in a two-month intensive inpatient treatment program during weekdays, followed by biweekly return visits of two days during the next four months, followed by six monthly return visits of two days. Several different health care professionals are involved, such as pediatricians, dieticians, psychologists, social workers, nurses and physiotherapists. Results will also be compared with a control group that receives usual care. The primary outcome is SDS-BMI. Secondary outcomes include quality of life using the EQ-5D and cardiovascular risk factors. Data will be collected at baseline and after six, 12 and 24 months. An economic evaluation will be conducted alongside this study. Healthcare consumption will be based on actual resource use, using prospective data collection during two years through cost diaries. Quality Adjusted Life Years (QALYs) will be calculated using the EQ-5D.

Discussion
This study will provide useful information on the effectiveness and cost-effectiveness of inpatient treatment in severely obese children and adolescents. Valuable information on long-term effects, after two years, is also included.
Background

In the Netherlands the prevalence of obesity in children and adolescents has increased during the last decades.\(^1\)\(^-\)\(^3\) Generally, when an increase in prevalence is observed, there is a skewed distribution to the right instead of a normal distribution, which means that a disproportional large increase in the prevalence of severe obesity is observed.\(^4\) The prevalence of obesity in children aged 4-15 years has increased from 0.2 to 2.6% in boys and from 0.5 to 3.3% in girls in the period 1980-2003.\(^3\) These trends are worrisome because obesity in children is associated with an increased risk of several chronic diseases such as diabetes mellitus type 2 and cardiovascular diseases and musculoskeletal, respiratory and psychosocial problems.\(^5,\)\(^6\) Obesity also tracks from childhood into adulthood and is predictive for significant health consequences in later life independent of adult BMI.\(^7,\)\(^9\) Besides having an adverse impact on healthy life years and quality of life, childhood obesity also has a substantial impact on healthcare utilization and results in a heavy financial burden for society.\(^10,\)\(^11\) Although many programs for the treatment of obesity exist, results have not been very promising, especially regarding their long-term effectiveness. Nevertheless, a recent systematic review of inpatient programs for children showed greater reductions in the percentage of overweight participants post treatment and at follow-up compared with results from a recent meta-analysis of outpatient treatments.\(^12\) Studies evaluating the effectiveness of treatment programs (with or without an inpatient period) aimed at children with severe obesity are relatively rare.\(^12,\)\(^13\) However, it has been suggested that ambulatory programs for severely obese children and adolescents are insufficiently effective and that there is a need for experienced, specialized pediatric obesity centers for intensive treatment by professionals with expertise in pediatric and adolescent medicine.\(^14,\)\(^15\) Spear et al. describe the need for comprehensive treatments that should be provided by multidisciplinary obesity care teams, including for example social workers, psychologists, dieticians, and exercise specialists.\(^16\) The ideal approach in such comprehensive treatments would include dietary modification, an increase in physical activity, a reduction in sedentary activity and behavior modification.\(^17,\)\(^18\) A promising alternative for ambulatory care is inpatient treatment in specialized centers as mentioned above.\(^12\) Heideheuvel (part of Merem Treatment Centers) is the only specialized clinic in the Netherlands offering an intensive combined lifestyle inpatient intervention, focusing on nutrition, physical activity and behavior change of the participants and their
parents. This lifestyle intervention has a duration of 12 months, with a six-month inpatient period and is designed for severely obese children and adolescents between 8 and 18 years. However, such a lengthy inpatient treatment program involves high costs and a considerable burden for both the child and the family. Therefore, a new intensive combined lifestyle intervention also with a duration of 12 months, but with a shorter inpatient period (2 months) was developed at Heideheuvel with the aim of being equally effective but less costly and disturbing for family life.

The objective of this study is to compare the cost-effectiveness of these two intensive one-year inpatient treatments to each other and to usual care for severely obese children and adolescents.

Methods/Design

Design
This study is designed as a randomized controlled clinical trial with three study arms. The cost-effectiveness of two intensive one-year treatments that vary in inpatient period length and usual care for severely obese children and adolescents will be evaluated. There is a one-year follow-up after treatment. Participants who meet the inclusion criteria and consent to participate in the study will be randomized to one of the three study arms (described under ‘interventions’). Because of the nature of the treatments evaluated in this study, parents and participants as well as professionals at Heideheuvel and in the usual care condition cannot be blinded to the type of intervention. A table of random numbers is used to randomize participants. At the beginning of the first year 40 (13-18 years) participants are randomized into: group A (10), group B (10) or group C (20). The participants in group C will be randomized into group A (10) or B (10) after one year of receiving usual care. This process is repeated for another 40 participants (8-13 years) after six months. At the end of the fourth year all 80 participants (40 in each inpatient treatment group) will have completed the program and one year of follow up (figure 1). Data collection started in August 2009 and will continue until July 2013. The Medical Ethics committee (METc) of VU University Medical Centre approved the study design, protocol and informed consent procedures.
Participants

The study population consists of children and adolescents aged 8-18 years referred to Heideheuvel by their own pediatrician. Pediatricians working at Heideheuvel screen the referred participants for eligibility to be included in the treatment. They must have a SDS-BMI ≥ 2.3 according to the growth curves based on the fourth Dutch National Growth Study of 1997 (this corresponds to the 99th percentile) and comorbidity related to obesity (e.g. obstructive sleep apnea syndrome, raised insulin, diabetes mellitus type 2, liver function disorders, dyslipidemia, worn out joints) or a SDS-BMI ≥ 3.0 (this corresponds to the 99.9th percentile). Participants will be excluded if they have syndromal or chromosomal determined obesity, obesity caused by endocrine disorders (hypothyroidism, Cushing syndrome, primary hyperinsulinemia, pseudohypoparathyroidism, acquired (structural) hypothalamic damage) or medicine use (e.g. oral steroids, antiepileptic drugs, antidepressants), severe psychiatric problems, an IQ below 75 or similar school level or if their parents are not willing to participate in the treatment. Written informed consents are obtained from both the participants and their parents.
**Interventions**

The intensive combined lifestyle interventions focus on nutrition, physical activity and behavior change of the participants and their parents. Many disciplines are involved, such as pediatricians, dieticians, psychologists, social workers, nurses, physiotherapists, general exercise therapists and exercise therapists Cesar (a specific type of exercise therapy in the Netherlands that is mainly focused on posture, balance and coordination). Additional individual meetings with a psychologist, dietician or social worker are offered if participants, parents or professionals indicate that this is needed. During the inpatient period, children and adolescents will participate in an exercise program four times a week and nutrition education/behavior modification sessions once per week. Behavior modification topics include self-regulation, self-awareness, goal setting, stimulus control, coping skills training, cognitive behavior strategies and contingency management. Behavior modification is achieved through the ‘5 steps of problem solving’-plan. The first step is to define the problem and learn to describe it. The second step is to search for possible solutions for the defined problem. Step 3 is to make an inventory of the possible consequences for each possible solution described in the second step. The fourth step is to choose the best solution from the possible solutions. The last step then is to implement this solution and to evaluate this afterwards. If the problem is not solved, one can go back to the first step. The nutritional education component of the program will use an approach not primarily aimed at caloric restriction but rather at structured eating and healthier choices, focusing on improving the quality of the dietary intake, and on trying to establish a flexible control of eating behavior. During the weekends at home in the inpatient period the participants and their parents are required to accomplish exercises regarding nutrition and physical activity. During the period when the children are home again the learned behavior is practiced at all times.

Group A will participate in a six-month intensive inpatient treatment program during weekdays, followed by six monthly return visits of two days. Group B will participate in a two-month intensive inpatient treatment program during weekdays, followed by biweekly return visits of two days during the next four months, then followed by six monthly return visits of two days. During the inpatient treatment phase and the two-day return visits all children and adolescents stay overnight at Heideheuvel. Parents of participants in groups A and B will attend one session every week during the inpatient period and after that
one session per return visit of their child. Group C will receive usual care during one year, after which the participants will be randomly allocated to the groups A and B. This implies that during this year they remain under the care of their pediatrician and other health care professionals that might be involved in their treatment like the general practitioner, dietician, physiotherapist and psychologist.

**Detailed descriptions of treatments A and B**

Treatment A already existed before the start of the study. Treatment B is based on treatment A, but includes a shorter inpatient period in the first half year to reduce the burden for parents and children. This expands the opportunity for implementation of the learned behavior at home. Treatment B also focuses more on involvement of the parents from the beginning.

The focus of both treatments is on knowledge and skills and implementation. In both treatments the same topics are covered during the educational sessions, but the form in which the education is given is slightly different (guidance by a psychologist, dietician or exercise therapist in treatment A and by group coaches in treatment B).

Both treatment A and B are divided into four phases: 1. assessment/knowledge acquisition phase (week 1-6/1-8), 2. Knowledge acquisition and skills building phase (week 7-18/9-18), 3. Implementation phase (week 19-26) and 4. Maintenance phase (27-52).

**Phase 1 (weeks 1-6 for treatment A, weeks 1-8 for treatment B)**

During the first phase extensive physical and psychosocial examinations are carried out. The children are medically examined and they have several individual appointments with among others the dietician and psychologist, both with and without their parents, to assess what the problem areas are for each child. During this period the children receive schooling at a study center at Heideheuvel, except for the primary school children. They go to primary schools in the neighborhood where the teachers can monitor dietary habits of the children. A very important secondary goal in this phase is also the group formation.
Phase 2 (weeks 7-18 for treatment A, weeks 9-18 for treatment B)
In the second phase, there are weekly (group A) or biweekly (group B after the inpatient period) educational group sessions for the children with a psychologist covering different topics, such as dealing with emotions, self-confidence and self-image. During this period, the children of treatment A go to a school in the vicinity of Heideheuvel. Children of treatment B continue to receive schooling at a study center at Heideheuvel during the inpatient period and the biweekly return visits, when they are home they go back to the school in their own neighborhood.

Phase 3 (weeks 19-26 for treatment A as well as for treatment B)
In the third phase, the knowledge acquired in the previous phases is put into practice. In weeks 19 and 20 the children of group A have the last sessions of the weekly education program supervised by a psychologist and group coach. The children of group B will have their last session in the last biweekly return visit. From week 20 on in group A, one weekly visit to a movement therapist can be exchanged for a visit to a sports center in the vicinity of the clinic, if the children like to perform sports not possible at the clinic. The children of group B continue to do exercise during their biweekly return visit. During phase 3 the children in treatment A go to a school in the vicinity of Heideheuvel Children of treatment B continue to receive schooling at a study center at Heideheuvel when they are there for their biweekly return visit, when they are home they go back to the school in their own neighborhood. Around week 22 the children in treatment A return to their families once for a maximum of one week. This is to practice the learned skills at home during a normal week and see which problems are encountered in their home environment. After this family leave the encountered problems are discussed and if necessary plans are adjusted before the children are going back home again.

Phase 4 (weeks 27-52 for treatment A as well as for treatment B)
In the fourth phase, the maintenance phase, the children live at home again and go to their own school. During this period, which is aimed at preserving the acquired skills and maintaining the new body weight, there are monthly two-day return visits for the children. During the second day of the return visits the parents also take part in the treatment. Each return visit a different topic related to the treatment is being discussed with the children in
sessions both with and without the parents attending. The topics discussed are: autonomy, the family, dealing with emotions, my body, self-confidence and self-image. The topics also help to look ahead and plan how to tackle possible problems in the future. During these return visits also problems encountered at home are discussed and used as educational examples.

Table 1 describes for both treatments in detail the number of appointments the children have with different professionals of the multidisciplinary team in different phases of the treatment. In addition to the contacts described in the table, two group coaches are always present during the day to provide ongoing learning and education. They can support the children in the learned behavior and observe the children and discuss possible difficulties. During the night there is always supervision of a night nurse. For more information on the different disciplines involved see Table 2.
### Table 1 - Details of treatment programs A and B in respect to visits to different health care professionals and treatment activities

<table>
<thead>
<tr>
<th>Disciplines/treatment parts</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 1 (weeks 1-6)</td>
<td>Phase 2 (weeks 7-18)</td>
</tr>
<tr>
<td>Exercise therapist</td>
<td>4G</td>
<td>4G</td>
</tr>
<tr>
<td>Cesar therapist</td>
<td>1G</td>
<td>1G</td>
</tr>
<tr>
<td>Dietician</td>
<td>1I, 1G</td>
<td>1I, 1G</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>Every other week 1I</td>
<td>Every other week 1I</td>
</tr>
<tr>
<td>Psychologist</td>
<td>2I this phase</td>
<td>Once this phase I</td>
</tr>
<tr>
<td>Nurse</td>
<td>Twice this phase I</td>
<td>Twice this phase I</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Once I this phase</td>
<td>-</td>
</tr>
<tr>
<td>Social worker (parents)</td>
<td>1G, 2I this phase</td>
<td>1G</td>
</tr>
<tr>
<td>Parents course (parents)</td>
<td>Twice this phase G</td>
<td>3 times this phase G</td>
</tr>
<tr>
<td>TTV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Education/group-activity children</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Education/group activity/training parents and children</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

G = group session
I = Individual session
**Measurements**

Primary outcome measure is (SDS) BMI. Secondary outcomes are quality of life and cardiovascular risk factors like blood pressure, bodily circumferences, serum lipids, glucose levels and insulin levels. Eating behavior and physical activity are also assessed. The EuroQol (EQ-5D) is used to measure quality of life and to calculate Quality Adjusted Life Years (QALYs) over the follow-up period of 24 months. Measurements will be done at four points in time: at baseline (start of treatment) and after six, 12 and 24 months.

**Height, weight and circumferences**

Height is recorded with a Holtain stadiometer fixed on the wall with an accuracy of 1 mm. The stadiometer is calibrated before every first measurement. Height is recorded three times of which the average is calculated. Weight is measured in light clothing without shoes and recorded with a calibrated SECA digital weight chair that has a limit of 230 kg and an accuracy of 0.005 kg.

Weight and height are used to calculate BMI (weight in kilograms divided by the square of height in meters). The degree of overweight is quantified using Cole’s least mean square method, which normalizes the BMI’s skewed distribution and expresses BMI as SDS-BMI. These calculations are performed using (http://www.growthanalyser.org; version 3.5, program by “Stichting Kind en Groei”, downloaded in July 2010). The data from the fourth Dutch growth study among children of 1997 are used as reference. The SDS-BMI indicates how many standard deviations a measurement is above or below the median of the distribution. Circumferences of the neck, waist, abdomen (WHO as well as maximum) and hip are measured with a tape measure. The participant has to stand up straight (in underwear) with the arms alongside the body and the feet in resting position. The circumferences are measured with an accuracy of 1 mm.

**Blood pressure**

Blood pressure is measured with a digital blood pressure monitor (Heine, type Gamma E60). A cuff size with a width of two-third of the upper arm length is used that completely covers the arm circumference. For most participants a 17 cm cuff size (CAO2, arm circumference 33-41 cm) is used. If necessary, a 14 cm cuff size (CAO1, arm circumference 22-32 cm) is
used. Blood pressure is measured in sitting position after sitting still for at least 5 minutes. Blood pressure is measured three times. For the analyses, the averages of the three systolic blood pressure and diastolic blood pressure readings are used.

**Table 2 - Explanation of different disciplines and treatment parts**

<table>
<thead>
<tr>
<th>Disciplines/treatment parts</th>
<th>Explanation of disciplines/treatment parts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents course (parents)</td>
<td>A course of several meetings for the parents in which different topics related to the treatment are being discussed under supervision of the social worker, such as making choices or handling temptations.</td>
</tr>
<tr>
<td>TTV</td>
<td>Temporarily therapy leave. A period with a maximum of 1 week in which the children of treatment A go home during the inpatient period to practice learned behavior in a normal setting during weekdays.</td>
</tr>
<tr>
<td>Education/group-activity children</td>
<td>Several topics related to the treatment are being discussed with the children under supervision of the group coaches such as motivation, bullying and self-image. Activities with the children are supervised by the group coaches. This can be something active like sport games or something to put an educational topic into practice.</td>
</tr>
<tr>
<td>Education/group activity/training parents and children</td>
<td>The educational sessions for both children and the parents together are always supervised by the group coaches and a social worker. Several topics related to the treatment are being discussed and occasionally the pediatrician or psychologist or dietician visits the session to discuss a certain topic. Activities with the children and their parents supervised by the group coaches and social worker. This can be something active like sport games or something to put an educational topic into practice.</td>
</tr>
</tbody>
</table>

**Bio-electrical impedance spectroscopy**

Bio-electrical impedance spectroscopy (BIS) measurements are conducted with a Body Impedance Analyzer BIA 101/s (Akern-SRL Systems by EQUIP Medikey BV). Two current electrodes (tetra-polar electrodes (3 M red Dot AG/AgCl)) are placed at the dorsal surfaces of the hand and foot on the distal portion of the second metacarpal and metatarsal, respectively. Two detector electrodes are placed at the posterior wrist between the styloid processes of the radius and ulna and at the anterior ankle between the tibial and fibular malleoli. The resistance (Ohm) is used in the analysis to determine fat mass (FM) and fat free mass (FFM). The equation used for the children and adolescents in this study for percentage body fat (%BF) is the adjusted Kushner equation \((Wt-[0.59(Ht2/R)+0.065(Wt)+0.04]/[0.754(Wt)]) \times 100\).

This equation is adjusted and validated by Newton et al.\(^{21}\)
**Blood measurements**

After an overnight fast, blood samples are obtained to measure lipid spectrum (cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) liver function (γ-GT, ALAT, ASAT) and C-reactive protein (CRP), hemoglobin, hematocrit, MCV, ferritin and HbA1C. In patients with a triglyceride level ≤ 4.5 mmol/l, LDL-cholesterol is calculated using the formula of Friedewald. Since this calculation is unreliable in patients with a triglyceride level > 4.5 mmol/l, LDL-cholesterol is measured directly in these patients using a Roche Cobas 6000 chemical analyzer. The method for this direct measurement is an enzymatic reaction with the transformation of LDL-cholesterol in a color product. High sensitive CRP measurement is performed turbidimetrically with a Roche Cobas 6000 chemical analyzer. To determine glucose tolerance and insulin resistance, the participants are given glucose, in a dose of 1.75 g per kilogram of body weight (up to a maximum of 75 g) orally. Blood samples are obtained at 0 and 120 minutes for the measurement of glucose and insulin levels. In accordance with the American Diabetes Association guidelines, impaired fasting glucose is defined as a fasting plasma glucose level between 5.6 - 6.9 mmol/l and impaired glucose tolerance as a 2-h post load glucose level in the oral glucose tolerance test (OGTT) between 7.8-11.0 mmol/l. Diabetes mellitus type 2 is defined as a fasting plasma glucose level of ≥ 7.0 mmol/l or a 2-h post load glucose level in the OGTT of ≥ 11.1 mmol/l.22

**Quality of life**

Quality of life is measured using the EQ-5D.23 The EQ-5D questionnaire contains a descriptive system of health related quality of life consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension there are three levels of severity (no problems/some or moderate problems/extreme problems). A standard vertical 20 cm visual analogue scale is also included to measure an individual’s direct valuation of their current health-related quality of life state. Utilities will be estimated using the Dutch tariff.24 Quality Adjusted Life Years (QALYs) will be calculated by multiplying the utilities with the amount of time a participant spent in a particular health state. Transitions between health states will be linearly interpolated.
CHAPTER 2

Cost measures
Cost calculations will be based on actual resource use, using prospective data collection during two years (the 12 months intervention period and the 12 months follow-up) through cost diaries. The costs of the interventions (inpatient care and recurrent return visits of two days) will be estimated using a bottom-up approach. Other costs include direct healthcare costs (e.g. costs of visits to the general practitioner, internist, physiotherapist, inpatient period), direct non-healthcare costs (informal care provided by parents and legal guardians and travel costs), and indirect costs (costs related to loss of productivity of the parents and legal guardians). Cost diaries are formatted as calendars on which health care utilization can be registered. The calendars will be sent to the families every three months. After three months the calendars will be returned by the parents, using stamped envelopes, also if there has been no health care utilization during that period. In case a calendar is not returned, use of health care will be inventoried by telephone calls and/or e-mails.

If available, standard costs recommended by the Dutch Health Insurance Council will be used to value resource use. Medication costs will be valued using prices of the Royal Dutch Society of Pharmacy.

Sample size calculation
Based on a previous study comparing intensive inpatient treatment with an ambulatory treatment in the same treatment center it is calculated that 40 participants in both intervention groups are sufficient to detect a 0.5 SDS-BMI difference between the two groups after one year (with $\alpha = 0.05$ and power = 0.8). Based on earlier experience in the same setting and with similar participants it is feasible to recruit these numbers of participants.

Statistical analyses
An intention-to-treat analysis will be performed. A per protocol analysis will also be performed after careful description of correlates of non-adherence and dropout.

To take into account the repeated measurements over time, we will use generalized estimating equations for panel data analysis, also known as cross-sectional time-series analysis, with the use of the Stata software XTGEE command; this will allow us to account
for the non-independence of repeated measurements of the same bio-indicator in the same participant over time. Linear regression will be applied for continuous outcomes and logistic regression for dichotomous outcomes. We will use age, sex, time point, and intervention group as explanatory variables in our models.

An economic evaluation from a societal perspective will be conducted alongside the randomized controlled trial. Multiple imputation will be used to impute missing cost and effect data. Five imputed data sets will be created, each of which will be analyzed separately. The results of these five analyses will be pooled using Rubin’s rules. Costs generally have a highly skewed distribution. Therefore, bootstrapping with 5000 replications will be used to estimate “approximate bootstrap confidence” (ABC) intervals around cost differences. Incremental cost-effectiveness and cost-utility ratios will be calculated by dividing the difference in total costs between the groups by the difference in SDS-BMI and QALYs, respectively. Non-parametric bootstrapping will also be used to estimate the uncertainty surrounding the incremental cost-effectiveness and cost-utility ratios (5000 replications). The bootstrapped cost-effect pairs will be plotted on a cost-effectiveness plane (CE plane) and used to estimate cost-effectiveness acceptability curves (CEA curves). CEA curves show the probability that the intervention is cost-effective in comparison with usual care for a range of ceiling ratios. The ceiling ratio is defined as the amount of money society is willing to pay to gain one unit of effect.
Discussion

This paper presents the design of a randomized controlled trial comparing the cost effectiveness of two intensive one-year inpatient treatments to each other and to usual care for severely obese children and adolescents. The study will not only provide insight in the effects of one year of treatment, but also the maintenance one year after the end of the treatment. Studies regarding the effectiveness and cost-effectiveness of treatment programs (with or without an inpatient period) for obese children and adolescents are relatively rare, especially for the severely obese. Kelly and Kirschenbaum reviewed published studies on inpatient treatment for childhood and adolescent obesity. Their review showed that programs containing an inpatient period had better weight-loss and subsequent weight maintenance compared with the outpatient treatments. The rates of attrition were also lower in the inpatient treatment groups. Our study can add important knowledge on the usefulness of inpatient treatment in severely obese children and adolescents.

An important strength of this study is the randomized controlled trial design. Another strength is that both young children (8-13 years of age) and adolescents (13-18 years of age) will be included in this study, since obesity is an important health problem in these age groups. This study provides information on the effectiveness and feasibility of the intervention in both age groups that differ in environmental and individual factors associated with obesity, such as the role of the parents and peers. Also participants of different ethnic groups and from rural and urban areas from different parts in the Netherlands will participate in the study. This will contribute to the generalizability of the outcomes to the general population of severely obese children and adolescents in the Netherlands. Moreover this study will provide information on the feasibility to implement the program on a larger scale and perhaps also in other settings such as regular hospitals.

A challenge of the study will be keeping the attrition rate to a minimum. The study population is expected to have a relatively low socioeconomic status (SES) and to present relatively many psychological problems and socially complicated family structures. This can interfere with adherence to the treatment program. The psychological characteristics of the patients and their parents will be described in a separate study. Another difficulty will be
the recruitment of participants, because of the extended inpatient periods. Especially in the group of children aged 8-13, we expect problems with recruitment because an inpatient period of two or six months imposes a very heavy burden on families and children. Also, because recruitment is nationwide, part of the parents will have to travel quite a lot, since their active participation and frequent presence during treatment is required. This can lead to high work absenteeism for the parents or loss of vacation days which will also be measured.

For the calculation of %BF the adjusted equation by Kushner et al is used,\(^\text{20}\) since the original equation by Kushner et al is developed to calculate total body water and is therefore not applicable. We have chosen for this equation after careful consideration as there are more suitable equations to calculate %BF specifically developed for obese children and adolescents such as the equations of Lazzer et al\(^\text{32}\) and Schaeffer et al.\(^\text{33}\) However we are limited in our choice because only resistance (R) is recorded. Cost calculations will be based on actual resource use; therefore prospective data collection through cost diaries during two years is used. However, the risk of this type of data collection is drop out; the longer the participant are followed, the higher the chance of loss to follow up. Also, bias can be introduced with this type of data collection, since it is based on self-reporting. People can forget to note absenteeism or visits to health care professionals, even with the use of the cost diaries. By prospectively collecting data we hope to get valid estimates of health care utilization.

The major cost savings as a result of treatment are expected to come about much later in the lives of these children, the effects on productivity, absenteeism, disease incidence and use of medical care potentially may have an effect after decades. To be able to predict such cost savings, this short term cost-effectiveness analysis is too limited because this study is based on actual resource use, using the actual costs of the interventions, direct healthcare costs, direct non-healthcare costs and indirect costs for the period of two years. In the long term the cost savings will be much higher than in this short term of two years, therefore these interventions are investments in the long term. To make models to predict these long term cost savings is risky, because the long term effects of such interventions are not known.
Despite the challenges mentioned above, the results of the study will offer valuable information to health care professionals as well as policy makers regarding treatment of severely obese children and adolescents.
References


Vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant and yeast-derived form of vitamin D. Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources. In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)2D (Figure 1). This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body.

exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production.

Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Vitamin D₂ is the plant and yeast-derived form of vitamin D. Vitamin D₃ – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources.

In humans, both vitamin D₂ and vitamin D₃ are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)₂D (Figure 1).

This process mainly occurs in the kidney and 1,25(OH)₂D is circulated throughout the body.
3

CARDIOMETABOLIC RISK FACTORS AND QUALITY OF LIFE IN SEVERELY OBESE CHILDREN AND ADOLESCENTS IN THE NETHERLANDS

Sabine Makkes
Carry Renders
Judith Bosmans
Olga van der Baan-Slootweg
Jaap Seidell

Abstract

Background
The prevalence of severe obesity in children and adolescents is increasing. However, little is known about cardiometabolic risk factors and quality of life of children with severe obesity. Therefore, the aim of this study was to assess the demographic characteristics and the prevalence of cardiometabolic risk factors and quality of life in severely obese children and adolescents undergoing intensive inpatient treatment for obesity.

Methods
Data were collected between August 2009 and April 2011 on 16 children (8-13y) and 64 adolescents (13-19y) with severe obesity (SDS-BMI >= 3.0 or SDS-BMI >= 2.3 and comorbidity) participating in an RCT evaluating two intensive inpatient treatment programs for obesity. Demographic, anthropometric, clinical characteristics and two components of the EuroQol for the assessment of quality of life are described.

Results
Eighty percent of participants in this study had at least one cardiometabolic risk factor in addition to severe obesity. Low HDL-cholesterol and hypertension were most prevalent (65.0% respectively 31.2%). The highest significant correlations were found between SDS-BMI and SDS-waist circumference, fasting plasma insulin and HOMA-IR (correlation coefficients respectively 0.80, 0.49, and 0.48). With regard to quality of life, the mean utility score of the participants was 0.79 on a scale of 0.0 to 1.0 on the EuroQol questionnaire and their mean individual valuation was 69.1 on a scale of 0 to 100.

Conclusion
Cardiometabolic risk factors were already highly prevalent in this group of severely obese children and adolescents. The score of 69.1 found for quality of life in this study suggests that participants experienced important limitations in their quality of life. However, quality of life was not associated with the prevalence of cardiometabolic risk factors.
Background

Worldwide there has been a large increase in the prevalence of obesity in children and adolescents in the last decades. In 2009 in the Netherlands, about 2% of the boys and girls were classified as obese. In comparison with 1980 these figures indicate a four to six fold higher prevalence for obesity. Moreover, the severity of obesity has also increased, both in the Netherlands as in other countries. Results from the 2009–2010 NHANES indicate that an estimated 16.9% of children and adolescents aged 2–19 years in the US are obese. The rate of severe childhood obesity has tripled in the last 25 years. This trend is worrisome, because obese children have a higher risk of diabetes mellitus type 2 and cardiometabolic risk factors such as high blood pressure, low HDL cholesterol, high triglycerides, high fasting insulin concentration. These cardiometabolic risk factors are often clustered together in individuals which increases the risk of cardiometabolic disease in young adulthood. In addition, childhood obesity often tracks into adulthood and is related to cardiometabolic disease, diabetes mellitus type 2 and even cancer in later life, independent of adult BMI. Besides these negative clinical consequences of obesity, low self-esteem and behavioral problems seem to be particularly common in obese children. Obese children and adolescents also have psychological problems and a lower health-related quality of life. Although it can be expected that the health consequences of severe obesity are even more serious than of obesity, little is known about the demographic, anthropometric and clinical characteristics of severely obese children and adolescents. This information is important as it will give more insight into the health risks of these children. Therefore, the objective of this article is to assess the prevalence of cardiometabolic risk factors and the quality of life in severely obese children and adolescents undergoing intensive inpatient treatment for obesity in the Netherlands.
Methods

Design
Data were collected between August 2009 and April 2011 on 16 children (8-13y) and 64 adolescents (13-19y) with severe obesity who participated in the Health Effects of Lifestyle Interventions in severely Obese children and adolescents Study (HELIOS). HELIOS is a randomized controlled trial (RCT) in which the cost-effectiveness of two treatment programs aimed at changing the lifestyle of both participants and their parents is compared. These children receive one year of intensive treatment starting with either an inpatient period of two or six months in a tertiary obesity center in Hilversum, the Netherlands. After the intensive treatment period, there is follow-up of one year. Details about the design of the study and the two treatment programs can be found elsewhere.\textsuperscript{15}

Participants
Inclusion criteria for the trial were a SDS-BMI $\geq 3.0$ (this corresponds to the 99.9th percentile) according to the growth curves based on the fourth Dutch nationwide growth study of 1997, or a SDS-BMI $\geq 2.3$ (this corresponds to the 99th percentile) and comorbidity (e.g. obstructive sleep apnea syndrome, raised insulin, diabetes mellitus type 2, liver function disorders, dyslipidemia, worn out joints). Participants were excluded from the trial if they had syndromal or chromosomal determined obesity; obesity caused by endocrine disorders (hypothyroidism, Cushing syndrome, primary hyperinsulinemia, pseudohypoparathyroidism, acquired (structural) hypothalamic damage) or medicine use (e.g. oral steroids, antiepileptic drugs, antidepressants); psychiatric problems; an IQ below 75 or similar school level or if their parents were not willing or able to participate in the treatment program and/or study.

Measurements
Data on demographic characteristics, comorbidities and quality of life were obtained by questionnaires completed by the participants and their parents. Participants were categorized into two main groups for ethnicity; Native Dutch and Immigrant (Western and Non-Western). When both parents were born abroad in different countries, the country in which the mother was born was used to classify the participant.\textsuperscript{16} Highest educational level attained by one of the parents was used for analysis and is divided into low (lower vocational
training, lower general secondary education and primary school and special primary education or less), medium (intermediate vocational training, higher general secondary training and pre-university education) or high (completed higher vocational training and university). To determine socio-economic status (SES) of the participants, we used status scores of the parents using data from The Netherlands Institute for Social Research. A status score is a measure for the social status of a postal code area and consists of three elements: income, level of education and level of unemployment. A status score below 0 means a SES above average and a status score above 0 means a SES below average (0 meaning average). Quality of life was measured using the EuroQol (EQ-5D-3 L). The EuroQol consists of two components; the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

Both the EQ-5D and EQ-VAS were completed by the participants. The EQ-5D descriptive system consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels of severity (no problems/some or moderate problems/extreme problems). The participants were asked to choose the level that best described their current health status for each dimension. The resulting health state was converted to a utility score using the Dutch EQ-5D valuation tariff. Utilities represent quality of life in a single number along a continuum ranging from 0.0 (death) to 1.0 (full health). In the EQ-VAS a standard vertical 20 cm visual analogue scale is used to measure an individual’s direct valuation of their current health-related quality of life on a scale of 0 (worst imaginable health state) to 100 (best imaginable health state). Comorbidity (acanthosis nigricans, Blount’s disease, gallstones, hirsutism and pseudogynecomastia) was determined by the treating pediatricians from obesity center Heideheuvel before start of the treatment and by ultrasound. A clear description of the anthropometric measurements that were performed can be found elsewhere. The equation used for the children and adolescents in this study to calculate percentage body fat (%BF) was the Kushner equation for total body water (TBW) adjusted by Newton et al. After an overnight fast, blood samples were obtained to measure lipid spectrum, high sensitive C-reactive protein (HS-CRP) and hemoglobin type A1C (HbA1C). To determine glucose tolerance and insulin resistance, the participants were given glucose, in a dose of 1.75 g per kilogram of body weight (up to a maximum of 75 g) orally. Blood samples were obtained at 0 and 120 minutes for the measurement of glucose and insulin levels. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the following equation: fasting plasma insulin (μU/L) x fasting glucose
(mmol/L)/22.5. Scores ordinarily range from 0 to 15, with higher scores indicating greater insulin resistance. Insulin resistance was determined using the cut-offs of Kurtoğlu et al. for participants in the prepubertal and pubertal stage (prepubertal: 2.67 in boys and 2.22 in girls, pubertal: 5.22 in boys and 3.82 in girls).24,25 For participants in the postpubertal stage, the adult cut-off of > 2.5 from Keskin et al. was used.26 The three pubertal stages, prepubertal, pubertal and postpubertal, were based on Tanner stages: prepubertal equals G/M1&P1; postpubertal equals G/M5&P5; pubertal equals all other Tanner stages. For all participants the presence of a number of well-known cardiometabolic risk factors was determined.27,28 The definitions of these cardiometabolic risk factors are included in the Additional file.

**Statistical analyses**
All analyses were performed with IBM SPSS Statistics for Windows, Version 20. Results were stratified by age, where participants in the age group 8 to 13 years were categorized as ‘children’ and participants in the age group 13 to 19 years were categorized as ‘adolescents’. Results were also stratified according to SDS-BMI median (SDS-BMI = 3.46). Independent Student’s t-tests were used to analyze differences in continuous measures between the age groups. Chi-square tests were used to analyze differences in categorical variables. Because several variables had distributions that deviated from normality, Spearman’s rank correlations were calculated. Spearman’s rank correlations were used to explore the relationship between SDS-BMI and anthropometric and laboratory measurements, such as blood pressure, blood lipids, insulin and glucose. In addition to SDS-BMI, also the relationship between utility score and these outcomes was explored. Also Pearson product-moment correlation coefficients were calculated but results are not shown in the tables. In addition logistic regression was used to determine the association between SDS-BMI and dichotomous classification of elevated cardiometabolic risk factors. A p-value below 0.05 was considered statistically significant.
Results

Demographic characteristics
Table 1 describes the demographic characteristics of the 80 participants. Of the participants, the mean age of the group was 14.8 years, 66.2% were girls and 20% fell in the age group 8 to 13 years. Approximately half of the participants (55.0%) were native Dutch. Of the immigrants, 5.0% were Western. Thirty-six percent of the participants’ parents were classified as having a low level of education and 40% and 17.5% as having a medium or high level of education, respectively. Over 60% of the participants lived in a family situation with a SES below average. About half of the participants lived in two parents family, 41.3% of the participants lived in a single parent family. No statistically significant differences were found in demographic characteristics between the children and adolescent groups, except for mean age. Acanthosis nigricans was the most common comorbidity among the participants (60%). Blount’s disease was only present in adolescents. The percentage of participants having gallstones differed significantly between children and adolescents, although in absolute numbers there were only 2 cases among children and 1 case among adolescents. Almost all boys had pseudogynecomastia, among children even 100%. Hirsutism was seen in approximately 9% of the girls. According to self-reported data by the parents of the participants, the weight of the participants started to increase disproportionally when they were about 5 years old and at the age of 9 the weight started to become a real problem.
CHAPTER 3

GENERAL INTRODUCTION

Table 1. Demographic characteristics, quality of life and comorbidity of the children and adolescents participating in HELIOS, for all participants together and stratified according to age group.

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 80)</th>
<th>Children (n = 16)</th>
<th>Adolescents (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>80</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Age (y)</td>
<td>14.8 (2.3)</td>
<td>11.3 (1.2)*</td>
<td>15.7 (1.6)*</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>33.8/66.2</td>
<td>50/50</td>
<td>29.7/70.3</td>
</tr>
<tr>
<td>Ethnicities (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native Dutch</td>
<td>55.0</td>
<td>68.8</td>
<td>51.6</td>
</tr>
<tr>
<td>Immigrants</td>
<td>45.0</td>
<td>31.2</td>
<td>45.5</td>
</tr>
<tr>
<td>Western (% of total)</td>
<td>5.0</td>
<td>0.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Non-Western (% of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moroccan</td>
<td>5.0</td>
<td>6.3</td>
<td>4.7</td>
</tr>
<tr>
<td>Dutch Antilles/Aruba</td>
<td>5.0</td>
<td>0.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Surinam</td>
<td>5.0</td>
<td>0.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Turkish</td>
<td>16.3</td>
<td>18.8</td>
<td>15.6</td>
</tr>
<tr>
<td>Other Non-Western</td>
<td>6.3</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Level of education of the parents (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>36.3</td>
<td>62.5†</td>
<td>29.7†</td>
</tr>
<tr>
<td>Medium</td>
<td>40.0</td>
<td>25.0†</td>
<td>43.8†</td>
</tr>
<tr>
<td>High</td>
<td>17.5</td>
<td>6.2†</td>
<td>20.3†</td>
</tr>
<tr>
<td>SES (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below average</td>
<td>62.5</td>
<td>73.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Above average</td>
<td>32.5</td>
<td>26.7</td>
<td>36.1</td>
</tr>
<tr>
<td>Household situation (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living together</td>
<td>55.0</td>
<td>56.2</td>
<td>54.7</td>
</tr>
<tr>
<td>Divorced</td>
<td>33.8</td>
<td>37.5</td>
<td>32.8</td>
</tr>
<tr>
<td>One parent family(mother)</td>
<td>7.5</td>
<td>0.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Other situation</td>
<td>3.8</td>
<td>6.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-SD utility score</td>
<td>0.79 (0.22)</td>
<td>0.72 (0.27)</td>
<td>0.80 (0.20)</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>69.1 (21.2)</td>
<td>76.1 (21.3)</td>
<td>67.4 (21.0)</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>60.0</td>
<td>56.2</td>
<td>60.9</td>
</tr>
<tr>
<td>Blount’s disease</td>
<td>3.8</td>
<td>0.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Gallstones</td>
<td>3.8</td>
<td>12.5*</td>
<td>1.6*</td>
</tr>
<tr>
<td>Hirsutism (only girls)</td>
<td>9.4</td>
<td>12.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Pseudogynecomastia (only boys)</td>
<td>92.6</td>
<td>100.0</td>
<td>89.5</td>
</tr>
</tbody>
</table>

Data are mean (SD).
Percentages are actual percentages, not valid percentages.
SD – standard deviation; SES – Socio-economic status.
A participant falls in the “Children” group if aged 8 to 13 years and falls in the “Adolescents” group if aged 13 to 19 years.
If both parents were born in the Netherlands, a participant was categorized as Native Dutch; if one of the parents was born abroad, a participant was categorized as Immigrant. Immigrant is further divided into Western and Non-Western, of which Non-Western if further subdivided into Morocco, former Dutch Antilles and Aruba, Surinam, Turkey and Other Non-Western.
SES below average corresponds to a status score of 0 or higher, SES above average corresponds to a status score below 0.
* P value <0.05.
† P value <0.10.
Quality of life

The mean EQ-5D utility score of the participants was 0.79 on a scale of 0.0 to 1.0 and their mean EQ VAS was 69.1 on a scale of 0 to 100. Children scored slightly lower than adolescents (0.72 vs. 0.80) on the EQ-5D. Participants with a SDS-BMI >= median had lower utility scores than participants with a SDS-BMI < median (0.77 vs. 0.80), although this was not significantly different. 20 children and adolescents (25%) reported having no problems at all on any of the five dimensions. Of the participants reporting any problems (75%), the most reported problem was pain; 57.3% reported having (some or extreme) problems with pain. This was followed by anxiety/depression (36.3%), usual activity (26.3%), mobility (25.1%) and finally self-care (3.8%). No differences were found between the adolescents and children. However, participants with a SDS-BMI >= median had slightly more problems with mobility (35% vs. 15.4%) and pain (66.7% vs. 48.7%) than participants with a SDS-BMI < median, although for mobility this was not statistically significant (Figure 1). Of the participants reporting any problems (some or extreme) on any of the five dimensions, the majority experienced some problems. Extreme problems were most often reported on the anxiety/depression dimension. Relatively boys had slightly more problems with activity whereas girls tended to have more problems with anxiety/depression, although these differences were not statistically significant. As for the EQ-VAS, children had a higher EQ VAS than adolescents (76.1 vs. 67.4). Also participants with a SDS-BMI < median scored higher on the EQ VAS than participants with a SDS-BMI >= median (73.7 vs. 64.7). These differences were not statistically significant.
Anthropometric measurements

Of the 80 participants the mean SDS-BMI was 3.4 and the mean percentage FM was 52% (Table 2). The SDS-BMI, SDS-waist circumference, fat mass percentage, systolic blood pressure, fasting plasma insulin, fasting plasma glucose, triglycerides and HOMA-IR were significantly higher in participants with a SDS-BMI >= median than in participants with a SDS-BMI < median. Also the distribution of sexes differed significantly between the SDS-BMI groups, with more girls in the lower SDS-BMI group. There was a statistically significant difference in SDS-BMI and SDS-waist circumference between boys and girls; 3.7 vs. 3.3 and 3.8 vs. 3.5. With regard to age, adolescents had a statistically significant higher systolic blood pressure and HS-CRP than children (data not shown). SDS-BMI was significantly correlated with SDS-waist circumference, percentage fat mass, systolic blood pressure, fasting plasma insulin, triglycerides and HOMA-IR (correlation coefficients respectively 0.80, 0.32, 0.37, 0.49, 0.37 and 0.48). We also looked at correlations between EQ-5D utility scores and anthropometric and laboratory measurements, but no significant correlations were found.
No relevant differences in anthropometric measurements were found between participants with an EQ-5D utility score < median and participants with a score >= median.

Table 2. Anthropometric and laboratory measurements of the children and adolescents participating in HELIOS, for all participants together and stratified according to SDS-BMI group and Spearman’s rank correlations.

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 80)</th>
<th>SDS-BMI &lt; median (n = 39)</th>
<th>SDS-BMI &gt;= median (n = 41)</th>
<th>Spearman’s R with SDS-BMI</th>
<th>Spearman’s R with EQ-5D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>14.8 (2.3)</td>
<td>14.4 (2.4)</td>
<td>15.2 (2.2)</td>
<td>0.19</td>
<td>0.05</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>33.8/66.2</td>
<td>17.9/82.1**</td>
<td>48.8/51.2**</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>3.4 (0.4)</td>
<td>3.1 (0.2)**</td>
<td>3.7 (0.3)**</td>
<td>-</td>
<td>-0.03</td>
</tr>
<tr>
<td>SDS-waist circumference</td>
<td>3.6 (0.3)</td>
<td>3.4 (0.2)**</td>
<td>3.8 (0.3)**</td>
<td>0.80**</td>
<td>-0.07</td>
</tr>
<tr>
<td>BIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>52.3 (4.4)</td>
<td>50.5 (3.8)**</td>
<td>53.9 (4.4)**</td>
<td>0.32**</td>
<td>-0.13</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121.9 (12.8)</td>
<td>117.5 (11.1)**</td>
<td>126.1 (13.0)**</td>
<td>0.37**</td>
<td>-0.09</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76.8 (11.1)</td>
<td>74.9 (9.4)</td>
<td>78.7 (12.4)</td>
<td>0.19</td>
<td>0.03</td>
</tr>
<tr>
<td>Puberty stage (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Prepubertal</td>
<td>8.8</td>
<td>12.8</td>
<td>4.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2 Pubertal</td>
<td>48.8</td>
<td>53.8</td>
<td>43.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3 Postpubertal</td>
<td>42.5</td>
<td>33.3</td>
<td>51.2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fasting plasma insulin (pmol/L)</td>
<td>98.6 (65.1)</td>
<td>72.6 (40.4)**</td>
<td>122.7 (74.4)**</td>
<td>0.49**</td>
<td>-0.12</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>4.7 (0.3)</td>
<td>4.6 (0.3)*</td>
<td>4.8 (0.3)*</td>
<td>0.19</td>
<td>-0.10</td>
</tr>
<tr>
<td>2-h plasma glucose (mmol/L)</td>
<td>5.8 (1.2)</td>
<td>5.8 (1.4)</td>
<td>5.9 (0.9)</td>
<td>0.14</td>
<td>-0.22*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.8 (0.7)</td>
<td>3.7 (0.8)</td>
<td>3.8 (0.7)</td>
<td>0.09</td>
<td>-0.13</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.0 (0.2)</td>
<td>1.1 (0.2)†</td>
<td>1.0 (0.2)†</td>
<td>-0.22†</td>
<td>-0.10</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.3 (0.6)</td>
<td>2.2 (0.6)</td>
<td>2.3 (0.7)</td>
<td>0.00</td>
<td>-0.08</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.0 (0.6)</td>
<td>0.8 (0.4)**</td>
<td>1.2 (0.6)**</td>
<td>0.37**</td>
<td>-0.18</td>
</tr>
<tr>
<td>HS-CRP (mg/l)</td>
<td>5.0 (4.6)</td>
<td>4.4 (4.6)</td>
<td>5.5 (4.6)</td>
<td>0.22</td>
<td>0.07</td>
</tr>
<tr>
<td>HbA1C (DCCT %)</td>
<td>5.5 (0.3)</td>
<td>5.5 (0.3)</td>
<td>5.5 (0.2)</td>
<td>0.05</td>
<td>0.07</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.0 (2.1)</td>
<td>2.2 (1.3)**</td>
<td>3.8 (2.4)**</td>
<td>0.48**</td>
<td>-0.15</td>
</tr>
</tbody>
</table>

Data are mean (SD).
SD – standard deviation; SDS-BMI – standard deviation of body mass index; SDS-waist circumference – standard deviation of waist circumference; BIS – Bio-electrical impedance spectroscopy; HDL – high-density lipoprotein; LDL – low-density lipoprotein; HS-CRP - high sensitive C-reactive protein; HbA1C – hemoglobin type A1C; HOMA-IR – homeostasis model assessment for insulin resistance; EQ-5D – EQ-5D descriptive system; R – correlation.
Median is 3.46.
† P value = 0.05.
* P value <0.05.
** P value < 0.01.
1 Three stages based on Tanner stages: ‘prepubertal’ equals G/M1&P1; ‘postpubertal’ equals G/MS&P5; ‘pubertal’ equals all other Tanner stages.
NA Not applicable.
**Cardiometabolic risk factors**

Table 3 shows that 80% of all participants had at least one cardiometabolic risk factor in addition to being obese. This was 74.4% in the lower SDS-BMI group and 85.4% in the higher SDS-BMI group. The most common cardiometabolic risk factors were low HDL-cholesterol (65.0%), hypertension (31.2%) and high triglycerides (11.2%). These risk factors were more present among participants with a SDS-BMI above the median than among participants with a SDS-BMI under the median, although these differences were not significant. Furthermore, children and adolescents with a higher SDS-BMI were four times more likely to have hypertension (OR 5.51, 95% CI 0.55, 22.18) and almost five times more likely to have a high insulin resistance (OR 5.35, 95% CI 1.39, 20.63). In the group with a SDS-BMI >= median fewer participants had no cardiometabolic risk factor in addition to their obesity than in the group with a SDS-BMI < median. Of the participants that had any cardiometabolic risk factor in addition to obesity, more children and adolescents in the highest SDS-BMI group had two or more cardiometabolic risk factor in addition to their obesity, whereas more children and adolescents in the lower SDS-BMI group had only one cardiometabolic risk factor in addition to their obesity. Additional analyses in which results were stratified by SDS-BMI < 3.0 (N = 9) or SDS-BMI >= 3.0 (N = 71) taken the inclusion criteria into account, showed that 66.7% respectively 81.7% had at least one cardiometabolic risk factor or more in addition to being obese (data not shown). When we looked at the group of children and the group of adolescents separately (data not shown), we saw that already 68.8% of the children between 8–13 years old had one cardiometabolic risk factor in addition to their obesity and 18.8% already had two additional cardiometabolic risk factors. Only 31.2% of the children had no additional cardiometabolic risk factors in addition to obesity, for adolescents this was even lower with 17.2% No differences were found for the different cardiometabolic risk factors between the group with a utility score < the median and the group with a utility score >= the median (data not shown). There was also no difference in prevalence of the number of risk factors between these groups. Participants with a higher utility score were not more likely to have any of the cardiometabolic risk factors included in Table 3 (data not shown). If we combine the cardiometabolic risk factors in our study according to the new IDF definition of MetS, the prevalence of MetS was 27.5% in our study population. When we took the degree of obesity into account, 23.1% in the lower SDS-BMI group had MetS, whereas 31.7% in the higher SDS-BMI group had MetS.
**Table 3. The prevalence of cardiometabolic risk factors (CRF) of the children and adolescents participating in HELIOS, for all participants together and stratified according to SDS-BMI group.**

<table>
<thead>
<tr>
<th>CRF</th>
<th>Total (n = 80)</th>
<th>SDS-BMI &lt; median (n = 39)</th>
<th>SDS-BMI &gt;= median (n = 41)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High triglycerides</td>
<td>9 (11.2)</td>
<td>3 (7.7)</td>
<td>6 (14.6)</td>
<td>2.47 (0.42, 14.64)</td>
</tr>
<tr>
<td>Low HDL-cholesterol</td>
<td>52 (65.0)</td>
<td>24 (61.5)</td>
<td>28 (68.3)</td>
<td>1.49 (0.55, 4.94)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (31.2)</td>
<td>9 (23.1)</td>
<td>16 (39.0)</td>
<td>5.51 (1.37, 22.18)*</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>1 (1.2)</td>
<td>1 (2.6)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>5 (6.2)</td>
<td>4 (10.3)</td>
<td>1 (2.4)</td>
<td>-</td>
</tr>
<tr>
<td>DMII</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High HOMA-IR</td>
<td>30 (37.5)</td>
<td>9 (23.1)**</td>
<td>21 (51.2)**</td>
<td>5.35 (1.39, 20.63)*</td>
</tr>
<tr>
<td>1 CRF (only obesity)</td>
<td>16 (20.0)</td>
<td>10 (25.6)</td>
<td>6 (14.6)</td>
<td>NA</td>
</tr>
<tr>
<td>2 CRF (1 in addition to obesity)</td>
<td>39 (48.8)</td>
<td>18 (46.2)</td>
<td>21 (51.2)</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;= 3 CRFs (&gt;2 in addition to obesity)</td>
<td>25 (31.3)</td>
<td>11 (28.2)</td>
<td>14 (34.1)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are n (% of total) and OR with 95% CI.

OR – Odds Ratio; SDS-BMI – standard deviation of body mass index; CI – confidence interval; HDL – High Density Lipoprotein; HOMA-IR – homeostasis model assessment for insulin resistance; DMII – Diabetes mellitus type 2.

Reference cut-off points for cardiometabolic risk from ‘The metabolic syndrome in children and adolescents – an IDF consensus report’ by Zimmet et al. [27].

Reference cut-off points HOMA-IR from ‘Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods’ by Kurtoglu et al. [25], ‘Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents’ by Keskin et al. for postpubertal stage [26].

CRFs are based on the IDF criteria including obesity, high triglycerides, low HDL-cholesterol, hypertension, impaired fasting glucose, impaired glucose tolerance and DMII. Since all participants fulfilled the IDF criterion for obesity, none of the participants had zero CRF. Participants with 1 CRF only had obesity and none of the other CRFs. Participants with 2 CRFs had 1 CRF in addition to obesity. Participants with 3 or more CRFs had 2 or more CRFs in addition to obesity. HOMA-IR is not taken into account in the number of CRFs.

Median is 3.49.

- Insufficient sample size.

* P value <0.05.

** P value < 0.01.

NA Not applicable.

**Discussion**

This study shows that 80% of the severely obese children and adolescents eligible for intensive inpatient treatment programs for severely obese had at least one cardiometabolic risk factor (in addition to obesity) indicating that they are at increased risk for severe health complications. Within this group, higher SDS-BMI was associated with a worse profile of several cardiometabolic risk factors. The mean EQ VAS of the participants was 69.1 on a scale of 0 to 100. Unfortunately, there are hardly studies that describe characteristics of this specific group of severely obese children and adolescents. Therefore there is little insight into the health risks of this group and the urgency to quickly detect this group and offer suitable treatment programs. Most studies included only obese participants and not severely obese or also obese participants, or had fewer participants than we did. Moreover
CHAPTER 3

often anthropometric and clinical characteristics of the study population are only described after treatment. In our study, we see a tendency; the higher the SDS-BMI and higher the degree of obesity, the higher the prevalence of MetS. This is also seen in a study by Weiss et al., although the z-scores of BMI in our study population are much higher. Weiss et al. found that 38.7% of the participants with moderate obesity (defined as 2.0 < SDS-BMI = < 2.5) and 49.7% with severe obesity (SDS-BMI > 2.5) were diagnosed with MetS. Thus, the prevalence of cardiometabolic risk factors seems to increase with worsening obesity, even in the upper regions. The most common cardiometabolic risk factor seen in our study population is low HDL-cholesterol (65.0%), followed by hypertension (31.2%) and high triglycerides (11.2%). In the Lafortuna study, hypertension was the most prevalent component of MetS (66.1% for Germans vs. 44.7% for Italians), followed by low HDL-cholesterol (39.5% vs. 37.4% respectively). Adolescents had higher prevalences of cardiometabolic risk factors than children in our study population. This was also found by Lafortuna et al., in which the prevalences of almost all components of MetS increased with age groups. There are only a few studies that looked at the relationship between childhood obesity and quality of life, and almost none that studied this association in severely obese children and adolescents. In our study we found that the average score on a scale of 0 to 100 was 69.1. Since we only included severely obese children and adolescents in our study population, we cannot directly compare our results to a similar group of normal weight children. However, we did compare our results with existing literature describing quality of life in obese children and adolescents. The EQ-VAS score of 69 found in this study suggests that participants experience important limitations in their quality of life. This was also found by Schwimmer et al. who used the PedsQL to assess quality of life in obese and normal weight children. They found that obese children had a significantly lower mean health-related quality of life score compared with healthy children and adolescents (mean score 67.0 vs. 83.0) and that they were 5.5 times more likely to have impaired health-related quality of life than a healthy child or adolescent, which is similar to a child or adolescent with cancer. Williams et al. also used the PedsQL 4.0 and compared schoolchildren with normal weight, overweight and obesity to each other. They found total mean scores of respectively 80.5, 79.3 and 74.0. The degree of obesity was taken into account by Varni et al. Severely obese children self-reported significantly lower overall health-related quality of life, physical health, psychosocial health, and school functioning in comparison with obese children. The results of a recent study.
by Philips et al. also suggest the ‘extremely obese’ are significantly more depressed, more socially anxious and have poorer quality of life in comparison with the ‘obese’. We report similar findings in our study (higher BMI, poorer quality of life), although our results were not statistically significant. We did not find a relationship between quality of life and the presence of cardiovascular risk factors, like Nadeau et al. did. In their study, a higher body mass index and greater number of comorbidities were associated with diminished health-related quality of life. The difference may be explained by the fact that Nadeau et al. used a disease specific questionnaire, which is probably more sensitive to detect limitations related to obesity than the general quality of life questionnaire we used in our study. All children that participated in this study were referred to obesity center Heideheuvel by their pediatricians. Since not every severely obese child or adolescent in the Netherlands will have been under the care of a pediatrician and therefore was not able to participate in the study, participants of HELIOS were probably a selection from the total group of severely obese children and adolescents in the Netherlands. It is unknown if the children and adolescents not being referred by pediatricians differ in characteristics from the children and adolescents that were being referred. It is possible that the children and adolescents that were to seek help from a pediatrician were also the ones already suffering from cardiometabolic risk factors. Also, the inclusion of participants with a SDS-BMI between 2.3 and 3.0 with comorbidity can lead to a preselected sample and therefore has a higher prevalence of these factors than a general population of obese children. In practice, seven participants had a SDS-BMI between 2.3-3.0 (2.9, 2.8, 2.9, 2.5, 2.8, 2.6, and 2.5). Of these participants, none had impaired fasting glucose, none had impaired glucose tolerance, none had diabetes mellitus type 2, four had insulin resistance, one had hypertension, and six had low HDL-cholesterol. Indeed, some of them already had cardiometabolic risk factors, but in general we saw a higher prevalence of these risk factors among those with a higher SDS-BMI. A strong point of this study is the large number of participants that came from all parts of the Netherlands. Many studies with a severely obese children and/or adolescents study population had fewer participants and participants for a limited area that did not present the country. This article was written since the prevalence of severe obesity is rising in children and adolescents worldwide; a good description of particularly this population is needed. The results in this article clearly demonstrate that most severely obese children and adolescents already have several cardiometabolic risk factors present and are at high risk for developing cardiometabolic
disease in young adulthood. These findings stress the importance and need of the early
detection of these children, of the availability of appropriate intensive treatment programs
and of the early screening for cardiometabolic risk factors. It is even more important to
prevent them from becoming severely obese, because effects of treatment can be lower
than desired resulting from the complexity within the group of severely obese children
and adolescents to prevent the development of cardiometabolic risk factors and diabetes
mellitus type 2 and impaired quality of life.

Conclusions
Cardiometabolic risk factors are already highly prevalent in this group of severely obese
children and adolescents, 80% had at least one cardiometabolic risk factor (in addition to
obesity). The score of 69.1 found for quality of life in this study suggests that participants
experience important limitations in their quality of life. However, quality of life is not
associated with the prevalence of cardiometabolic risk factors.
References

Vitamin D3

Figure 1: Synthesis of the active vitamin D metabolite - 1,25(OH)2D throughout the body.

Inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D

Vitamin D-binding protein. Two metabolic steps are necessary to convert metabolites. In the bloodstream, vitamin D is mainly transported by liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)2D for full biological activity. Vitamin D is transported to the kidney and 1,25(OH)2D is circulated throughout the body.

In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert metabolites. In the bloodstream, vitamin D is mainly transported by liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)2D for full biological activity. Vitamin D is transported to the kidney and 1,25(OH)2D is circulated throughout the body.

Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are the major forms of vitamin D. Vitamin D2 is the plant and yeast-derived form of vitamin D. Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9).

The two major sources of vitamin D in the Western diet are sunlight and dairy products. Vitamin D is synthesized in the skin when exposed to sunlight and is then transported to the liver and kidneys where it undergoes two hydroxylation processes to become the active form, 1,25-dihydroxyvitamin D3 (1,25(OH)2D). This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body.

Vitamin D deficiency is more prevalent in certain populations, such as those with limited sun exposure, individuals with darker skin, and those who live in regions with lower latitudes or higher altitudes. Additionally, vitamin D deficiency is more common in the winter months when sunlight is limited. It is also influenced by factors such as age, gender, and body mass index. Vitamin D deficiency can lead to a range of health problems, including bone disorders, decreased immune function, and increased risk of certain cancers.

In summary, vitamin D is an important nutrient that plays a crucial role in maintaining bone health and overall well-being. It is essential to ensure adequate intake of vitamin D through dietary sources, supplementation, or sunlight exposure to prevent deficiency and associated health risks.
Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant and yeast-derived form of vitamin D. Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources.

In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)2D (Figure 1).

This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body.
EFFECTIVENESS OF TWO INTENSIVE INPATIENT TREATMENTS FOR SEVERELY OBESE CHILDREN AND ADOLESCENTS

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Submitted
Abstract

Background/Objectives
Intensive inpatient lifestyle treatment may be a suitable alternative for severely obese children and adolescents who do not benefit from ambulatory obesity treatment. The aim was to evaluate the effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and cardiometabolic risk factors.

Subjects/Methods
The study was designed as a randomized controlled trial with two active treatment groups. Eighty participants (8-19 years) with severe obesity received treatment at a specialized childhood obesity center in the Netherlands. Severe obesity was defined as a SDS-BMI ≥ 3.0 or a SDS-BMI ≥ 2.3 in combination with obesity-related comorbidity. Participants received an intensive one-year lifestyle treatment with an inpatient period of either two months and biweekly return visits during the next four months (short-stay group) or six months (long-stay group), both followed by six monthly return visits.
Outcomes were assessed at baseline, six and 12 months and included SDS-BMI as primary outcome and cardiometabolic risk factors such as SDS-waist circumference, systolic- and diastolic blood pressure, and blood measurements as secondary outcomes.
To evaluate differences in the course of the primary- and secondary outcomes over time between the two treatment groups, Generalized Estimating Equations (GEE) were performed.

Results
No differences in the course of SDS-BMI or secondary outcomes over time were found between the two treatment groups after one year of treatment. SDS-BMI decreased statistically significantly after one year of treatment compared with baseline in both groups (0.33 (0.48) in the short-stay and 0.52 (0.49) in the long-stay group). Similar results were found for SDS-waist circumference, diastolic blood pressure and HDL-cholesterol.

Conclusions
Since there were no differences in effects between the short- and long-stay treatment and considering the burden of the long-stay treatment for children and families, we recommend implementation of the short-stay treatment.
Introduction

During the last few decades, the prevalence of (severe) obesity in children and adolescents has been rising worldwide.\textsuperscript{1-5} In the Netherlands, the upward trend of severe childhood obesity resulted in a seven-fold increase in prevalence since 1980, and in 2010 it was estimated that the prevalence was 0.56\% (approximately 18 500 children and adolescents).\textsuperscript{6}

Childhood obesity increases the risk of cardiometabolic risk factors such as hyperlipidemia, hypertension and diabetes mellitus type 2, as well as respiratory and musculoskeletal conditions and liver abnormalities.\textsuperscript{7,8} Previous studies have shown that 62-80\% of severely obese children and adolescents have at least one cardiometabolic risk factor in addition to being severely obese.\textsuperscript{9,10} Moreover, (severe) obesity has a negative impact on psychosocial health.\textsuperscript{11-14} Severely obese children report quality of life levels similar to children diagnosed with cancer.\textsuperscript{15} Furthermore, there is a high probability that childhood obesity tracks into adulthood leading to health problems later in life.\textsuperscript{16,17}

Research shows that obesity treatment should incorporate a combination of nutrition, physical activity and behavioral change, and be family-based.\textsuperscript{18-22} Several studies have shown that obesity treatment can reduce weight in obese children and adolescents, and that this may reduce the serious immediate and long-term burden on physical and psychosocial health for these obese individuals and society as a whole.\textsuperscript{23-25} However, most research has focused on obese children and adolescents while research among severely obese children and adolescents is relatively rare. Evidence suggests that ambulatory obesity treatment for severely obese children and adolescents is insufficiently effective in the long-term and that more intensive treatment is needed.\textsuperscript{26-29}

Currently in the Netherlands, Heideheuvel is the only specialized childhood obesity center offering treatment for severely obese children and adolescents. Their intensive one-year lifestyle treatment was modeled after the treatment developed by Braet et al\textsuperscript{30} and originally included a six-month inpatient period. This treatment proved to be more effective in improving SDS-BMI and cardiometabolic risk factors in comparison with ambulatory obesity treatment.\textsuperscript{31} However, an inpatient period of six months is expensive and poses
a considerable burden on both the participants and their families. Therefore, a modified treatment was developed with a two-month inpatient period. The aim of this study was to evaluate the effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods (i.e. two months vs. six months) for severely obese children and adolescents with regard to SDS-BMI and cardiometabolic risk factors such as SDS-waist circumference, systolic- and diastolic blood pressure, and blood measurements directly after treatment.

**Subjects and Methods**

**Study Design and Population**
This study was designed as a randomized controlled trial with two active treatment groups and a follow-up of 24 months. This paper reports on the effectiveness of the two treatments directly after one year of treatment. The Medical Ethics Committee of the VU University Medical Center (Amsterdam, the Netherlands) approved the study protocol. Prior to randomization, written informed consent was obtained from both the participants and their parents/caregivers. Details of the study have been described elsewhere.

The study population consisted of 80 participants (8-19 years) with severe obesity. All participants were referred to a specialized childhood obesity center by their local pediatrician after insufficient response to ambulatory obesity treatment. Severe obesity was defined as a SDS-BMI ≥ 3.0 (99.9th age- and sex-specific percentile of BMI in the fourth Dutch nationwide growth study of 1997), or a SDS-BMI ≥ 2.3 (99th age- and sex-specific percentile of BMI in the fourth Dutch nationwide growth study of 1997) in combination with obesity-related comorbidity. Participants were excluded from the study if they had syndromal or chromosomal determined obesity; obesity caused by endocrine or medicine use; psychiatric problems; an IQ below 75 or similar school level or if their parents/caregivers were not willing or able to participate in the treatment and/or study.

**Intervention Conditions**
Both groups received an intensive one-year lifestyle treatment with either an inpatient period of two months (short-stay group) or six months (long-stay group). During weekdays, the short-stay group participated in a two-month inpatient treatment, followed by biweekly...
return visits of two days during the next four months, then followed by six monthly return visits of two days. The long-stay group participated in a six-month inpatient treatment during weekdays, followed by six monthly return visits of two days. The treatment focused on nutrition, physical activity and behavior change and required active participation of the parents/caregivers. Treatment was delivered at a specialized childhood obesity center, Heideheuvel, in the Netherlands. A more detailed description of the content, frequency and intensity of the treatment can be found elsewhere.32

Randomization and Blinding
The primary researcher, who was not blinded to treatment allocation, randomized all participants to the short-stay (40 participants) and long-stay group (40 participants) using a table of random numbers.33,34 Because it was logistically not possible to provide treatment to all participants at the same time, a group of 20 participants was randomized to a one-year waiting-list group, after which they were randomly allocated to one of the treatment groups. Four participants dropped out of the study while being in the waiting-list group, leading to a waiting-list group of 16 participants. Four additional participants were recruited to replace the four participants that dropped out of the study to ensure a study population of 80 participants.

Because of the nature of the treatment, participants, their parents/caregivers and healthcare professionals could not be blinded to the treatment.

Measurements
Demographic characteristics included ethnicity, educational level, socio economic status (SES) and household situation.32

Outcome measures were collected at baseline and six and 12 months of follow-up. SDS-BMI was the primary outcome in this study and cardiometabolic risk factors (i.e. SDS-waist circumference, systolic- and diastolic blood pressure, and blood measurements) the secondary outcomes.
BMI was calculated as weight/height$^2$ (kg/m$^2$). The degree of overweight was quantified using Cole’s least mean square method, which normalizes the BMI’s skewed distribution and expresses BMI as SDS-BMI.$^{35}$ SDS-BMI was calculated with the Growth Analyser$^{36}$ using the fourth Dutch nationwide growth study of 1997 as reference.

Waist circumference was measured with a tape measure with an accuracy of 1 mm. SDS-waist circumference was calculated with the Growth Analyser$^{36}$ using the fourth Dutch nationwide growth study of 1997 as reference.

Blood pressure was measured three times in sitting position after sitting still for at least 5 minutes. For the analyses, the averages of the three systolic blood pressure and diastolic blood pressure readings were used.

Blood measurements included fasting insulin, 2h-insulin, fasting glucose, 2h-glucose, HDL-cholesterol, triglycerides and homeostasis model assessment for insulin resistance (HOMA-IR) after an overnight fast.

**Statistical analyses**
The sample size was calculated to detect a 0.5 SDS-BMI difference between the two groups after one year of treatment which is considered a clinically meaningful effect size.$^{38}$ Based on a Power of 80% and a two-tailed significance level of 5%, two groups of 40 participants were needed.$^{32}$

Analyses were performed according to the intention-to-treat principle. Baseline characteristics were compared between the two treatment groups. Independent Student’s t-tests were used for continuous variables and Chi-square tests for categorical variables using IBM SPSS Statistics for Windows, Version 21 (SPSS 21).$^{39}$ Statistical significance was set at $P$-value $< 0.05$.

To evaluate differences in the course of the primary- and secondary outcomes over time between the two treatment groups, Generalized Estimating Equations (GEE) were performed.$^{40}$ GEE were used to adjust for the correlation between repeated measures
obtained in the same participant. In all models, an exchangeable correlation structure was specified and adjustment for baseline values was applied to assess the actual effects of treatment on the primary- and secondary outcomes independent of differences in baseline values.\textsuperscript{40} To evaluate the effects of the two treatment groups at different time points specifically (i.e. between baseline and six months follow-up and between six- and 12 months follow-up, respectively), time was treated as a categorical variable according to the common approach described earlier by Fitzmaurice et al.\textsuperscript{41}

For each outcome, two types of analyses were performed: 1) crude analyses which were only adjusted for baseline values and 2) analyses which were adjusted for baseline values and additional covariates.

Covariates were selected by first assessing them using a forward approach and were considered relevant when the treatment effect changed with 10% or more after inclusion of the covariate.\textsuperscript{42} All covariates were also tested for possible effect modification and if the interaction term was statistically significant (i.e. a \( P \)-value \( \leq 0.05 \)), stratified models were presented.

\textit{Additional Analyses}

To evaluate the effectiveness of the two treatments in comparison with the waiting-list group in the course of the primary- and secondary outcomes over time, GEE were performed as well.\textsuperscript{40}

In the per protocol analysis, only participants who took part in at least 75\% of the treatment sessions were included. In the complete case analysis, only participants with complete follow-up on the primary outcome SDS-BMI (baseline, six and 12 months) were included. In both the per protocol and complete case analyses, the primary- and secondary outcomes over time were evaluated with GEE.
Results

Participants

In total, 169 participants were referred to Heideheuvel by their local pediatrician after insufficient response to ambulatory obesity treatment. Of them, 89 were excluded based on either a decision made by the staff of Heideheuvel (N=46) or by the family (N=43). This left 80 participants to be included in the study (Figure 1).

![Flow-chart of participants](image)

**Figure 1. Flow-diagram of participants.**
A one-year waiting-list group of 20 participants was involved. Four participants dropped out of the study while being in the waiting-list group, leading to a waiting-list group of 16 participants.

At baseline, no relevant differences were found between the two treatment groups (Table 1). Sixty-eight participants (85%) did not drop out of treatment. Of these 68 participants, 61 participants (76%) took part in at least 75% of the treatment sessions and were considered...
as per protocol participants. Complete follow-up on the primary outcome SDS-BMI was obtained from 37 short-stay and 30 long-stay group participants (84%). Per protocol and not per protocol participants, and participants with and without complete follow-up did not differ from each other with regard to baseline characteristics.

**Table 1. Baseline characteristics of the study population.**

<table>
<thead>
<tr>
<th></th>
<th>Total N=80</th>
<th>Short-stay group N=40</th>
<th>Long-stay group N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean (SD)]</td>
<td>14.8 (2.3)</td>
<td>14.5 (2.4)</td>
<td>15.0 (2.2)</td>
</tr>
<tr>
<td>Female [n (%)]</td>
<td>53 (66.3)</td>
<td>28 (70.0)</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Ethnicities [% of total]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>61.5</td>
<td>69.2</td>
<td>53.8</td>
</tr>
<tr>
<td>Non-Western</td>
<td>38.5</td>
<td>30.8</td>
<td>46.2</td>
</tr>
<tr>
<td>Educational level of the parents/caregivers [% of total]^1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>38.7</td>
<td>38.5</td>
<td>38.9</td>
</tr>
<tr>
<td>Medium/intermediate</td>
<td>42.7</td>
<td>43.6</td>
<td>41.7</td>
</tr>
<tr>
<td>High</td>
<td>18.7</td>
<td>17.9</td>
<td>19.4</td>
</tr>
<tr>
<td>SES [% of total]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below average</td>
<td>65.8</td>
<td>59.5</td>
<td>71.8</td>
</tr>
<tr>
<td>Above average</td>
<td>34.2</td>
<td>40.5</td>
<td>28.2</td>
</tr>
<tr>
<td>Household situation [% of total]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living together</td>
<td>55.0</td>
<td>62.5</td>
<td>47.5</td>
</tr>
<tr>
<td>Divorced</td>
<td>33.8</td>
<td>32.5</td>
<td>35.0</td>
</tr>
<tr>
<td>One parent family(mother)</td>
<td>7.5</td>
<td>2.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Other situation</td>
<td>3.8</td>
<td>2.5</td>
<td>5.0</td>
</tr>
<tr>
<td>SDS-BMI [mean (SD)]</td>
<td>3.4 (0.39)</td>
<td>3.4 (0.39)</td>
<td>3.4 (0.39)</td>
</tr>
</tbody>
</table>

Abbreviations: SD – standard deviation; SDS-BMI – standard deviation of body mass index; SES – socio economic status.
The short-stay group participated in a two-month intensive inpatient treatment during weekdays, followed by biweekly return visits of two days during the next four months, then followed by six monthly return visits of two days. The long-stay group participated in a six-month intensive inpatient treatment during weekdays, followed by six monthly return visits of two days.

^1Educational level was classified according to the definition of Statistics Netherlands (http://www.cbs.nl).

**Intention-to-treat analyses**

**Primary outcome**

Mean (SD) SDS-BMI was 3.4 (0.4) in both treatment groups at the start of the treatment. The course of SDS-BMI over time is graphically presented in Figure 2. SDS-BMI decreased statistically significantly in the first six months in both groups. Participants were on average able to maintain this weight-loss during the second half year of treatment. SDS-BMI after 12 months of treatment was statistically significantly lower compared with baseline (mean difference (SD) 0.33 (0.48) in the short-stay and 0.52 (0.49) in the long-stay group). This decrease in SDS-BMI corresponds to an average (SD) weight-loss of 8.1 (14.3) kg in the short-stay and 12.6 (13.6) kg in the long-stay group.
exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production.

Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant and yeast-derived form of vitamin D. Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources.

In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)2D (Figure 1).

This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body.

Table 2 shows the crude and adjusted results of the GEE. Sex, ethnicity and socio economic status were included as covariates in the adjusted analyses. After six months of treatment, SDS-BMI of participants in the short-stay group was higher compared with the long-stay group (adjusted models β = 0.23, 95% CI 0.09; 0.36). However, after one year of treatment, there was no statistically significant difference in SDS-BMI between the two treatment groups (adjusted models β = 0.15, 95% CI -0.06; 0.35).

Secondary outcomes
Statistically significant improvements were seen after one year of treatment compared with baseline in both treatment groups in SDS-waist circumference, diastolic blood pressure and HDL-cholesterol. In the short-stay group, systolic blood pressure improved statistically significantly in comparison with baseline as well.

In the crude and adjusted GEE, no statistically significantly differences in secondary outcomes between the short-stay and long-stay groups were found at any point in time (Table 2).
<table>
<thead>
<tr>
<th>Primary outcome measure</th>
<th>Short-stay Mean (SD)</th>
<th>Long-stay Mean (SD)</th>
<th>Crude Beta (95% CI)</th>
<th>Adjusted Beta (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SDS-BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.4 (0.4)</td>
<td>3.4 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>3.1 (0.5)</td>
<td>2.9 (0.6)</td>
<td>0.22 (0.09; 0.35)</td>
<td>0.23 (0.09; 0.36)</td>
</tr>
<tr>
<td>12-months</td>
<td>3.1 (0.6)</td>
<td>2.9 (0.7)</td>
<td>0.18 (-0.03; 0.40)</td>
<td>0.18 (-0.04; 0.40)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>0.10 (-0.11; 0.31)</td>
<td>0.15 (-0.06; 0.35)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SDS-waist circumference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.2 (0.4)</td>
<td>3.1 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>2.7 (0.5)</td>
<td>2.5 (0.5)</td>
<td>0.13 (-0.03; 0.30)</td>
<td>0.12 (-0.05; 0.30)</td>
</tr>
<tr>
<td>12-months</td>
<td>2.7 (0.7)</td>
<td>2.5 (0.7)</td>
<td>0.08 (-0.18; 0.34)</td>
<td>0.02 (-0.23; 0.27)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>0.14 (-0.07; 0.35)</td>
<td>0.15 (-0.07; 0.37)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>122.7 (12.3)</td>
<td>121.1 (13.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>117.1 (13.9)</td>
<td>116.7 (13.4)</td>
<td>-0.63 (-4.73; 3.48)</td>
<td>0.17 (-3.98; 4.33)</td>
</tr>
<tr>
<td>12-months</td>
<td>118.4 (11.2)</td>
<td>120.0 (15.3)</td>
<td>-2.84 (-7.27; 1.60)</td>
<td>-2.25 (-6.95; 2.45)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>0.59 (-4.65; 5.82)</td>
<td>0.44 (-4.86; 5.75)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>75.7 (9.9)</td>
<td>78.0 (12.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>68.5 (7.9)</td>
<td>68.3 (11.2)</td>
<td>1.49 (-2.04; 5.02)</td>
<td>0.47 (-3.17; 4.11)</td>
</tr>
<tr>
<td>12-months</td>
<td>68.6 (8.1)</td>
<td>67.1 (12.0)</td>
<td>3.02 (-0.72; 6.76)</td>
<td>2.35 (-1.64; 6.34)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>-0.42 (-4.40; 3.56)</td>
<td>-1.21 (-5.21; 2.80)</td>
</tr>
<tr>
<td><strong>Fasting insulin (μU/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.8 (9.3)</td>
<td>14.6 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>11.9 (9.3)</td>
<td>12.9 (10.8)</td>
<td>-0.98 (-4.50; 2.55)</td>
<td>-1.41 (-5.20; 2.39)</td>
</tr>
<tr>
<td>12-months</td>
<td>11.7 (9.1)</td>
<td>14.1 (10.1)</td>
<td>-1.27 (-4.25; 1.70)</td>
<td>-2.15 (-5.39; 1.09)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>-1.10 (-3.60; 1.40)</td>
<td>-2.30 (-5.75; 1.16)</td>
</tr>
<tr>
<td><strong>2h-insulin (μU/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70.7 (49.9)</td>
<td>60.8 (36.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>63.0 (56.9)</td>
<td>52.4 (37.7)</td>
<td>1.16 (-17.21; 19.52)</td>
<td>-0.80 (-19.82; 18.22)</td>
</tr>
<tr>
<td>12-months</td>
<td>67.9 (47.4)</td>
<td>65.3 (54.5)</td>
<td>-0.54 (-23.38; 22.48)</td>
<td>-2.89 (-26.49; 20.71)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>0.65 (-15.50; 16.80)</td>
<td>1.86 (-13.59; 17.31)</td>
</tr>
<tr>
<td><strong>Fasting glucose (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.7 (0.4)</td>
<td>4.7 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>4.8 (0.4)</td>
<td>4.8 (0.3)</td>
<td>0.03 (-0.11; 0.16)</td>
<td>0.02 (-0.13; 0.16)</td>
</tr>
<tr>
<td>12-months</td>
<td>4.8 (0.4)</td>
<td>4.9 (0.3)</td>
<td>-0.06 (-0.19; 0.08)</td>
<td>-0.01 (-0.12; 0.11)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>-0.04 (-0.16; 0.08)</td>
<td>-0.02 (-0.14; 0.10)</td>
</tr>
<tr>
<td><strong>2h-glucose (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.0 (1.2)</td>
<td>5.6 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>5.4 (1.1)</td>
<td>5.1 (1.0)</td>
<td>-0.02 (-0.47; 0.42)</td>
<td>-0.02 (-0.51; 0.47)</td>
</tr>
<tr>
<td>12-months</td>
<td>5.8 (1.1)</td>
<td>5.3 (1.4)</td>
<td>0.32 (-0.24; 0.87)</td>
<td>0.29 (-0.32; 0.89)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>0.35 (-0.06; 0.77)</td>
<td>0.35 (-0.07; 0.76)</td>
</tr>
<tr>
<td><strong>HDL-cholesterol (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.1 (0.3)</td>
<td>1.0 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>1.2 (0.3)</td>
<td>1.1 (0.2)</td>
<td>0.04 (-0.02; 0.11)</td>
<td>0.04 (-0.03; 0.11)</td>
</tr>
<tr>
<td>12-months</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
<td>-0.07 (-0.17; 0.04)</td>
<td>-0.04 (-0.14; 0.07)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>0.07 (-0.03; 0.17)</td>
<td>0.09 (-0.02; 0.20)</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.0 (0.6)</td>
<td>1.0 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>1.1 (1.0)</td>
<td>1.0 (0.5)</td>
<td>0.09 (-0.14; 0.31)</td>
<td>0.04 (-0.15; 0.22)</td>
</tr>
<tr>
<td>12-months</td>
<td>1.2 (0.9)</td>
<td>1.1 (0.7)</td>
<td>0.09 (-0.18; 0.35)</td>
<td>0.04 (-0.22; 0.29)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>0.09 (-0.18; 0.37)</td>
<td>0.06 (-0.17; 0.29)</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.9 (2.0)</td>
<td>3.1 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>2.5 (2.0)</td>
<td>2.8 (2.4)</td>
<td>-0.17 (-0.96; 0.61)</td>
<td>-0.26 (-1.11; 0.59)</td>
</tr>
<tr>
<td>12-months</td>
<td>2.5 (2.0)</td>
<td>3.1 (2.4)</td>
<td>-0.33 (-1.02; 0.37)</td>
<td>-0.44 (-1.17; 0.30)</td>
</tr>
<tr>
<td>Overall effect*</td>
<td></td>
<td></td>
<td>-0.31 (-1.11; 0.49)</td>
<td>-0.52 (-1.28; 0.25)</td>
</tr>
</tbody>
</table>

Adjusted models corrected for baseline, sex, ethnicity, and economic status.
Abbreviations: CI – confidence interval; SD – standard deviation; SDS-BMI – standard deviation of body mass index; SDS-waist circumference – standard deviation of waist circumference; HDL – high-density lipoprotein; HOMA-IR – homeostasis model assessment for insulin resistance.

*Overall effect can be interpreted as the average difference over time between the two treatment groups.
Analyses stratified by sex

Primary outcome
Sex was identified as an effect modifier. The course of SDS-BMI over time for boys and girls in the short-stay group followed the same course as described under the intention-to-treat analyses. However, in the long-stay group, SDS-BMI in boys decreased even further in the second six months of treatment, whereas girls showed an increase in SDS-BMI.

Results of the crude and adjusted GEE stratified by sex are reported in Tables 3 (boys) and 4 (girls). Only for girls, SDS-BMI of participants in the short-stay group was higher compared with the long-stay group after six months of treatment, (adjusted models $\beta = 0.20$, 95% CI 0.07; 0.33). After one year of treatment, there was no statistically significant difference in SDS-BMI between the two treatment groups for either sex.

Secondary outcomes
Analyses stratified by sex showed statistically significant improvements in SDS-waist circumference, diastolic blood pressure and HDL-cholesterol after one year of treatment compared with baseline.

For girls there was a statistically significant difference in HDL-cholesterol between the short-stay and long-stay group after six months of follow-up (adjusted models $\beta = 0.11$, 95% CI 0.03; 0.19). There were no statistically significant differences in secondary outcomes between the treatment groups after one year of treatment after stratification by sex as demonstrated by the crude and adjusted GEE (Table 3 & 4).
Table 3. Effects on outcomes after six and 12 months of follow-up for both treatment groups according to the intention-to-treat principle, boys only.

<table>
<thead>
<tr>
<th>Primary outcome measure</th>
<th>Short-stay Mean (SD)</th>
<th>Long-stay Mean (SD)</th>
<th>Crude Beta (95% CI)</th>
<th>Adjusted Beta (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDS-BMI Baseline</td>
<td>3.7 (0.4)</td>
<td>3.7 (0.4)</td>
<td>0.25 (-0.03; 0.52)</td>
<td>0.23 (-0.07; 0.53)</td>
</tr>
<tr>
<td>6-months</td>
<td>3.4 (0.6)</td>
<td>3.1 (0.7)</td>
<td>0.34 (-0.09; 0.77)</td>
<td>0.31 (-0.14; 0.76)</td>
</tr>
<tr>
<td>12-months</td>
<td>3.4 (0.7)</td>
<td>2.9 (0.8)</td>
<td>0.25 (-0.15; 0.64)</td>
<td>0.26 (-0.15; 0.67)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>0.25 (-0.15; 0.64)</td>
<td>0.26 (-0.15; 0.67)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg) Baseline</td>
<td>124.3 (15.0)</td>
<td>125.1 (14.0)</td>
<td>3.34 (-5.35; 12.03)</td>
<td>4.31 (-3.56; 12.19)</td>
</tr>
<tr>
<td>6-months</td>
<td>122.0 (18.7)</td>
<td>120.2 (11.9)</td>
<td>-1.46 (-9.12; 6.20)</td>
<td>0.45 (-6.74; 7.64)</td>
</tr>
<tr>
<td>12-months</td>
<td>122.1 (12.3)</td>
<td>123.3 (14.4)</td>
<td>0.52 (-9.22; 10.25)</td>
<td>2.04 (-8.27; 12.36)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>0.52 (-9.22; 10.25)</td>
<td>2.04 (-8.27; 12.36)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg) Baseline</td>
<td>77.7 (11.0)</td>
<td>80.9 (9.2)</td>
<td>-1.61 (-8.46; 5.24)</td>
<td>-2.91 (-9.17; 3.35)</td>
</tr>
<tr>
<td>6-months</td>
<td>64.4 (8.0)</td>
<td>68.2 (10.0)</td>
<td>0.78 (-4.44; 6.00)</td>
<td>0.73 (-4.54; 6.00)</td>
</tr>
<tr>
<td>12-months</td>
<td>69.4 (8.3)</td>
<td>66.5 (11.7)</td>
<td>5.28 (-0.21; 10.76)</td>
<td>3.86 (-2.23; 9.94)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>5.28 (-0.21; 10.76)</td>
<td>3.86 (-2.23; 9.94)</td>
</tr>
<tr>
<td>Fasting insulin (µU/L) Baseline</td>
<td>15.3 (7.7)</td>
<td>16.2 (13.2)</td>
<td>-0.14 (-0.31; 0.03)</td>
<td>-0.14 (-0.25; 0.06)</td>
</tr>
<tr>
<td>6-months</td>
<td>12.4 (12.6)</td>
<td>11.8 (11.0)</td>
<td>0.78 (-4.44; 6.00)</td>
<td>0.73 (-4.54; 6.00)</td>
</tr>
<tr>
<td>12-months</td>
<td>11.1 (5.8)</td>
<td>14.4 (13.8)</td>
<td>-0.82 (-4.84; 3.20)</td>
<td>-1.15 (-5.06; 2.76)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>-0.82 (-4.84; 3.20)</td>
<td>-1.15 (-5.06; 2.76)</td>
</tr>
<tr>
<td>2h-insulin (µU/L) Baseline</td>
<td>75.4 (50.2)</td>
<td>53.3 (34.6)</td>
<td>13.21 (-21.43; 47.84)</td>
<td>14.30 (-18.69; 47.29)</td>
</tr>
<tr>
<td>6-months</td>
<td>64.5 (68.2)</td>
<td>38.6 (20.2)</td>
<td>12.81 (-14.94; 20.56)</td>
<td>3.47 (-16.01; 22.96)</td>
</tr>
<tr>
<td>12-months</td>
<td>65.1 (41.3)</td>
<td>62.7 (33.8)</td>
<td>21.31 (-7.19; 49.81)</td>
<td>22.60 (-5.09; 50.30)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>21.31 (-7.19; 49.81)</td>
<td>22.60 (-5.09; 50.30)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L) Baseline</td>
<td>4.6 (0.2)</td>
<td>4.8 (0.4)</td>
<td>0.14 (-0.05; 0.34)</td>
<td>0.14 (-0.05; 0.34)</td>
</tr>
<tr>
<td>6-months</td>
<td>4.8 (0.3)</td>
<td>4.7 (0.3)</td>
<td>0.14 (-0.05; 0.34)</td>
<td>0.14 (-0.05; 0.34)</td>
</tr>
<tr>
<td>12-months</td>
<td>4.7 (0.3)</td>
<td>5.0 (0.2)</td>
<td>0.14 (-0.05; 0.34)</td>
<td>0.14 (-0.05; 0.34)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>0.14 (-0.05; 0.34)</td>
<td>0.14 (-0.05; 0.34)</td>
</tr>
<tr>
<td>2h-glucose (mmol/L) Baseline</td>
<td>6.3 (1.1)</td>
<td>5.7 (0.9)</td>
<td>0.43 (-0.47; 1.33)</td>
<td>0.48 (-0.39; 1.34)</td>
</tr>
<tr>
<td>6-months</td>
<td>5.7 (1.5)</td>
<td>4.9 (0.9)</td>
<td>0.43 (-0.47; 1.33)</td>
<td>0.48 (-0.39; 1.34)</td>
</tr>
<tr>
<td>12-months</td>
<td>5.6 (0.9)</td>
<td>6.0 (1.1)</td>
<td>-0.40 (-1.06; 0.27)</td>
<td>-0.43 (-1.14; 0.29)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>-0.40 (-1.06; 0.27)</td>
<td>-0.43 (-1.14; 0.29)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L) Baseline</td>
<td>1.1 (0.3)</td>
<td>1.0 (0.2)</td>
<td>-0.08 (-0.18; 0.13)</td>
<td>-0.08 (-0.19; 0.03)</td>
</tr>
<tr>
<td>6-months</td>
<td>1.1 (0.4)</td>
<td>1.1 (0.2)</td>
<td>-0.08 (-0.18; 0.13)</td>
<td>-0.08 (-0.19; 0.03)</td>
</tr>
<tr>
<td>12-months</td>
<td>1.2 (0.5)</td>
<td>1.2 (0.4)</td>
<td>-0.08 (-0.18; 0.13)</td>
<td>-0.08 (-0.19; 0.03)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>-0.08 (-0.18; 0.13)</td>
<td>-0.08 (-0.19; 0.03)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L) Baseline</td>
<td>1.0 (0.5)</td>
<td>1.2 (0.7)</td>
<td>0.13 (-0.30; 0.56)</td>
<td>0.06 (-0.31; 0.44)</td>
</tr>
<tr>
<td>6-months</td>
<td>1.1 (0.7)</td>
<td>1.1 (0.7)</td>
<td>0.13 (-0.30; 0.56)</td>
<td>0.06 (-0.31; 0.44)</td>
</tr>
<tr>
<td>12-months</td>
<td>1.4 (0.9)</td>
<td>1.4 (0.9)</td>
<td>-0.06 (-0.51; 0.63)</td>
<td>-0.04 (-0.56; 0.48)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>-0.06 (-0.51; 0.63)</td>
<td>-0.04 (-0.56; 0.48)</td>
</tr>
<tr>
<td>HOMA-IR Baseline</td>
<td>3.1 (1.5)</td>
<td>3.5 (3.0)</td>
<td>0.40 (-0.77; 1.58)</td>
<td>0.37 (-0.80; 1.54)</td>
</tr>
<tr>
<td>6-months</td>
<td>2.7 (2.7)</td>
<td>2.5 (2.4)</td>
<td>0.40 (-0.77; 1.58)</td>
<td>0.37 (-0.80; 1.54)</td>
</tr>
<tr>
<td>12-months</td>
<td>2.3 (1.2)</td>
<td>3.3 (3.3)</td>
<td>-0.17 (-1.05; 0.72)</td>
<td>-0.27 (-1.12; 0.59)</td>
</tr>
<tr>
<td>Overall effect¹</td>
<td></td>
<td></td>
<td>-0.17 (-1.05; 0.72)</td>
<td>-0.27 (-1.12; 0.59)</td>
</tr>
</tbody>
</table>

Adjusted models corrected for baseline, ethnicity, and socio economic status.
Abbreviations: CI – confidence interval; SD – standard deviation; SDS-BMI – standard deviation of body mass index; SDS-waist circumference – standard deviation of waist circumference; HDL – high-density lipoprotein; HOMA-IR – homeostasis model assessment for insulin resistance.

¹Overall effect can be interpreted as the average difference over time between the two treatment groups.
Additional Analyses

Waiting-list group
During the waiting list period, mean (SD) SDS-BMI increased from 3.55 (0.31) to 3.61 (0.53) in the year prior to the start of treatment, but this was not statistically significant (Figure 2).

The crude and adjusted GEE showed that the SDS-BMI of participants in the short-stay group and long-stay group was statistically significantly lower (0.32, 95% CI -0.43; -0.21 and 0.49, 95% CI -0.62; -0.36, respectively) after one year of treatment compared with the waiting-list group (data not shown).

There was a statistically significant improvement in SDS-waist circumference, systolic- and diastolic blood pressure, fasting insulin, HDL-cholesterol, and HOMA-IR after one year of treatment in the two treatments groups in comparison with the waiting-list group (data not shown).

Per protocol and complete case analyses
In the additional analyses the course of SDS-BMI over time followed the same course as in the intention-to-treat analyses.

After one year of treatment, there was no statistically significant difference in SDS-BMI between the two treatment groups (data not shown).

There were statistically significant improvements in both treatment groups in SDS-waist circumference, diastolic blood pressure and HDL-cholesterol after one year of treatment compared with baseline. In the short-stay group, systolic blood pressure improved statistically significantly in comparison with baseline as well. Additionally, in the per protocol analyses, in the short-stay group also fasting insulin, 2h-glucose and HOMA-IR improved statistically significantly.
In the complete case analyses, after one year of treatment there were no statistically significant differences between the treatment groups in any of the secondary outcomes; in the per protocol analyses there was a statistically significant difference between the treatment groups in HDL-cholesterol (data not shown).
Table 4. Effects on outcomes after six and 12 months of follow-up for both treatment groups according to the intention-to-treat principle, girls only.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Short-stay Mean (SD)</th>
<th>Long-stay Mean (SD)</th>
<th>Crude Beta (95% CI)</th>
<th>Adjusted Beta (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome measure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>3.3 (0.3)</td>
<td>3.3 (0.3)</td>
<td>0.19 (0.06; 0.31)</td>
<td>0.20 (0.07; 0.33)</td>
</tr>
<tr>
<td>6-months</td>
<td>3.0 (0.5)</td>
<td>2.8 (0.5)</td>
<td>0.06 (-0.16; 0.28)</td>
<td>0.07 (-0.14; 0.28)</td>
</tr>
<tr>
<td>12-months</td>
<td>3.0 (0.5)</td>
<td>3.0 (0.6)</td>
<td>0.08 (-0.14; 0.30)</td>
<td>0.06 (-0.17; 0.30)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS-waist circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.05 (-0.15; 0.26)</td>
<td>0.00 (-0.22; 0.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-months</td>
<td>1.32 (-4.84; 7.49)</td>
<td>-0.27 (-6.22; 5.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.0 (0.3)</td>
<td>3.0 (0.3)</td>
<td>1.00 (-0.05; 0.25)</td>
<td>1.00 (-0.06; 0.26)</td>
</tr>
<tr>
<td>6-months</td>
<td>2.6 (0.4)</td>
<td>2.5 (0.5)</td>
<td>-0.03 (-0.27; 0.22)</td>
<td>-0.07 (-0.28; 0.15)</td>
</tr>
<tr>
<td>12-months</td>
<td>2.6 (0.6)</td>
<td>2.6 (0.6)</td>
<td>-0.10 (-0.15; 0.26)</td>
<td>-0.00 (-0.22; 0.22)</td>
</tr>
<tr>
<td>Overall effect†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin (μU/L)</td>
<td>13.2 (10.0)</td>
<td>13.6 (6.4)</td>
<td>1.28 (-3.24; 5.80)</td>
<td>0.68 (-4.19; 5.55)</td>
</tr>
<tr>
<td>6-months</td>
<td>11.7 (7.8)</td>
<td>13.6 (10.9)</td>
<td>-1.68 (-5.66; 2.30)</td>
<td>-3.21 (-7.96; 1.55)</td>
</tr>
<tr>
<td>12-months</td>
<td>11.9 (10.2)</td>
<td>13.9 (7.2)</td>
<td>-2.51 (-6.87; 1.81)</td>
<td>-3.21 (-8.78; 2.37)</td>
</tr>
<tr>
<td>Overall effect†</td>
<td>-0.32 (-5.57; 4.92)</td>
<td>-0.56 (-5.86; 4.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>683.8 (63.5)</td>
<td>675.5 (62.5)</td>
<td>1.28 (-3.24; 5.80)</td>
<td>0.68 (-4.19; 5.55)</td>
</tr>
<tr>
<td>6-months</td>
<td>683.8 (63.5)</td>
<td>675.5 (62.5)</td>
<td>1.28 (-3.24; 5.80)</td>
<td>0.68 (-4.19; 5.55)</td>
</tr>
<tr>
<td>12-months</td>
<td>68.3 (6.3)</td>
<td>67.5 (12.5)</td>
<td>1.28 (-3.24; 5.80)</td>
<td>0.68 (-4.19; 5.55)</td>
</tr>
<tr>
<td>Overall effect†</td>
<td>-0.32 (-5.57; 4.92)</td>
<td>-0.56 (-5.86; 4.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2h-insulin (μU/L)</strong></td>
<td>122.0 (11.2)</td>
<td>118.7 (12.6)</td>
<td>1.23 (-1.52; 6.13)</td>
<td>1.94 (-2.19; 6.07)</td>
</tr>
<tr>
<td>6-months</td>
<td>115.2 (11.5)</td>
<td>114.3 (14.1)</td>
<td>-2.71 (-9.22; 1.81)</td>
<td>-2.39 (-6.75; 1.96)</td>
</tr>
<tr>
<td>12-months</td>
<td>117.3 (10.9)</td>
<td>117.9 (15.9)</td>
<td>1.32 (-4.84; 7.49)</td>
<td>2.24 (1.83; 5.58)</td>
</tr>
<tr>
<td>Overall effect†</td>
<td>-0.32 (-5.57; 4.92)</td>
<td>-0.56 (-5.86; 4.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>68.9 (50.4)</td>
<td>67.0 (65.4)</td>
<td>2.70 (-3.72; 31.81)</td>
<td>-4.80 (-38.42; 28.82)</td>
</tr>
<tr>
<td>6-months</td>
<td>68.9 (50.4)</td>
<td>67.0 (65.4)</td>
<td>2.70 (-3.72; 31.81)</td>
<td>-4.80 (-38.42; 28.82)</td>
</tr>
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<td>12-months</td>
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<td>Overall effect†</td>
<td>-0.32 (-5.57; 4.92)</td>
<td>-0.56 (-5.86; 4.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2h-glucose (mmol/L)</strong></td>
<td>74.8 (9.5)</td>
<td>76.3 (13.6)</td>
<td>1.94 (-2.19; 6.07)</td>
<td>1.94 (-2.19; 6.07)</td>
</tr>
<tr>
<td>6-months</td>
<td>70.2 (7.5)</td>
<td>68.4 (12.2)</td>
<td>-2.25 (-6.63; 2.13)</td>
<td>-2.39 (-6.75; 1.96)</td>
</tr>
<tr>
<td>12-months</td>
<td>68.3 (6.3)</td>
<td>67.5 (12.5)</td>
<td>-3.71 (-9.22; 1.81)</td>
<td>-4.17 (-10.08; 1.74)</td>
</tr>
<tr>
<td>Overall effect†</td>
<td>1.32 (-4.84; 7.49)</td>
<td>-0.27 (-6.22; 5.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>5.9 (1.3)</td>
<td>5.6 (1.2)</td>
<td>0.73 (-0.01; 1.48)</td>
<td>0.71 (-0.11; 1.54)</td>
</tr>
<tr>
<td>6-months</td>
<td>5.2 (1.0)</td>
<td>5.3 (1.1)</td>
<td>-0.26 (-0.77; 0.25)</td>
<td>-0.23 (-0.80; 0.34)</td>
</tr>
<tr>
<td>12-months</td>
<td>5.8 (1.2)</td>
<td>4.9 (1.4)</td>
<td>0.73 (-0.01; 1.48)</td>
<td>0.71 (-0.11; 1.54)</td>
</tr>
<tr>
<td>Overall effect†</td>
<td>0.34 (-0.18; 0.87)</td>
<td>0.21 (-0.24; 0.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.1 (0.2)</td>
<td>1.0 (0.2)</td>
<td>0.11 (0.03; 0.19)</td>
<td>0.11 (0.03; 0.19)</td>
</tr>
<tr>
<td>6-months</td>
<td>1.2 (0.2)</td>
<td>1.1 (0.2)</td>
<td>0.07 (-0.18; 0.05)</td>
<td>-0.03 (-0.14; 0.09)</td>
</tr>
<tr>
<td>12-months</td>
<td>1.2 (0.2)</td>
<td>1.2 (0.3)</td>
<td>0.07 (-0.18; 0.05)</td>
<td>-0.03 (-0.14; 0.09)</td>
</tr>
<tr>
<td>Overall effect†</td>
<td>0.08 (-0.02; 0.18)</td>
<td>0.10 (-0.01; 0.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.8 (2.3)</td>
<td>2.9 (1.4)</td>
<td>0.49 (-1.53; 0.55)</td>
<td>-0.73 (-1.96; 0.51)</td>
</tr>
<tr>
<td>6-months</td>
<td>2.5 (1.7)</td>
<td>2.9 (2.4)</td>
<td>-0.49 (-1.31; 0.51)</td>
<td>-0.63 (-1.72; 0.46)</td>
</tr>
<tr>
<td>12-months</td>
<td>2.5 (2.2)</td>
<td>3.0 (1.6)</td>
<td>-0.40 (-1.31; 0.51)</td>
<td>-0.63 (-1.72; 0.46)</td>
</tr>
<tr>
<td>Overall effect†</td>
<td>-0.29 (-1.13; 0.55)</td>
<td>-0.75 (-1.46; 0.04)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted models corrected for baseline, ethnicity, and socio economic status.

Abbreviations: CI – confidence interval; SD – standard deviation; SDS-BMI – standard deviation of body mass index; SDS-waist circumference – standard deviation of waist circumference; HDL – high-density lipoprotein; HOMA-IR – homeostasis model assessment for insulin resistance.

†Overall effect can be interpreted as the average difference over time between the two treatment groups.
Discussion

In this randomized controlled trial, two intensive lifestyle treatments for severely obese children and adolescents with varying inpatient periods (two or six months) were compared. Both treatments showed statistically significant improvements in SDS-BMI and cardiometabolic risk factors after treatment compared with baseline. However, after one year of treatment, there were no statistically significant differences in SDS-BMI or cardiometabolic risk factors between the two treatment groups. In an additional analysis, it was shown that SDS-BMI and cardiometabolic risk factors of participants in both treatment groups improved statistically significantly after one year of treatment compared with participants in a waiting-list group.

The decreases in SDS-BMI that were observed in this study correspond to an average (SD) weight-loss of 8.1 (14.3) kg in the short-stay and 12.6 (13.6) kg in the long-stay group, which is generally considered a clinically relevant improvement.\textsuperscript{38} The treatment can be considered as a last resort for participants and their parents/caregivers since the children in this study were referred to the specialized childhood obesity center because they did not respond to treatment in an ambulatory setting. Therefore, this finding is particularly hopeful.

Many of the participants’ parents were of Non-Western origin and had a lack of proficiency in the Dutch language which complicated treatment in some cases due to communication problems. Despite this, considerable improvements in SDS-BMI were achieved. Also, a relatively high percentage of the participants came from single-parent families and had a low SES background which can be considered a less favorable home environment to retain weight-loss. However, our results showed that weight reductions achieved after the intensive (partly) inpatient treatment period were on average maintained in the second part of the treatment in which only monthly follow-up visits were provided.\textsuperscript{43-45}
Ambulatory obesity treatment often seems less effective for severely obese children in comparison with children and adolescents with a lesser degree of obesity. Therefore, an inpatient treatment seems more appropriate for these children and adolescents. An inpatient setting provides a more supportive environment than ambulatory obesity treatment where children often have to deal with a less supportive home environment every day. The large decrease in SDS-BMI we observed might therefore be explained by the extensive inpatient period in the treatments in our study. During the past decennia in the Netherlands several studies have evaluated the effects of treatments for children and adolescents with (severe) obesity. Most of these studies, however, evaluated ambulatory treatment programs and included populations that consisted of a combination of obese and severely obese participants. A Dutch study by Hofsteenge et al among severely obese children that were on average less obese than the participants followed in our study, showed that SDS-BMI after 18 months of treatment was statistically significantly lower in the intervention group than in the control group. However, this effect was only observed in obese adolescents from Western origin and not in those of Non-Western origin.

Another Dutch study by Vos et al followed a group of severely obese children and adolescents receiving ambulatory obesity treatment for three months. Directly after treatment, SDS-BMI had decreased and after one year of follow-up in which 2-3 refresher sessions were offered, SDS-BMI decreased even further. The decrease in SDS-BMI after one year was comparable to the decrease in SDS-BMI in our study after six months after which SDS-BMI stabilized. Only among boys in the long-stay group we also found a further decrease in SDS-BMI in the second half year. A possible explanation for this difference in favor of severely obese boys, could be that puberty may contribute to a more beneficial weight development in boys.

The only other study (van der Baan et al) in the Netherlands that also evaluated treatment with an inpatient period of six months among severely obese children using the same inclusion criteria as our study, showed a decrease in SDS-BMI after six months that was comparable with our study. However, this study showed a slight increase in SDS-BMI in the second half year of follow-up. This might be due to the fact that there were no return visits after the six-month inpatient period.
Research among severely obese children and adolescents is relatively rare. The few studies performed in the Netherlands and other countries show that among severely obese adolescents, improvements in SDS-BMI during obesity treatment can be maintained during follow-up. However, changing behavior is a difficult and complex process. Therefore, it is important to also have sufficient support available for parents and children after the most intensive treatment period to maintain learned changes. Regular return visits or refresher sessions seem essential to prevent relapse.

Strengths and Limitations
This study has several strengths. First, it is unique with regard to the intensity of the treatments studied, since most lifestyle treatments for severely obese children and adolescents do not include an inpatient period. Moreover, although the duration of treatment was long with one year, this did not result in a high attrition rate; only 12 participants (15%) dropped out of treatment. Compared with other studies evaluating the effects of obesity treatment in adolescents this rate is rather low. Because participants will go back to their home environment after treatment, it is very important that the family of the participants is involved as well. Therefore, a second strength of this study is that not only the participants were involved in the treatment, but that the treatment was family-based with active parental participation. Finally, both treatment groups were compared with a waiting-list group as well in an additional analysis. Therefore, this study not only gives insight into the effects of the intensive treatments compared with each other, but also as compared with a waiting-list group receiving usual care.

There are several limitations as well. The treatments pose a high burden on the participating families. The frequent visits resulted in high time investments for parents and associated time costs. Moreover, parents/caregivers often needed to take time off from work to participate in treatment resulting in productivity losses. In addition, children were placed in an environment completely new to them and were away from their families, home, school and friends for an extended period of time, especially in the long-stay group. Another limitation is that, although a waiting-list group was included, data were available for only 16 participants as four participants in the waiting-list group dropped out of the study. Due to practical reasons, we were unable to recruit more participants into the waiting-list group prior to treatment.
Implications
To ensure long-term maintenance of weight-loss after intensive treatment, continuous monitoring and periodic intensive return visits seem essential. Treatment in specialized childhood obesity centers is costly and poses a high burden, so preferably this continuous treatment is organized in the home environment making it more feasible and less expensive than continuous treatment in specialized childhood obesity centers. It is of the utmost importance that the organization and transfer of treatment from an inpatient setting to an ambulatory setting is prepared carefully, to ensure that participants are not lost to follow-up and receive the appropriate continuous treatment. Special attention to attrition from the continuous treatment in the ambulatory setting is needed.

Conclusions
No statistically significant differences were found between the short-stay and long-stay treatments after one year of follow-up. However, both treatments resulted in statistically significant improvements in comparison with baseline and were statistically significantly more effective than a waiting list condition.

Based on these results, we recommend implementation of the short-stay treatment because of the lower burden for the participating families and the lower costs of treatment. However, whether this treatment should be implemented on a wider scale depends on whether the effects of the inpatient treatment in comparison with usual care are sustained over a longer period of time.
References


CH2

Figure 1:

throughout the body.

D (1,25(OH)2D) for full biological activity. Vitamin D is transported to

liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage

major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin

vitamin D3 – the more common form of vitamin D in nature – is

produced by the skin and is also derived from animal food sources.

In humans, both vitamin D2 and vitamin D3 are converted into several

metabolites. In the bloodstream, vitamin D is mainly transported by

inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin

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ECONOMIC EVALUATION COMPARING TWO INTENSIVE INPATIENT TREATMENTS FOR SEVERELY OBESE CHILDREN AND ADOLESCENTS

Sabine Makkes
Johanna van Dongen
Carry Renders
Olga van der Baan-Slootweg
Jaap Seidell
Judith Bosmans

Submitted
Abstract

Background and objectives
Considering the large economic consequences of severe childhood obesity to society, we aimed to conduct an economic evaluation comparing two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and quality-adjusted life-years (QALYs).

Methods
An economic evaluation from a societal perspective alongside a randomized controlled trial with a 24-month follow-up. Eighty participants (8-19 years) with severe obesity were included. Participants received an intensive one-year lifestyle treatment with an inpatient period of two months (short-stay group) or six months (long-stay group). Data were collected at baseline, six, 12 and 24 months and included SDS-BMI and QALYs.

Results
SDS-BMI decreased in the first six months of treatment, stabilized in the second six months and increased during the second year in both groups. After 24 months, SDS-BMI was similar in both groups, but remained lower than baseline values (mean difference -0.24, 95% CI -0.42; -0.06). There was no difference in QALYs between the groups after 24 months. For SDS-BMI, the probability of the short-stay treatment being cost-effective in comparison with the long-stay treatment was 1 at a willingness-to-pay of 0 €/unit of effect, which slowly decreased to 0.54 for larger willingness-to-pay values.

Conclusions
Based on the results of this study, the short-stay treatment is considered to be cost-effective from the societal perspective in comparison with the long-stay treatment. Future research should provide insight in whether the short stay treatment is cost-effective in comparison with usual care.
Introduction

During a period of three decades, the prevalence of obesity and severe obesity in children and adolescents has increased dramatically worldwide.\textsuperscript{1-5} Currently, 4\%-6\% of children and adolescents in the United States have severe obesity.\textsuperscript{3,6-7}

Hyperlipidemia, hypertension, diabetes mellitus type 2, respiratory and musculoskeletal conditions and liver abnormalities are frequent complications of childhood obesity.\textsuperscript{8-12} Severely obese children and adolescents are also more likely to suffer from psychosocial problems,\textsuperscript{13-15} and report quality of life scores similar to children diagnosed with cancer.\textsuperscript{16-17}

Next to these physical and psychosocial complications, childhood obesity is related to increased healthcare utilization and costs.\textsuperscript{18-21} Furthermore, when severe obesity is present in childhood, there is a high probability that it tracks into adulthood\textsuperscript{22-23} leading to health problems and accompanying healthcare costs also later in life.\textsuperscript{22, 24} Thus, reductions in childhood obesity may lead to short-term economic benefits for children and longer-term benefits for adults.\textsuperscript{18,25}

For severe childhood obesity in particular, effective treatment could reduce the serious immediate and long-term burden on physical and psychosocial health for the obese individuals and society as a whole. However, severely obese children may warrant more intensive treatment than obese children.\textsuperscript{26-27}

Currently in the Netherlands, Heideheuvel is the only specialized childhood obesity center offering treatment for severely obese children and adolescents. Originally, this intensive one-year lifestyle treatment included a six-month inpatient period. However, an inpatient period of six months is expensive and poses a considerable burden on both the participants and their families. Therefore, an adapted treatment was developed with a two-month inpatient period.\textsuperscript{28}

Considering the large economic consequences of severe childhood obesity to society, it is important to evaluate the cost-effectiveness of available treatments in order to
help decision-makers determine which treatment should be reimbursed with the scarce resources available for healthcare. However, studies on the effectiveness of inpatient lifestyle treatments for severely obese children and adolescents are scarce\textsuperscript{29-30} and, to the best of our knowledge, there are no studies on the cost-effectiveness of such treatments. Therefore, the aim of this study was to conduct an economic evaluation from a societal perspective comparing two intensive one-year lifestyle treatments with varying inpatient periods (i.e. two months vs. six months) for severely obese children and adolescents with regard to SDS-BMI and quality-adjusted life-years (QALYs).

**Patients and Methods**

**Study Design and Population**
An economic evaluation from a societal perspective was performed alongside a randomized controlled trial with two treatment groups and a follow-up of 24 months. The Medical Ethics Committee of the VU University Medical Center (Amsterdam, the Netherlands) approved the study protocol. Prior to randomization, written informed consent was obtained from both the participants and their parents/caregivers. The treatment lasted one year after which the participants were followed up for another year. Details of the study have been described elsewhere.\textsuperscript{28}

The study population consisted of 80 participants (8-19 years) with severe obesity. All participants were referred to a specialized childhood obesity center by their local pediatrician after insufficient response to ambulatory obesity treatment. Severe obesity was defined as a SDS-BMI $\geq$ 3.0 (99.9th age- and sex-specific percentile of BMI in the fourth Dutch nationwide growth study of 1997), or a SDS-BMI $\geq$ 2.3 (99th age- and sex-specific percentile of BMI in the fourth Dutch nationwide growth study of 1997) in combination with obesity-related comorbidity.\textsuperscript{28}

**Intervention Conditions**
Both groups received an intensive one-year lifestyle treatment with either an inpatient period of two months (short-stay group) or six months (long-stay group). The treatment focused on nutrition, physical activity and behavior change and required active participation.
of the parents/caregivers. Treatment was delivered at a specialized childhood obesity center, Heideheuvel, in the Netherlands. A more detailed description of the content, frequency and intensity of the treatment can be found elsewhere.\textsuperscript{28}

*Randomization and Masking*

The primary researcher, who was not blinded to treatment allocation, randomized all participants to the short-stay (40 participants) and long-stay group (40 participants) using a table of random numbers.\textsuperscript{31-32}

Because of the nature of the treatment, participants, their parents/caregivers and healthcare professionals could not be blinded to the treatment.

*Effect Measures*

Data were collected at baseline, six, 12 and 24 months and included SDS-BMI and QALYs.

BMI was calculated as weight/height\textsuperscript{2} (kg/m\textsuperscript{2}). The degree of overweight was quantified using Cole's least mean square method, which normalizes the BMI's skewed distribution and expresses BMI as SDS-BMI.\textsuperscript{33} SDS-BMI was calculated with the Growth Analyser\textsuperscript{34} using the fourth Dutch nationwide growth study of 1997 as reference.

QALYs were estimated using the EuroQol (EQ-5D).\textsuperscript{35} The EQ-5D descriptive system consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels of severity (no problems/some or moderate problems/extreme problems). Per dimension, participants were asked to choose the level that best described their current health status. The resulting health state was converted to a utility score using the Dutch EQ-5D valuation tariff.\textsuperscript{36} Utilities represent quality of life in a single number with anchors at 0.0 (death) and 1.0 (full health). QALYs were subsequently calculated by multiplying the utility of a health state by the duration of time spent in a particular health state. Transitions between health states were linearly interpolated.
CHAPTER 5

Costs

Costs were measured from a societal perspective. Not only treatment costs were taken into account, but also the costs of healthcare utilization, transportation and lost productivity of the parents/caregivers. Appendix 1 lists the cost categories and unit prices used in this study. Treatment costs were estimated based on prices paid. Healthcare utilization, transportation, and lost productivity data were collected using cost dairies, which were sent to the parents/caregivers every three months.

Dutch standard costs were used to value healthcare utilization.\textsuperscript{37} Transportation costs were estimated in accordance with the Dutch manual of costing.\textsuperscript{37} Lost productivity consisted of hours taken off from work by parents/caregivers because of the treatment. Average productivity costs per working hour by sex were used to estimate lost productivity costs.\textsuperscript{37} All prices were adjusted to 2010 Euros using Dutch price index figures.\textsuperscript{38} During the second year of the trial, costs and effects were discounted at 4% and 1.5% respectively.\textsuperscript{37}

Statistical Analyses

The sample size was calculated to detect a 0.5 SDS-BMI difference between the two groups after one year of treatment which is considered a clinically meaningful effect size.\textsuperscript{39} Based on a power of 80% and a two-tailed significance level of 5%, two groups of 40 participants were needed.\textsuperscript{28}

Analyses were performed according to the intention-to-treat principle. Baseline characteristics were compared between the two treatment groups and between participants with and without complete follow-up. Independent Student’s t-tests were used for continuous variables and Chi-square tests for categorical variables using IBM SPSS Statistics for Windows, Version 21 (SPSS 21).\textsuperscript{40} Statistical significance was set at P-value < 0.05.

Missing data were imputed using multiple imputation, stratified by treatment group. Sex, household situation, ethnicity and Socio-Economic Status were used as predictors in the imputation model. Using Predictive Mean Matching and Fully Conditional Specification, 15 complete data sets were created in SPSS 21 (Loss of Efficiency ≤ 5%).\textsuperscript{41} Pooled estimates were calculated according to Rubin’s rules.\textsuperscript{42}
Both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) were performed. Effectiveness at 24-month follow-up was analyzed using linear regression, adjusted for baseline values. Ninety-five percent confidence intervals around differences in total and disaggregated costs were estimated using bias corrected and accelerated bootstrapping with 5000 replications. Seemingly unrelated regression (SUR) analyses were performed to estimate cost and effect differences while taking into account the correlation between costs and effects. Subsequently, incremental cost-effectiveness ratios (ICERs) were calculated by dividing the total cost differences by the effect differences. The uncertainty surrounding the ICERs was graphically illustrated by plotting bootstrapped incremental SUR on cost-effectiveness planes (CE-planes). Finally, a summary measure of the joint uncertainty of costs and effects was presented using cost-effectiveness acceptability curves (CEACs). CEACs indicate the probability of an intervention being cost-effective in comparison with usual care at different values of willingness-to-pay (i.e. the maximum amount of money decision-makers are willing to pay per unit of effect gained). These analyses were performed with Stata Statistical Software version 12.

Sensitivity Analyses
Two sensitivity analyses were performed to test the robustness of the results. In the first sensitivity analysis, the analyses were repeated without discounting of costs and effects. In the per protocol analysis, only participants who took part in at least 75% of the treatment sessions were included. A post-hoc analysis was performed stratified for sex.

Results

Participants
In total, 169 participants were referred by their local pediatrician after insufficient response to ambulatory obesity treatment. Of them, 89 were excluded based on either a decision made by the staff of Heideheuvel (N=46) or by the family (N=43). This left 80 participants to be included in the study (Figure 1).
At baseline, no relevant differences were found between the two treatment groups (Table 1). Complete follow-up was obtained from 24 short-stay and 25 long-stay group participants (61%) on the effect measures. Fifty-five percent had complete cost measures in the first half year, 40% in the second half year, 61% in the third half year and 24% in the fourth half
year. There were no statistically significant differences in baseline characteristics between participants with and without complete follow-up.

Table 1. Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Total N=80</th>
<th>Short-stay group N=40</th>
<th>Long-stay group N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean (SD)]</td>
<td>14.8 (2.3)</td>
<td>14.5 (2.4)</td>
<td>15.0 (2.2)</td>
</tr>
<tr>
<td>Female [n (%)]</td>
<td>53 (66.3)</td>
<td>28 (70.0)</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Ethnicities [% of total]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>61.5</td>
<td>69.2</td>
<td>53.8</td>
</tr>
<tr>
<td>Non-Western</td>
<td>38.5</td>
<td>30.8</td>
<td>46.2</td>
</tr>
<tr>
<td>Educational level of the parents/caregivers [% of total]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>38.7</td>
<td>38.5</td>
<td>38.9</td>
</tr>
<tr>
<td>Medium/intermediate</td>
<td>42.7</td>
<td>43.6</td>
<td>41.7</td>
</tr>
<tr>
<td>High</td>
<td>18.7</td>
<td>17.9</td>
<td>19.4</td>
</tr>
<tr>
<td>SES [% of total]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below average</td>
<td>65.8</td>
<td>59.5</td>
<td>71.8</td>
</tr>
<tr>
<td>Above average</td>
<td>34.2</td>
<td>40.5</td>
<td>28.2</td>
</tr>
<tr>
<td>Household situation [% of total]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living together</td>
<td>55.0</td>
<td>62.5</td>
<td>47.5</td>
</tr>
<tr>
<td>Divorced</td>
<td>33.8</td>
<td>32.5</td>
<td>35.0</td>
</tr>
<tr>
<td>One parent family(mother)</td>
<td>7.5</td>
<td>2.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Other situation</td>
<td>3.8</td>
<td>2.5</td>
<td>5.0</td>
</tr>
<tr>
<td>SDS-BMI [mean (SD)]</td>
<td>3.4 (0.39)</td>
<td>3.4 (0.39)</td>
<td>3.4 (0.39)</td>
</tr>
</tbody>
</table>

Abbreviations: EQ-5D – EQ-5D descriptive system; SD – standard deviation; SDS-BMI – standard deviation of body mass index; SES – Socio-economic status.

The short-stay group participated in a two-month intensive inpatient treatment during weekdays, followed by biweekly return visits of two days during the next four months, then followed by six monthly return visits of two days. The long-stay group participated in a six-month intensive inpatient treatment during weekdays, followed by six monthly return visits of two days.

*Educational level was classified according to the definition of Statistics Netherlands (http://www.cbs.nl).

**Effectiveness**

SDS-BMI decreased in the first six months of treatment, stabilized in the second six months and increased during the second year in both groups. The increase in SDS-BMI in the long-stay group was larger than in the short-stay group. After 24 months, SDS-BMI was similar in both groups, but remained lower than baseline values (mean difference 24 months and baseline -0.24, 95% CI -0.42; -0.06).

The mean multiply pooled utility score based on the Dutch tariff for the EQ-5D was 0.77 (S 0.04) in the short-stay group at baseline and 0.88 (SE 0.02) and 0.87 (SE 0.02) after 12 and 24 months, respectively. The pooled utility scores for the long-stay group were 0.80 (SE 0.03),
0.91 (SE 0.01) and 0.90 (SE 0.02) at baseline and after 12 and 24 months respectively. The mean number of QALYs gained after 24 months was 1.68 (SE 0.03) in the short-stay group and 1.75 (SE 0.03) in the long-stay group, however this was not statistically significant (mean difference -0.07, 95% CI -0.16; 0.02) (Table 2).

Table 2. Multiply imputed pooled mean costs and effects per participant in the long-stay group and short-stay group and mean cost and effect differences between both groups during the 24-month follow-up.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Short-stay group</th>
<th>Long-stay group</th>
<th>Mean difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=40</td>
<td>N=40</td>
<td></td>
</tr>
<tr>
<td>Clinical outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>3.20 (0.13)</td>
<td>3.18 (0.13)</td>
<td>0.02 (-0.30; 0.33)</td>
</tr>
<tr>
<td>QALY</td>
<td>1.68 (0.03)</td>
<td>1.75 (0.03)</td>
<td>-0.07 (-0.16; 0.02)</td>
</tr>
<tr>
<td>Cost category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>22,320 (0)</td>
<td>46,609 (0)</td>
<td>-24,289 (0)</td>
</tr>
<tr>
<td>Healthcare</td>
<td>1,018 (203)</td>
<td>425 (111)</td>
<td>593 (219; 1,158)</td>
</tr>
<tr>
<td>Primary healthcare</td>
<td>868 (192)</td>
<td>294 (86)</td>
<td>573 (263; 1,141)</td>
</tr>
<tr>
<td>Secondary healthcare</td>
<td>150 (29)</td>
<td>131 (32)</td>
<td>20 (-72; 96)</td>
</tr>
<tr>
<td>Transportation</td>
<td>1,137 (69)</td>
<td>1,460 (113)</td>
<td>-323 (-639; -97)</td>
</tr>
<tr>
<td>Lost productivity</td>
<td>3,362 (484)</td>
<td>2,982 (585)</td>
<td>380 (-1,229; 1,791)</td>
</tr>
<tr>
<td>Total costs</td>
<td>27,837 (603)</td>
<td>51,476 (695)</td>
<td>-2,3639 (-25,418; -21,896)</td>
</tr>
</tbody>
</table>

Data are mean (SE).
Abbreviations: CI – confidence interval; EQ-5D – EQ-5D descriptive system; QALYs – quality adjusted life years; SDS-BMI – standard deviation of body mass index.
All costs are expressed in 2010 Euros.

Figure 2. SDS-BMI for the short-stay and long-stay group during 24 months of follow-up.
Error Bars indicate SE.
Costs
Mean total costs in the short-stay group were statistically significantly lower than in the long-stay group (mean difference -€23,639). Treatment costs were the greatest contributor to this cost difference. In the short-stay group, healthcare costs were statistically significantly higher and transportation costs statistically significantly lower than in the long-stay group (Table 2).

Economic evaluation
The results of the CEA and CUA are presented in Table 3. For SDS-BMI, the ICER was -1,479,463 Euros per point SDS-BMI indicating that one point higher in SDS-BMI in the short-stay group is associated with savings of €1,479,463 in comparison with the long-stay group. The difference in SDS-BMI between both groups after 24 months was very small leading to this very large ICER that is difficult to interpret. In the CE-plane, 46% and 54% of the incremental cost-effect pairs were located in the South-East (SE) and South-West (SW) quadrants, respectively (Figure 3A), confirming the small difference in effects between the groups and the statistically significant difference in costs. The CEAC for SDS-BMI shows that the probability that the short-stay treatment is cost-effective in comparison with the long-stay treatment is 1 at values of willingness-to-pay between 0 and 50,000 €/point SDS-BMI (Figure 3B). This probability slowly decreased to 0.54 for larger values of willingness-to-pay.

An ICER of 344,744 was found for QALYs at 24 months, meaning that one point decrease in QALY in the short-stay group is associated with savings of €344,744 in comparison with the long-stay group. The CE plane and CEAC for QALYs showed that the short-stay treatment was cost-effective in comparison with the long-stay treatment (data not shown).

Sensitivity Analyses
The overall conclusions did not change in the sensitivity analyses (Table 3). However, a post-hoc analysis revealed different effects for boys and girls. The results for boys were in line with the main analyses, namely a difference in SDS-BMI between the groups in favor of the long-stay group. Although this difference was larger than in the main analysis, it was still not statistically significant. However, in girls the difference in SDS-BMI was in favor of the short-stay group. The ICER indicates that one point decrease in SDS-BMI in the short-stay group
in comparison with the long-stay group is associated with savings of €237,482. For QALYs gained results were similar to the main analyses for both sexes.

Table 3. Differences in pooled and mean costs and effects (95% confidence intervals), incremental cost-effectiveness ratios and the distribution of incremental cost-effect pairs around the quadrants of the cost-effectiveness plane.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Sample size</th>
<th>Outcome</th>
<th>ΔCost [€] (95% CI)</th>
<th>ΔEffect (95% CI)</th>
<th>ICER [€/point]</th>
<th>Distribution CE-plane (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SS</td>
<td>LS</td>
<td></td>
<td></td>
<td>SE1</td>
</tr>
<tr>
<td><strong>Main analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>40 40</td>
<td>-23,639</td>
<td>-25,418; -21,896</td>
<td>0.02 (-0.30; 0.33)</td>
<td>-1,479,463</td>
<td>0.0 45.7 54.3 0.0</td>
</tr>
<tr>
<td>QALYs</td>
<td>40 40</td>
<td>-23,639</td>
<td>-25,418; -21,896</td>
<td>-0.07 (-0.16; 0.02)</td>
<td>344,744</td>
<td>0.0 6.2 93.8 0.0</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>15 12</td>
<td>-22,097</td>
<td>-24,680; -18,439</td>
<td>0.22 (-0.40; 0.83)</td>
<td>-102,644</td>
<td>0.0 24.6 75.4 0.0</td>
</tr>
<tr>
<td>QALYs</td>
<td>15 12</td>
<td>-22,097</td>
<td>-24,680; -18,439</td>
<td>-0.12 (-0.28; 0.04)</td>
<td>188,553</td>
<td>0.0 6.2 93.8 0.0</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>28 25</td>
<td>-24,280</td>
<td>-26,980; -22,336</td>
<td>-0.10 (-0.26; 0.47)</td>
<td>237,482</td>
<td>0.0 71.0 29.0 0.0</td>
</tr>
<tr>
<td>QALYs</td>
<td>28 25</td>
<td>-24,280</td>
<td>-26,980; -22,336</td>
<td>-0.04 (-0.15; 0.07)</td>
<td>664,178</td>
<td>0.0 23.6 76.4 0.0</td>
</tr>
<tr>
<td><strong>Sensitivity analysis I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>40 40</td>
<td>-23,633</td>
<td>-25,415; -21,887</td>
<td>0.02 (-0.31; 0.34)</td>
<td>-1,457,311</td>
<td>0.0 45.7 54.3 0.0</td>
</tr>
<tr>
<td>QALYs</td>
<td>40 40</td>
<td>-23,633</td>
<td>-25,415; -21,887</td>
<td>-0.07 (-0.16; 0.02)</td>
<td>341,946</td>
<td>0.0 6.2 93.8 0.0</td>
</tr>
<tr>
<td><strong>Sensitivity analysis II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>31 30</td>
<td>-23,880</td>
<td>-26,324; -21,694</td>
<td>0.02 (-0.31; 0.34)</td>
<td>-1,311,672</td>
<td>0.0 46.2 53.8 0.0</td>
</tr>
<tr>
<td>QALYs</td>
<td>31 30</td>
<td>-23,880</td>
<td>-26,324; -21,694</td>
<td>-0.08 (-0.17; 0.02)</td>
<td>310,841</td>
<td>0.0 5.9 94.1 0.0</td>
</tr>
</tbody>
</table>

Abbreviations: CE-plane – cost-effectiveness plane; CI – confidence interval; ICER – incremental cost-effectiveness ratio; QALYs – quality adjusted life years; SDS-BMI – standard deviation of body mass index; LS – long-stay group; SS – short-stay group.

Main analysis: analysis with costs discounted for 2010.
Sensitivity analysis I: analysis without costs discounted for 2010.
Sensitivity analysis II: analysis with per protocol participants only (per protocol ≥ 75 percent of treatment followed).
Positive cost differences indicate more costs for the short-stay group. Negative effect differences indicate a beneficial effect in favor of the short-stay group.

1 Refers to the northeast quadrant of the CE-plane, indicating that the SS is more effective and more costly compared with the LS.
2 Refers to the southeast quadrant of the CE-plane, indicating that the SS is more effective and less costly compared with the LS.
3 Refers to the southwest quadrant of the CE-plane, indicating that the SS is less effective and less costly compared with the LS.
4 Refers to the northwest quadrant of the CE-plane, indicating that the SS is less effective and more costly compared with the LS.
exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production.

Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D\(_2\) (ergocalciferol) and vitamin D\(_3\) (cholecalciferol). Vitamin D\(_2\) is the plant and yeast-derived form of vitamin D. Vitamin D\(_3\) – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources.

In humans, both vitamin D\(_2\) and vitamin D\(_3\) are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)\(_2\)D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)\(_2\)D (Figure 1).

This process mainly occurs in the kidney and 1,25(OH)\(_2\)D is circulated throughout the body.

Figure 1: Synthesis of the active vitamin D metabolite - 1,25(OH)\(_2\)D

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Figure 3A. Cost-effectiveness plane for the difference in SDS-BMI at 24-months (societal perspective).

Figure 3B. Cost-effectiveness acceptability curve for the difference in SDS-BMI at 24-months (societal perspective).
Discussion

The present study aimed to conduct an economic evaluation comparing two intensive one-year treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and QALYs, with an additional year of follow-up. In both groups, SDS-BMI decreased in the first six months of treatment, tended to stabilize in the second six months followed by an increase during the second year of follow-up. After 24 months, SDS-BMI was similar in both groups, but remained lower than baseline values. Societal costs were statistically significantly lower for the short-stay group in comparison with the long-stay group with treatment costs being the main contributor. The higher healthcare costs among participants in the short stay group can be explained by the fact that they were more dependent on healthcare outside the center as their inpatient period was shorter. Parents/caregivers in the long stay group had higher travelling costs as they had to travel to the center more frequently during the first half year of treatment. Contrary to our expectations, lost productivity costs were highest in the short-stay group. CE-planes and CEACs showed that the short-stay treatment was cost-effective in comparison with the long-stay treatment for values of willingness to pay ranging from 0 to 83,000 and 163,000 for SDS-BMI and QALYs respectively.

Only few studies evaluated the effectiveness of obesity treatments in severely obese children and adolescents. Most studies showed weight-loss during the intensive treatment period, but weight-gain during follow-up. Two studies evaluated treatments including an inpatient period, similar to our study. They reported substantial weight-loss directly after treatment, however long-term results were not presented. Our study confirms the effectiveness of inpatient treatment on SDS-BMI for severely obese children and adolescents during treatment, but this was not maintained during one year of follow-up after treatment. Kelly et al stated that the ultimate goal of lifestyle interventions should be to improve the quality of life in children and adolescents with severe obesity. In our study, utility scores increased with 0.11 points on a scale of 0.0-1.0 in both groups during the one-year treatment. Remarkably, this improvement in quality of life was maintained during the additional year of follow-up with no statistically significant between the groups, despite an increase in SDS-BMI during that year.
Strengths and Limitations
This study has several strengths. First, to our knowledge, this study was the first to evaluate the (cost-) effectiveness of inpatient treatments for severely obese children and adolescents. Secondly, this study was designed as a randomized controlled trial, reducing the risk of bias. Moreover, costs and effects were collected prospectively under ‘real life’ conditions. Thirdly, the CEA was conducted from a societal perspective, which meant that not only treatment costs were taken into account, but also the costs of healthcare utilization, transportation and lost productivity of the parents/caregivers, although these were relatively low. Fourthly, the total follow-up of 24 months was relatively long in comparison with other studies carried out among severe obese youth.

There are also some limitations to our study. Firstly the high rate of missing data; only 24% had complete cost data available in the last half year of follow-up. Multiple imputation was used to deal with missing data, to avoid the inefficiency associated with complete-case analyses and to prevent bias through selective drop-out. Secondly, since the power calculation was based on detecting a difference of 0.5 SDS-BMI, the study was underpowered to detect relevant cost differences, which was reflected in wide confidence intervals around the cost differences. Finally, no usual care group was included in the CEA after 24 months since a waiting-list group receiving usual care for only one year where after they were allocated to one of the treatment groups was available.

Implications
For severely obese children and adolescents with insufficient response to ambulatory obesity treatment, inpatient treatment may be a promising alternative. However, definitive conclusions regarding the cost-effectiveness of the short-stay treatment should be postponed until information is available about the cost-effectiveness in comparison with usual care. In our study the weight-loss was promising during the intensive treatment although it was not maintained during one year of follow-up after treatment. Investments in intensive treatments will only be justified if weight-loss is sustained over a longer period after treatment. Moreover, maintenance of weight-loss is necessary to prevent the long-term health and economic burden of childhood obesity. Therefore, continuous treatment, monitoring, and periodic intensive return visits after intensive treatment seem essential to
ensure long-term maintenance of weight-loss. In our study, continuation of the monthly
return visits of two days for one year after treatment has ended, will lead to additional costs
of €7878 per participant. Future studies should evaluate whether costs of such intensive
follow-up weigh up against the effects. On the other hand, inpatient treatment is costly and
poses a high burden on the families participating, so preferably this continuous treatment
is organized in the home environment making it more feasible and less expensive making it
more feasible and less expensive than intensive treatment in specialized childhood obesity
centers.

**Conclusion**

In conclusion, inpatient treatment may be a promising alternative for severely obese
children and adolescents with insufficient response to ambulatory obesity treatment. After
24 months there were no differences in SDS-BMI and QALYs gained between the groups.
Costs were statistically significantly lower for the short-stay treatment in comparison with
the long-stay treatment. Based on these results, the short-stay treatment can be regarded
as cost-effective from the societal perspective in comparison with the long-stay treatment.
exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production.

Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Vitamin D₂ is the plant and yeast-derived form of vitamin D. Vitamin D₃ – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources.

In humans, both vitamin D₂ and vitamin D₃ are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)₂D (Figure 1).

This process mainly occurs in the kidney and 1,25(OH)₂D is circulated throughout the body.

Appendix 1. Price weight used for the valuation of resources consumed during treatment and follow-up

<table>
<thead>
<tr>
<th>Units [Units of measurement]</th>
<th>Unit cost [€, 2010]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct healthcare costs</strong></td>
<td></td>
</tr>
<tr>
<td>Primary care</td>
<td></td>
</tr>
<tr>
<td>General Practitioner [per visit]</td>
<td>28.35</td>
</tr>
<tr>
<td>Dietitian [per visit]</td>
<td>27.33</td>
</tr>
<tr>
<td>Mental healthcare</td>
<td></td>
</tr>
<tr>
<td>Social worker [per visit]</td>
<td>65.80</td>
</tr>
<tr>
<td>Psychologist [per visit]</td>
<td>80.99</td>
</tr>
<tr>
<td>Physical therapy</td>
<td></td>
</tr>
<tr>
<td>Physiotherapy [per visit]</td>
<td>36.44</td>
</tr>
<tr>
<td>Cesar therapy [per visit]</td>
<td>35.43</td>
</tr>
<tr>
<td>Haptonomy [per visit]</td>
<td>36.44</td>
</tr>
<tr>
<td>Manuel therapist [per visit]</td>
<td>35.43</td>
</tr>
<tr>
<td>Orthopedist [per visit]</td>
<td>72.89</td>
</tr>
<tr>
<td>Secondary care</td>
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</tr>
<tr>
<td>Outpatient clinic [per visit]</td>
<td>72.89</td>
</tr>
<tr>
<td><strong>Direct non-healthcare costs</strong></td>
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</tr>
<tr>
<td>Transport [km]</td>
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<tr>
<td>Car</td>
<td>0.20</td>
</tr>
<tr>
<td>Public transport</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Indirect non-healthcare costs</strong></td>
<td></td>
</tr>
<tr>
<td>Absenteeism paid labor [per hour]</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>32.89</td>
</tr>
<tr>
<td>Mother</td>
<td>26.26</td>
</tr>
</tbody>
</table>
CHAPTER 5

References


34. *Growth Analyser* [computer program]: Stichting Kind en Groei; 2010.


In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D. This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body.

Vitamin D production.

In some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant and yeast-derived form of vitamin D. Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources. Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant and yeast-derived form of vitamin D. Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources.
exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production.

Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D\textsubscript{2} (ergocalciferol) and vitamin D\textsubscript{3} (cholecalciferol). Vitamin D\textsubscript{2} is the plant and yeast-derived form of vitamin D. Vitamin D\textsubscript{3} – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources.

In humans, both vitamin D\textsubscript{2} and vitamin D\textsubscript{3} are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)\textsubscript{2}D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)\textsubscript{2}D (Figure 1).

This process mainly occurs in the kidney and 1,25(OH)\textsubscript{2}D is circulated throughout the body.

Figure 1: Synthesis of the active vitamin D metabolite - 1,25(OH)\textsubscript{2}D
HEALTH-RELATED QUALITY OF LIFE IN SEVERELY OBESE CHILDREN AND ADOLESCENTS AFTER INTENSIVE LIFESTYLE TREATMENT

Meeke Hoedjes
Sabine Makkes
Jutka Halberstadt
Hanneke Noordam
Carry Renders
Olga van der Baan-Slootweg
Jaap Seidell

Submitted
Abstract

Importance
Intensive lifestyle treatment in severely obese children and adolescents is expected to improve generic and weight-related health-related quality of life (HRQoL) through weight-loss. Assessment of long-term changes in HRQoL in severely obese children and adolescents participating in intensive lifestyle treatments may provide valuable information on the effectiveness of such treatments.

Objective
To examine changes in generic and weight-related HRQoL in severely obese children and adolescents directly after intensive lifestyle treatment and at follow-up one year later, and to examine whether changes in SDS-BMI are associated with changes in generic and weight-related HRQoL.

Design
Prospective observational study (HELIOS) with a one-year follow-up after a one-year intensive lifestyle treatment.

Setting
Specialized childhood obesity center in the Netherlands.

Participants
Referred sample of 120 children and adolescents (8-19 years) with severe obesity defined as a SDS-BMI ≥ 3.0 or a SDS-BMI ≥ 2.3 in combination with obesity-related comorbidity. Dropout rate was 17.5%.

Intervention
All participants received an intensive one-year lifestyle treatment that focused on nutrition, physical activity and behavior change with varying inpatient periods, i.e. two months or six months.

Main Outcome Measure(s)
Generic (KIDSCREEN-52, PedsQL 4.0 and EuroQol) and weight-related (IWQOL-Kids) HRQoL at baseline, after treatment (12 months) and at follow-up (24 months).

Results
Improvements in generic and weight-related HRQoL overall and domain scores were observed after treatment (PedsQL overall $b=9.94$, 95% CI: 6.66-13.2; IWQOL-Kids overall...
exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production. Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Vitamin D₂ is the plant and yeast-derived form of vitamin D. Vitamin D₃ – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources. In humans, both vitamin D₂ and vitamin D₃ are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)₂D (Figure 1). This process mainly occurs in the kidney and 1,25(OH)₂D is circulated throughout the body.

**Figure 1:** Synthesis of the active vitamin D metabolite - 1,25(OH)₂D

Conclusions and Relevance
Severely obese children and adolescents experienced statistically significant long-term improvements in generic and weight-related HRQoL after participating in an intensive one-year lifestyle treatment in comparison with baseline, even when participants partially regained their weight. This study shows that it is important to evaluate the effects of intensive lifestyle treatment on generic and weight-related HRQoL in severely obese children and adolescents.
Introduction

Childhood obesity is associated with somatic health problems and with negative self-evaluation, bullying, social stigma, symptoms of depression and anxiety, resulting in a negative impact on physical and psychosocial health in children and adolescents.\textsuperscript{1-9} Therefore, severely obese children and adolescents frequently report an impaired health-related quality of life (HRQoL), with HRQoL-scores similar to individuals diagnosed with cancer.\textsuperscript{10} Intensive lifestyle treatment is expected to improve HRQoL through weight-loss. However, only a few studies have reported on the long-term effects of intensive lifestyle treatment on HRQoL in children and adolescents. These studies indicate that intensive lifestyle treatment may result in improvements in overall HRQoL and in the physical, mental and social-wellbeing domains.\textsuperscript{11-13} In addition, previous research suggests that weight-related HRQoL may be more responsive to weight-loss after intensive lifestyle treatment than generic HRQoL.\textsuperscript{11,14} Therefore, it has been recommended to evaluate both generic and weight-related HRQoL in studies among obese children and adolescents.\textsuperscript{11,15,16}

There is a lack of studies examining the long-term effects of intensive lifestyle treatments on HRQoL,\textsuperscript{11} especially in severely obese children and adolescents. Moreover, little is known about the effects of intensive lifestyle treatment on the different domains of HRQoL.\textsuperscript{13} Such knowledge can provide valuable information on the effectiveness of these treatments for severely obese children and adolescents.\textsuperscript{17}

The main objective of this study was to examine changes in generic and weight-related HRQoL in severely obese children and adolescents participating in an intensive one-year lifestyle treatment with an inpatient period, directly after treatment and at follow-up one year later. A secondary objective was to examine whether changes in SDS-BMI were associated with changes in generic and weight-related HRQoL.
Methods

Study Design and Population
This study was a prospective observational study of children and adolescents receiving an intensive one-year lifestyle treatment with an inpatient period that focused on nutrition, physical activity and behavior change.\textsuperscript{18} Measurements were conducted at baseline, after treatment (12 months), and at follow-up (24 months).

The study population consisted of 120 participants (8-19 years) with severe obesity. Participants were referred by their local pediatrician after insufficient response to ambulatory obesity treatment. Severe obesity was defined as a SDS-BMI $\geq$ 3.0 (99.9th age- and sex-specific percentile of BMI in the fourth Dutch nationwide growth study of 1997), or a SDS-BMI $\geq$ 2.3 (99th age- and sex-specific percentile of BMI in the fourth Dutch nationwide growth study of 1997) in combination with obesity-related comorbidity.\textsuperscript{18}

Intervention Conditions
Participants received an intensive one-year lifestyle treatment with either an inpatient period of two months (short-stay group, 80 participants) or six months (long-stay group, 40 participants). The short-stay group participated in a two-month inpatient treatment during weekdays with homework assignments in weekends, followed by biweekly return visits of two days during the next four months, then followed by six monthly return visits of two days. The long-stay group participated in a six-month inpatient treatment during weekdays with homework assignments in weekends, followed by six monthly return visits of two days. The treatment focused on nutrition, physical activity and behavior change and required active participation of the parents/caregivers. Treatment was delivered at a specialized childhood obesity center in the Netherlands. A more detailed description of the content, frequency, intensity, and duration of the treatment can be found elsewhere.\textsuperscript{18,19}
CHAPTER 6

Measurements

HRQoL questionnaires
Child self-report questionnaires were used to assess HRQoL. To determine generic HRQoL and all of its domains, the KIDSCREEN-52, Pediatric Quality of Life Inventory (PedsQL 4.0) and EuroQol (EQ-5D and EQ-VAS) were used. To determine weight-related HRQoL, the Impact of Weight on Quality of Life-Kids (IWQOL-Kids) was used.

The KIDSCREEN-52\textsuperscript{20,21} contains 52 items divided among 10 domains: 1) Physical well-being; 2) Psychological well-being; 3) Moods and emotions; 4) Self-perception; 5) Autonomy; 6) Relations with parents and home life; 7) Social support and peers; 8) School environment; 9) Social acceptance (bullying); and 10) Financial resources. Each item is rated using a 5-point-Likert-type scale assessing either the frequency (never, seldom, quite often, very often, always) or the intensity (not at all, slightly, moderately, very, extremely) of certain behaviors, feelings, or attitudes, based on a recall period of one week. According to the KIDSCREEN-52 handbook, summary-scores were calculated and Rasch Person Parameters (PP) were assigned to each possible summary-score. The PPs were transformed into T-values with a mean of 50 and a standard deviation (SD) of approximately 10. Higher scores indicate better HRQoL. Since the KIDSCREEN-52 does not provide a one-dimensional overall measure of generic HRQoL, KIDSCREEN-10 index-scores were additionally derived from the KIDSCREEN-52.\textsuperscript{22} Similar to scoring of the KIDSCREEN-52, KIDSCREEN-10 scores were also transformed into T-values.

The PedsQL 4.0\textsuperscript{23} contains 23 items and consists of four domains: 1) Physical Functioning; 2) Emotional Functioning; 3) Social Functioning; 4) School Functioning. The PedsQL 4.0 assesses how much of a problem each item has been during the past month with a 5-point Likert-type scale varying from 0 (never a problem) to 4 (almost always a problem). Scores are transformed on a scale from 0 to 100. Three summary-scores can be calculated, with higher scores indicating a better HRQoL: a Total Scale-Score (23 items), a Physical Health Summary-Score (8 items), and a Psychosocial Health Summary-Score (15 items).
The EuroQol consists of two components; the EQ-5D descriptive system (EQ-5D) and the EQ visual analogue scale (EQ-VAS). The EQ-5D consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels of severity (no problems/some or moderate problems/extreme problems).\textsuperscript{24} Per dimension, participants were asked to choose the level that best described their current health status. The resulting health state was converted to a utility score using the Dutch EQ-5D valuation tariff.\textsuperscript{25} Utilities represent HRQoL in a single number with anchors at 0.0 (death) and 1.0 (full health). In the EQ-VAS, a standard vertical 20 cm visual analogue scale is used to measure an individual’s direct valuation of their current HRQoL on a scale of 0 (worst imaginable health state) to 100 (best imaginable health state).\textsuperscript{24}

The IWQOL-Kids\textsuperscript{15,26} contains 27 items on four domains: 1) Physical comfort; 2) Body esteem; 3) Social life; and 4) Family relations. Each item begins with the phrase “Because of my weight” and contains five response options, ranging from “always” (1) to “never” (5). The recall period is one week. IWQOL-Kids scores range from 0 to 100, with higher scores indicating a better HRQoL.

**Covariates**

Demographic characteristics were assessed at baseline and included the following.

Ethnicity of participants was classified into two categories; Western and Non-Western. Western ethnicity included native Dutch as well as Western immigrants. Non-Western ethnicity included all Non-Western immigrant categories. When both parents were born abroad but in different countries, the country in which the mother was born was used to classify the participant.\textsuperscript{27}

Highest educational level attained by one of the parents/caregivers was divided into low (lower vocational training, lower general secondary education and primary school and special primary education or less), medium/intermediate (intermediate vocational training, higher general secondary training and pre-university education) or high (completed higher vocational training and university).\textsuperscript{28,29}
To determine socio-economic status (SES) of the participants, we used status scores of the parents using data from The Netherlands Institute for Social Research. A status score is a measure for the social status of a postal code area and consists of three elements: income, level of education and level of unemployment. A status score below 0 means a SES above average and a status score above 0 means a SES below average (0 meaning average). For the statistical analyses, SES was dichotomized into ‘above average’ and ‘below average’.

Household situation was categorized as ‘married/living together’, ‘divorced’, ‘one parent family’, and ‘other situation’. For the statistical analyses, household situation was dichotomized into ‘parents living together’ (‘married/living together’) and ‘parents not living together’ (‘divorced’, ‘one parent family’, and ‘other situation’).

BMI was calculated as weight/height² (kg/m²). SDS-BMIs were calculated with the Growth Analyser using the fourth Dutch nationwide growth study of 1997 as reference.

Statistical Analyses
Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.

Mean and frequency tables were used to describe baseline characteristics. Differences between completers of treatment and dropouts of treatment were tested using Independent Student’s t-tests for continuous variables and Chi-square tests for categorical variables.

Generalized Linear Mixed Models (GLMM) were used to analyze changes in HRQoL-scores over time using the HRQoL-scores as dependent variables and time (baseline, directly after treatment and at follow-up one year later) as independent categorical variable. All models were adjusted for the following covariates: age, sex, ethnicity, educational level of the parents/caregivers, SES, household situation, and duration of inpatient treatment.

Partial correlations were used to examine associations between changes in SDS-BMI and changes in HRQoL. First, for SDS-BMI and for all overall HRQoL- and domain-scores, deltas were calculated from baseline to directly after treatment, from baseline to follow-up, and from directly after treatment to follow-up. For each combination of deltas, a Pearson product-
moment correlation coefficient was calculated. Pearson product-moment correlation coefficients were adjusted for the following covariates: age, sex, ethnicity, educational level of the parents/caregivers, SES, household situation, and duration of inpatient treatment.

Sensitivity analyses
Participants with complete data on the overall scores of the four HRQoL questionnaires (at baseline, directly after treatment and at follow-up one year later) were considered to have complete follow-up. If participants missed one or more overall scores of the four HRQoL questionnaires, participants were considered to have incomplete follow-up. In the sensitivity analysis, only participants with complete follow-up were included.

Results

Table 1 shows the baseline characteristics of the study population. Of the 120 participants, 99 (82.5%) completed the intensive one-year lifestyle treatment. Completers of treatment did not differ from dropouts of treatment (N = 21) in any of the variables shown in Table 1.

A significant reduction in mean SDS-BMI as compared with baseline was seen after the intensive one-year lifestyle treatment, followed by partial regain of the lost weight at follow-up one year later (Figure 1).

![Figure 1. SDS-BMI from baseline to directly after treatment and at follow-up one year later. Error Bars indicate SE.](image)
Table 1. Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Total N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean (SD)]</td>
<td>14.8 (2.4)</td>
</tr>
<tr>
<td>Female [n (%)]</td>
<td>81 (67.5)</td>
</tr>
<tr>
<td>Ethnicities [% of total]</td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>76 (63.3)</td>
</tr>
<tr>
<td>Non-Western</td>
<td>41 (34.2)</td>
</tr>
<tr>
<td>Educational level of the parents/caregivers [% of total]</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>44 (36.7)</td>
</tr>
<tr>
<td>Medium/intermediate</td>
<td>47 (39.2)</td>
</tr>
<tr>
<td>High</td>
<td>23 (19.2)</td>
</tr>
<tr>
<td>SES [% of total]</td>
<td></td>
</tr>
<tr>
<td>Below average</td>
<td>73 (60.8)</td>
</tr>
<tr>
<td>Above average</td>
<td>41 (34.2)</td>
</tr>
<tr>
<td>Household situation [% of total]</td>
<td></td>
</tr>
<tr>
<td>Married/living together</td>
<td>62 (51.7)</td>
</tr>
<tr>
<td>Divorced</td>
<td>38 (31.7)</td>
</tr>
<tr>
<td>One parent family (mother)</td>
<td>14 (11.7)</td>
</tr>
<tr>
<td>Other situation</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Duration of inpatient treatment program [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Two months</td>
<td>80 (66.7)</td>
</tr>
<tr>
<td>Six months</td>
<td>40 (33.3)</td>
</tr>
<tr>
<td>SDS-BMI [mean (SD)]</td>
<td>3.4 (0.4)</td>
</tr>
</tbody>
</table>

Abbreviations: SD = Standard Deviation; SDS-BMI = Standard Deviation Score of Body Mass Index; SES = Socio-Economic Status.

Changes in generic and weight-related HRQoL

Table 2 shows mean HRQoL-scores at baseline, directly after the intensive one-year lifestyle treatment (12 months) and at follow-up one year later (24 months). In addition, it shows changes in mean HRQoL-scores from baseline to directly after treatment, from baseline to follow-up, and from directly after treatment to follow-up.

Mean overall generic HRQoL-scores on the PedsQL 4.0 improved after treatment ($B=9.94$, 95% CI: 6.66; 13.2) and at follow-up ($B=10.0$, 95% CI: 6.82; 13.2) in comparison with baseline. Mean overall generic PedsQL-scores did not change significantly during the year after treatment ($B=0.08$, 95% CI: -3.00; 3.16). The PedsQL 4.0 showed statistically significant improvements in all domains of generic HRQoL, both after treatment and at follow-up, with the largest improvements in the ‘social functioning’ domain.
Scores in the domains ‘physical wellbeing’, ‘self-perception’ and ‘social acceptance and bullying’ of the KIDSCREEN-52 improved statistically significantly at 12 and 24 months of follow-up as compared with baseline (Table 2).

Mean overall weight-related HRQoL-scores on the IWQoL-Kids improved after treatment ($B=11.2$, 95% CI: 7.37; 15.1) and at follow-up ($B=8.92$, 95% CI: 4.63; 13.2) in comparison with baseline. Mean overall weight-related HRQoL-scores did not change significantly during the year after treatment ($B=-2.32$, 95% CI: -6.19; 1.56). Weight-related HRQoL significantly improved in all domains, except for ‘family relations’. The largest improvement was observed in the ‘body esteem’ domain (Table 2).

Mean EQ-5D scores significantly improved after treatment ($B=0.09$, 95% CI: 0.05; 0.13) and at follow-up ($B=0.08$, 95% CI: 0.03; 0.13) in comparison with baseline. Mean EQ-5D scores did not change significantly during the year after treatment ($B=-0.09$, 95% CI: 0.03; 0.13) in comparison with baseline. Mean EQ-VAS scores did not change significantly during the year after treatment ($B=-4.70$, 95% CI: -9.11; -0.29).

Mean EQ-VAS score did not change from baseline to follow-up.
Table 2. Changes in HRQoL-scores from baseline to directly after treatment (12 months) and at follow-up (24 months).

<table>
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<tr>
<th>Generic HRQoL</th>
<th>HRQoL-score</th>
<th>Effects</th>
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<tbody>
<tr>
<td></td>
<td>% of total¹</td>
<td>Mean (SE) Mean (SE) Adjusted² Beta (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months 24 months</td>
</tr>
<tr>
<td></td>
<td>12 months vs. baseline</td>
<td>24 months vs. 12 months</td>
</tr>
<tr>
<td></td>
<td>24 months vs. baseline</td>
<td>Adjusted² Beta (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Adjusted² Beta (95% CI)</td>
<td>Adjusted² Beta (95% CI)</td>
</tr>
<tr>
<td>KIDSSCREEN-10</td>
<td>Physical wellbeing</td>
<td>69.7 48.4(1.0) 47.8(1.0) 49.8(1.3) -0.60(-2.56; 1.36) 2.05 (-0.10; 4.19) 1.45(-0.75; 3.64)</td>
</tr>
<tr>
<td>KIDSSCREEN-52</td>
<td>Psychological wellbeing</td>
<td>72.5 41.1(0.8) 44.3(0.8) 45.3(1.2) 3.23(1.46; 5.00) 0.93(-1.06; 2.92) 4.16(192; 6.39)</td>
</tr>
<tr>
<td></td>
<td>Moods and emotions</td>
<td>72.2 48.0(1.0) 49.3(1.2) 50.3(1.4) 1.29(-0.90; 3.48) 0.98(-1.50; 3.45) 2.27(-0.22; 4.77)</td>
</tr>
<tr>
<td></td>
<td>Self-perception</td>
<td>72.5 40.0(0.9) 43.2(0.8) 42.5(1.2) 3.26(1.69; 4.83) -0.76(-2.57; 1.05) 2.50(0.70; 4.31)</td>
</tr>
<tr>
<td></td>
<td>Autonomy</td>
<td>72.5 51.4(0.9) 49.5(1.1) 51.4(1.2) -1.93(-4.06; 0.20) 1.97(-0.14; 4.07) 0.04(-2.23; 2.31)</td>
</tr>
<tr>
<td></td>
<td>Parent relation and home life</td>
<td>72.2 51.1(1.3) 48.8(1.4) 50.0(1.5) -2.30(-4.57; -0.03) 1.16(-1.29; 3.61) -1.14(-3.54; 1.27)</td>
</tr>
<tr>
<td></td>
<td>Financial resources</td>
<td>71.4 51.6(1.2) 50.1(1.4) 50.9(1.4) -1.55(-3.99; 0.89) 0.85(-1.45; 3.15) -0.71(-3.58; 2.16)</td>
</tr>
<tr>
<td></td>
<td>Social support &amp; peers</td>
<td>72.5 51.2(1.0) 50.2(1.3) 52.6(1.5) -0.94(-3.49; 1.62) 2.31(-0.17; 4.80) 1.38(-1.30; 4.05)</td>
</tr>
<tr>
<td></td>
<td>School environment</td>
<td>69.4 51.8(1.1) 50.0(1.5) 51.0(1.2) -1.76(-4.67; 1.15) 0.99(-1.58; 3.57) 0.77(-3.13; 1.59)</td>
</tr>
<tr>
<td></td>
<td>Social acceptance and bullying</td>
<td>70.0 40.9(1.4) 47.5(1.4) 47.0(1.5) 6.66(3.96; 9.36) -0.49(-2.92; 1.95) 6.17(3.23; 9.11)</td>
</tr>
<tr>
<td>PedsQL 4.0</td>
<td>Overall</td>
<td>71.9 67.8(1.8) 77.8(1.6) 77.8(1.7) 9.94(6.66; 13.2) 0.08(-3.00; 3.16) 10.0(6.82; 13.2)</td>
</tr>
<tr>
<td></td>
<td>Psychosocial health summary</td>
<td>71.9 66.8(2.0) 75.6(1.9) 76.9(2.0) 8.79(5.04; 12.5) 1.30(-1.83; 4.42) 10.1(6.49; 13.7)</td>
</tr>
<tr>
<td></td>
<td>Physical health summary</td>
<td>72.2 70.0(1.8) 81.9(1.7) 79.5(2.2) 11.9(4.39; 15.2) -2.34(-6.73; 2.06) 9.53(5.10; 13.9)</td>
</tr>
<tr>
<td></td>
<td>Physical functioning</td>
<td>72.2 70.0(1.8) 81.9(1.7) 79.5(2.2) 11.9(4.39; 15.2) -2.34(-6.73; 2.06) 9.53(5.10; 13.9)</td>
</tr>
<tr>
<td></td>
<td>Emotional functioning</td>
<td>72.2 65.8(2.6) 73.4(2.7) 75.2(2.6) 7.59(6.29; 12.5) 1.78(-2.91; 6.48) 9.37(4.74; 14.0)</td>
</tr>
<tr>
<td></td>
<td>Social functioning</td>
<td>72.2 70.2(2.4) 82.3(2.0) 82.0(2.2) 12.1(10.10; 16.2) -0.28(-3.63; 3.07) 11.9(7.83; 15.9)</td>
</tr>
<tr>
<td></td>
<td>School functioning</td>
<td>71.4 64.6(2.1) 70.9(2.3) 73.0(2.5) 6.32(1.49; 11.1) 2.13(-2.15; 6.40) 8.44(3.81; 13.1)</td>
</tr>
<tr>
<td>EuroQol</td>
<td>EQ-5D</td>
<td>71.9 0.80(0.02) 0.89(0.02) 0.88(0.02) 0.09(0.05; 0.13) -0.01(-0.06; 0.04) 0.08(0.03; 0.13)</td>
</tr>
<tr>
<td></td>
<td>EQ-VAS</td>
<td>71.9 69.0(2.0) 75.4(1.6) 70.7(2.3) 6.40(3.35; 10.5) -4.70(-9.11; -0.29) 1.70(-2.67; 6.07)</td>
</tr>
</tbody>
</table>
### Table 2. Changes in HRQoL-scores from baseline to directly after treatment (12 months) and at follow-up (24 months) (continued).  

<table>
<thead>
<tr>
<th>Weight-Related HRQoL</th>
<th>HRQoL-score</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td><strong>IWQOL-Kids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>65.8</td>
<td>70.8(2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical comfort</td>
<td>70.6</td>
<td>70.4(2.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body esteem</td>
<td>70.8</td>
<td>53.2(2.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social life</td>
<td>68.9</td>
<td>74.5(2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family relations</td>
<td>68.8</td>
<td>90.8(1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = Confidence Interval; HRQoL = Health-Related Quality of Life; SE = Standard Error; CI = Confidence Interval. Statistically significant values (P value < 0.05) are printed bold.

\(^1\) Total refers to 360 cases in the dataset (120 participants x 3 time points).

\(^2\) Generalized Linear Mixed Model with HRQoL-score as dependent variable and time as independent variable, adjusted for age, gender, ethnicity (Western, Non-Western), educational level of the parents/caregivers (low, medium/intermediate, high), SES (below average, above average), household situation (parents living together/parents not living together), and duration of inpatient treatment (two months or six months).
Correlation between changes in SDS-BMI and HRQoL

Table 3 shows that larger weight-loss at follow-up was correlated with larger improvements in physical HRQoL domains of all questionnaires. A larger decrease in SDS-BMI from baseline to follow-up was correlated with a larger improvement in the ‘physical wellbeing’ domain of the KIDSCREEN-52 ($R_{adjusted} = -0.279; p<0.05$), the ‘physical functioning’ domain of the PedsQL 4.0 ($R_{adjusted} = -0.304; p<0.05$), and the ‘physical comfort’ domain of the IWQOL-Kids ($R_{adjusted} = -0.380; p<0.01$). From directly after treatment to follow-up, a larger increase in SDS-BMI was correlated with a larger decrease in the ‘physical functioning’ domain of the PedsQL 4.0 ($R_{adjusted} = -0.273; p<0.05$) and the ‘physical comfort’ domain of the IWQOL-Kids ($R_{adjusted} = -0.329; p<0.05$). Changes in generic and weight-related HRQoL from baseline to directly after treatment were not correlated with changes in SDS-BMI.

Sensitivity analysis

Analyses restricted to those who had complete follow-up (N = 53) showed slightly lower HRQoL-scores at baseline and somewhat larger improvements, but conclusions remained essentially the same.

Similar results in the magnitude and directions of the correlations were found, although the level of significance sometimes changed because of the smaller statistical power.
Table 3. Partial correlations between change in SDS-BMI and changes in HRQoL-score over time.

<table>
<thead>
<tr>
<th>Changes over time</th>
<th>12 months</th>
<th>24 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>12 months</td>
<td>baseline</td>
</tr>
<tr>
<td>Generic HRQoL</td>
<td>R adjusted(^1)</td>
<td>R adjusted(^1)</td>
<td>R adjusted(^1)</td>
</tr>
<tr>
<td>KIDSCREEN-10</td>
<td>-0.025</td>
<td>-0.122</td>
<td>-0.279*</td>
</tr>
<tr>
<td>KIDSCREEN-52</td>
<td>-0.213</td>
<td>-0.188</td>
<td>-0.331**</td>
</tr>
<tr>
<td></td>
<td>-0.096</td>
<td>-0.122</td>
<td>-0.056</td>
</tr>
<tr>
<td></td>
<td>0.091</td>
<td>-0.051</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td>-0.010</td>
<td>-0.013</td>
<td>0.138</td>
</tr>
<tr>
<td></td>
<td>-0.176</td>
<td>0.017</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>0.066</td>
<td>-0.281*</td>
<td>-0.087</td>
</tr>
<tr>
<td></td>
<td>0.040</td>
<td>-0.183</td>
<td>-0.168</td>
</tr>
<tr>
<td></td>
<td>-0.188</td>
<td>-0.079</td>
<td>0.252</td>
</tr>
<tr>
<td></td>
<td>0.017</td>
<td>0.079</td>
<td>0.211</td>
</tr>
<tr>
<td></td>
<td>0.073</td>
<td>0.138</td>
<td>0.211</td>
</tr>
<tr>
<td>PedsQL 4.0</td>
<td>R adjusted(^1)</td>
<td>R adjusted(^1)</td>
<td>R adjusted(^1)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>-0.036</td>
<td>-0.133</td>
</tr>
<tr>
<td></td>
<td>Psychosocial health summary</td>
<td>-0.024</td>
<td>-0.005</td>
</tr>
<tr>
<td></td>
<td>Physical health summary</td>
<td>-0.053</td>
<td>-0.304*</td>
</tr>
<tr>
<td></td>
<td>Physical functioning</td>
<td>-0.053</td>
<td>-0.304*</td>
</tr>
<tr>
<td></td>
<td>Emotional functioning</td>
<td>-0.018</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>Social functioning</td>
<td>-0.078</td>
<td>-0.137</td>
</tr>
<tr>
<td></td>
<td>School functioning</td>
<td>0.030</td>
<td>0.012</td>
</tr>
<tr>
<td>EuroQol</td>
<td>EQ-SD</td>
<td>0.063</td>
<td>-0.345**</td>
</tr>
<tr>
<td></td>
<td>EQ-VAS</td>
<td>-0.138</td>
<td>-0.316*</td>
</tr>
<tr>
<td>Weight-Related HRQoL</td>
<td>R adjusted(^1)</td>
<td>R adjusted(^1)</td>
<td>R adjusted(^1)</td>
</tr>
<tr>
<td>IWQOL-Kids</td>
<td>Overall</td>
<td>-0.077</td>
<td>-0.185</td>
</tr>
<tr>
<td></td>
<td>Physical comfort</td>
<td>-0.105</td>
<td>-0.380**</td>
</tr>
<tr>
<td></td>
<td>Body esteem</td>
<td>-0.052</td>
<td>-0.127</td>
</tr>
<tr>
<td></td>
<td>Social life</td>
<td>0.028</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Family relations</td>
<td>-0.015</td>
<td>-0.041</td>
</tr>
</tbody>
</table>

Abbreviations: HRQoL = Health-Related Quality of Life.
SDS-BMI = Standard Deviation Score of Body Mass Index.
R = Pearson product-moment correlation coefficient.
\(^1\) Partial correlation between HRQoL-score and SDS-BMI, adjusted for age, gender, ethnicity (Western, Non-Western), educational level of the parents/caregivers (low, medium/intermediate, high), SES (below average, above average), household situation (parents living together/parents not living together), and duration of inpatient treatment (two months or six months).
P-value s <0.05 are printed bold.
* 2-sided P-value < 0.05.
** 2-sided P-value < 0.01.
*** 2-sided P-value < 0.001.
Discussion

This study showed that severely obese children and adolescents experienced significant long-term improvements in generic and weight-related HRQoL after participating in an intensive one-year lifestyle treatment, even when participants partially regained weight. Larger weight-loss at follow-up was weakly to moderately correlated with larger improvements in the physical HRQoL domains of all questionnaires.

To our knowledge, there are no other studies examining changes in HRQoL among severely obese children and adolescents participating in an intensive lifestyle treatment similar in the intensity of treatment and the length of follow-up. In addition, no other study assessed changes in all domains of generic and weight-related HRQoL. Furthermore, most other studies assessing the effects of lifestyle treatment in children and adolescents included either obese children and adolescents only or included both obese and severely obese children and adolescents, whereas only severely obese children and adolescents were included in our study.

Although our study is not completely comparable to other studies assessing the effects of lifestyle treatment in children and adolescents with regard to the severity of obesity, the intensity of treatment, and the length of follow-up, the results of our study were generally in line with those found in other studies involving less severely obese children and adolescents, less intensive lifestyle treatment, and a shorter follow-up period.

Several studies showed statistically significant improvements in IWQOL-Kids scores directly after lifestyle treatment.\textsuperscript{15,32,33} However, no improvements were observed on the ‘family relations’ domain.\textsuperscript{32,33} This was in line with our study.

Hofsteenge et al, Poeta et al, Quinlan et al, and Yackobovitch-Gavan et al found similar improvements in PedsQL 4.0 scores as in our study. However, in contrast to our findings, they did not find improvements in the ‘school functioning’ domain.\textsuperscript{32,34-36}
Our finding that a reduction in SDS-BMI was correlated with an improvement in the physical HRQoL domain was confirmed by other studies examining the correlation between the degree of weight-loss and improvement in generic HRQoL as measured by the PedsQL 4.0. \textsuperscript{14,34,36}

This study has several strengths. First, it is unique with regard to the large number of participants and the duration and intensity of the treatment studied. The intensive lifestyle treatment had a length of one year, which did not result in high dropout of treatment; 82.5 % (99 of the 120) of the participants completed treatment. The follow-up at two years after baseline provided the opportunity to observe that improvements in HRQoL were generally maintained, even after partial regain of the lost weight in the year after treatment.

This study also had some limitations. It was not possible to attribute the improvements in HRQoL to specific aspects of the intensive one-year lifestyle treatment. To be able to determine whether intensive lifestyle treatment leads to improvements in HRQoL, as observed in this study, a randomized controlled trial should be conducted that includes a control group of severely obese children and adolescents receiving ambulatory lifestyle treatment.

An additional limitation is the use of SDS-BMI as an outcome measure. Neither SDS-BMI nor BMI are optimal outcome measures to examine change in body fatness in children and adolescents. These measures are both influenced by the pubertal stage, which makes them less reliable. \textsuperscript{37} SDS-BMI was chosen because it is the most practically applicable measure.

Our findings have some important implications for clinical practice. For physicians and other healthcare professionals involved in the treatment for severely obese children and adolescents, it is important to know what kind of effects can be expected from intensive lifestyle treatment, so they can communicate these expected effects to severely obese patients and their parents before treatment. In our study, improvements in many psychosocial domains of the different HRQoL questionnaires persisted after the one-year treatment and were not related to the degree of weight-loss, suggesting that weight-loss is not necessary for improvements in these areas. For healthcare insurance companies and
policymakers, it is important to know that intensive lifestyle treatment for severely obese children and adolescents does not only lead to weight-loss, but also leads to long-term improvements in generic and weight-related HRQoL, despite partial weight regain (e.g., with regard to decision making on reimbursement of the costs of intensive lifestyle treatment).

Conclusions
In conclusion, both generic and weight-related HRQoL improved in severely obese children and adolescents after an intensive one-year lifestyle treatment with an inpatient period. Although participants partially regained their weight during the year following treatment, improvements in HRQoL were maintained. Larger long-term decreases in SDS-BMI were correlated with larger improvements in the physical HRQoL domains.
References

Vitamin D3

Synthesis of the active vitamin D metabolite - 1,25(OH)2D

Figure 1: Throughout the body.

D (1,25(OH)2D) for full biological activity. Vitamin D is transported to the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D. This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body.

Vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert 25(OH)D to the active form 1,25(OH)2D for the conversion of 25(OH)D to the active form 1,25(OH)2D.

Vitamin D3 – the more common form of vitamin D in nature – is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant and yeast-derived form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to 1,25(OH)2D, the most active form of vitamin D. Vitamin D 2 is the plant and yeast-derived form of vitamin D. In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert 25(OH)D to the active form 1,25(OH)2D for the conversion of 25(OH)D to the active form 1,25(OH)2D.
exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production. Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant and yeast-derived form of vitamin D. Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources. In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)2D (Figure 1). This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body.
7 GENERAL DISCUSSION
Worldwide the prevalence of obesity in children and adolescents has increased substantially.\(^1\) Despite a stabilization in the prevalence of childhood obesity, there is an increase in the prevalence of severe childhood obesity.\(^2\) Childhood obesity can have a negative impact on physical and psychosocial health and results in a heavy financial burden for society.\(^3\)-\(^10\) To counteract the negative consequences, interventions to treat childhood obesity are of the utmost importance. Although many treatments for childhood obesity exist, results on the effectiveness of these interventions have not been very promising, especially regarding their long-term effectiveness. Moreover, studies evaluating the effectiveness of treatments (with or without an inpatient period) aimed at children with severe obesity are relatively rare.\(^11\)-\(^12\)

The overall objective of this study, the Health Effects of Lifestyle Interventions in Obese children and adolescents Study (HELIOS), was to evaluate the cost-effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods (two or six months) for severely obese children and adolescents from a societal perspective over a period of two years (Chapter 5). The specific objectives of this thesis were:

- To describe the design of HELIOS and the intensive one-year lifestyle treatment in detail (Chapter 2).
- To describe the demographic characteristics and cardiometabolic risk factors of the study population of severely obese children and adolescents included in HELIOS (Chapter 3).
- To evaluate the effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and cardiometabolic risk factors (Chapter 4).
- To evaluate the cost-effectiveness comparing two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and quality-adjusted life-years (QALYs) (Chapter 5).
- To examine changes in health-related quality of life (HRQoL) in severely obese children and adolescents participating in an intensive one-year lifestyle treatment with an inpatient period (Chapter 6).
Main findings and comparison with existing literature

Design of the study
In Chapter 2 of this thesis the development and design of the study are described, which aimed to evaluate the cost-effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods to each other and to usual care for severely obese children and adolescents. This study was designed as a randomized controlled trial with two active treatment groups and a follow-up of 24 months. The study population consisted of 80 participants (8-19 years) with severe obesity. All participants were referred to a specialized childhood obesity center by their local pediatrician after insufficient response to ambulatory lifestyle treatment. Both groups received an intensive one-year lifestyle treatment with either an inpatient period of two months (short-stay group) or six months (long-stay group). During weekdays, the short-stay group participated in a two-month inpatient treatment, followed by biweekly return visits of two days during the next four months, then followed by six monthly return visits of two days. The long-stay group participated in a six-month inpatient treatment during weekdays, followed by six monthly return visits of two days. The treatment focused on nutrition, physical activity and behavior change and required active participation of the parents/caregivers. Intensive lifestyle treatment incorporating a combination of dietary, physical activity, and behavioral counseling, provided by a multidisciplinary team (including for example social workers, psychologists, dieticians, and exercise specialists) seems the most effective treatment for obese children.\textsuperscript{13-15} Parental involvement and parent modeling of healthy behaviors have been identified as crucial components of childhood obesity treatment. Therefore, it is important that family is involved in treatment. This is confirmed by the fact that the most successful obesity treatments are family-based.\textsuperscript{16-20}

The intensive one-year lifestyle treatment evaluated in this thesis was modeled after the treatment developed by Braet et al.,\textsuperscript{21} and originally included a six-month inpatient period. However, an inpatient period of six months is very long and expensive, and poses a considerable burden on both the participants and their families. Therefore, a modified one-year treatment with a two-month inpatient period, followed by biweekly return visits during the next four months was developed. The second half year of both treatments consisted of monthly return visits. Chapter 2 describes the design of the randomized controlled trial to
evaluate these treatments. In summary, 80 participants were randomized into one of the two groups. Data were collected at baseline and after six, 12 and 24 months. An economic evaluation was conducted alongside this study. Healthcare consumption was based on actual resource use, using prospective data collection during two years through cost diaries. Quality Adjusted Life Years (QALYs) were calculated using the EuroQol (EQ-5D).

**Cardiometabolic risk factors**
The results in Chapter 3 clearly show that cardiometabolic risk factors were highly prevalent in this group of severely obese children and adolescents. Eighty percent of participants in this study had at least one cardiometabolic risk factor in addition to severe obesity. Low HDL-cholesterol and hypertension were most prevalent (65.0% respectively 31.2%). The highest significant correlations were found between SDS-BMI and SDS-waist circumference, fasting plasma insulin and HOMA-IR (correlation coefficients respectively 0.8, 0.5, and 0.5). This indicates a strong positive relation between SDS-BMI and SDS-waist circumference, and a moderate positive relation between SDS-BMI and fasting plasma insulin and HOMA-IR. In addition, a higher SDS-BMI tended to be associated with a higher prevalence of clustering of cardiometabolic risk factors. The results of this study are in agreement with other studies, since clinical and population-based studies suggest that both the number and severity of risk factors for cardiovascular disease increase with the degree of obesity in both childhood and adolescence.\(^{22-26}\)

Health-related quality of life (HRQoL) was measured with the EuroQol questionnaire. The mean utility score of the participants on this questionnaire was 0.8 on a scale of 0.0 to 1.0 and their mean individual valuation was 69.1 on a scale of 0 to 100. This score suggests that participants seem to experience important limitations in their HRQoL. Since only severely obese children and adolescents were included in this study population, these results cannot directly be compared with a similar group of normal weight children. The findings that cardiometabolic risk factors are highly prevalent among severely obese children and adolescents and that HRQoL is impaired in this group is important, as it stresses the need for early detection and treatment of severe obesity and comorbidity in these children even more.
Effectiveness of the treatments

In Chapter 4, the effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and cardiometabolic risk factors directly after one year of treatment was evaluated. It was demonstrated that intensive lifestyle treatment with a two- or six-month inpatient period resulted in statistically significant improvements in SDS-BMI and cardiometabolic risk factors in severely obese children and adolescents after one year as compared with baseline. On the other hand, no statistically significant differences in the course of SDS-BMI or cardiometabolic risk factors over time were found between the two treatment groups. In an additional analysis, it was shown that SDS-BMI and cardiometabolic risk factors of participants in both treatment groups improved statistically significantly after one year of treatment compared with participants in a waiting-list group. This finding is important, because the children in this study were referred to the specialized childhood obesity center because they did not respond to treatment in an ambulatory setting. Therefore, this treatment can be considered as a last resort for participants and their parents/caregivers. An inpatient setting provides a more supportive environment than an ambulatory setting where children often have to deal with a less supportive home environment every day. The large decrease in SDS-BMI that was observed was, most likely, the result of the extensive inpatient period in the treatments in this study.

In the Netherlands, only few studies among severely obese children and adolescents have been conducted, and most focused on lifestyle treatment in ambulatory settings. Two studies showed an improvement in SDS-BMI after treatment compared with baseline. Another study, however, did not find a statistically significant decrease in SDS-BMI compared with baseline. Only one Dutch study compared intensive lifestyle treatment with an inpatient period vs. intensive lifestyle treatment in an ambulatory setting in severely obese children and adolescents. Both treatments proved to be effective in improving SDS-BMI and cardiometabolic risk factors, however, the treatment with the inpatient period led to better results after one year in comparison with the ambulatory lifestyle treatment. In general, intensive lifestyle treatments containing an inpatient period seem to result in more weight-loss and subsequent weight maintenance compared with the ambulatory form.
This study confirms the effectiveness of inpatient treatment on SDS-BMI for severely obese children and adolescents during treatment, but this was not fully maintained during one year of follow-up after treatment. Intensive lifestyle treatment with an inpatient period may offer an alternative for severely obese children and adolescents who seem resistant to intensive lifestyle treatment in ambulatory form and are too young for or have restraints to bariatric surgery.

Cost-effectiveness of the treatments
The cost-effectiveness comparing two intensive one-year lifestyle treatments with varying inpatient periods for severely obese children and adolescents with regard to SDS-BMI and quality-adjusted life-years (QALYs) after two years of follow-up was evaluated in Chapter 5. After two years there were no statistically significant differences in SDS-BMI and QALYs gained between the two treatment groups. Costs were statistically significantly lower for the short-stay treatment group in comparison with the long-stay treatment group. Based on these results, the short-stay treatment can be regarded as cost-effective from the societal perspective in comparison with the long-stay treatment. Also taking into account the lower burden for the participating families, the short-stay treatment group is preferred over the long-stay treatment group. To our knowledge, this study was the first to evaluate the cost-effectiveness of intensive lifestyle treatments with an inpatient period for severely obese children and adolescents. Cost-effectiveness planes (CE-planes) and cost-effectiveness acceptability curves (CEACs) showed that the short-stay treatment was cost-effective in comparison with the long-stay treatment for values of willingness to pay ranging from 0 to 83,000 and 163,000 for SDS-BMI and QALYs respectively. Utility scores increased with 0.1 points on a scale of 0.0-1.0 in both groups during the one-year treatment. Remarkably, this improvement in quality of life was maintained during the year following treatment with no statistically significant difference between the groups, despite an increase in SDS-BMI during that year.

Health-related quality of life
Chapter 6 shows that severely obese children and adolescents experienced statistically significant long-term improvements in generic and weight-related HRQoL after participating in an intensive one-year lifestyle treatment in comparison with baseline. Although participants
partially regained their weight during the year following treatment, improvements in many psychosocial domains of the different HRQoL questionnaires persisted after one year of treatment in this study. This could suggest that weight-loss is not primarily responsible for the observed improvements in these areas of quality of life. Larger long-term decreases in SDS-BMI were correlated with larger improvements in the physical HRQoL domains of all questionnaires. To our knowledge, no other study examining changes in HRQoL among severely obese children and adolescents participating in an intensive lifestyle treatment was similar in the degree of severity of obesity, the intensity of treatment, and the length of follow-up. In addition, no other study assessed changes in all domains of generic and weight-related HRQoL. Several other studies showed statistically significant improvements in weight-related HRQoL directly after lifestyle treatment. Nevertheless, no improvements were observed on the ‘family relations’ domain in two of these studies, which was in line with this study.

Generic and weight-related HRQoL should be assessed in studies evaluating the effect of intensive lifestyle treatment for severely obese children and adolescents.
**Strengths and limitations**

This study is an important contribution to the limited number of studies available on the cost-effectiveness of treatments for severely obese children and adolescents. However, when interpreting the results of this study several strengths and limitations should be taken into account.

**Design and execution of the study**

An important strength of the design of the study is the fact that a randomized controlled trial was performed to compare the cost-effectiveness of the treatments. A randomized controlled trial is generally considered the gold standard for a clinical trial. Randomization maximizes statistical power, minimizes selection bias and allocation bias (or confounding) and thereby maximizes internal validity. Randomization reduces the risk of selection bias which arises when participants are allocated to intervention groups or an intervention group and control group by methods other than randomization (e.g. researchers can consciously or unconsciously preferentially enroll participants between treatment groups). A good randomization procedure is unpredictable so that researchers cannot guess the next participant’s treatment allocation based on prior treatment allocation. Allocation bias can occur when covariates that affect the outcome are not equally distributed between treatment groups, and the treatment effect is confounded with the effect of the covariates. For example, without randomization, it is unclear whether participants in one group were perhaps already more motivated to lose weight to begin with than participants in the other group. This makes it difficult to attribute results to the intervention and to rule out the possibility that they were caused by (baseline) differences in covariates between the groups. In addition, a pragmatic design was used which allows for evaluation of the treatments under circumstances that resemble routine practice conditions where possible. Thus, costs and effects in this study were collected prospectively under ‘real life’ conditions which greatly facilitates the generalizability of the results of this study (external validity). Effects were mostly measured at the childhood obesity center; only if participants were not able or willing to come to the center data were based on self-report.
A second strength of the design of the study is the comparison of both treatment groups with a waiting-list group in an additional analysis. This not only gives insight in the effects of the intensive treatments compared with each other but also in comparison with usual care. Furthermore, the follow-up of two years was relatively long in comparison with other studies carried out among severe obese youth. Finally, the cost-effectiveness analysis (CEA) was conducted from a societal perspective, which means that not only treatment costs were taken into account, but also the costs of contacts with other healthcare providers, transportation and lost productivity of the parents/caregivers.

With respect to the CEA, cost calculations were based on actual resource use with cost diaries covering a six-month period each during two years. Bias may have been introduced by using cost diaries, since they are based on self-reporting. Moreover, although the cost diaries should be filled in prospectively, people may have forgotten to note work absenteeism or visits to healthcare professionals at the time these occurred. We expect that at least part of the cost diaries was filled out retrospectively, which introduces a risk of recall bias.

Although a follow-up of two years is long in this field of research, the major cost savings as a result of treatment are expected to come about much later in the lives of these children and adolescents. It is well known that childhood obesity often tracks into adulthood. Thus, the effects of reducing obesity in childhood on productivity, absenteeism, disease incidence and use of healthcare may potentially appear after decades. These long-term effects on costs cannot be taken into account in the limited setting of a randomized controlled trial. Modeling is needed to estimate these long-term effects.

**Study population**
A first strength with regard to the study population is that both young children (8-13 years of age) and adolescents (13-18 years of age) were included in this study. Although obesity is an important health problem in both of these age groups, most studies only include adolescents. It may be hypothesized that children, who have been obese for a shorter period of time, are more capable of losing weight as behavior is not as fixed already as with older participants. Unfortunately, in this study the numbers of participants were too small to stratify according to age groups. The role of the parents can also differ for children and
adolescents, as well as the environment (primary school or high school) and the influence of their peers. Also, participants of different ethnic groups and from rural and urban areas from different parts in the Netherlands participated in the study. This is important, because the prevalence of severe obesity among ethnic groups (Turkish and Moroccan) is higher than in the native Dutch population. The study population had a relatively low socioeconomic status (SES). Research suggests that the percentage of severe obesity is higher among those with low income. Since low SES was overrepresented in this study population, it is an adequate reflection of the actual Dutch population which contributes to the generalizability of the outcomes to the general population of severely obese children and adolescents in the Netherlands.

An important limitation is that data were available from only 16 participants in the waiting-list group, as four participants dropped out of the study. Due to practical reasons, we were unable to include more participants in the waiting-list group prior to treatment. Among other things, parents were more reluctant to have children in the age of 8-13 in the long-stay treatment group. Since participants were randomly assigned, it was hard to include participants in this age range for the waiting-list group. Additionally, the participants of the waiting-list group were allocated to one of the treatment groups after one year, so a comparison of the treatment groups with a waiting-list group after the total follow-up of two years was not possible.

Since not all severely obese children and adolescents reach out to a general practitioner for help dealing with their overweight, it is possible that the participants followed in this study are a specific selection of the overall population of severely obese children and adolescents. It is unknown if and how these children and adolescents differ from the ones not reaching out and therefore not referred to the specialized childhood obesity center.

Data collection and analysis
Limitations with regard to collected data that need to be considered are the high rate of missing data in the analyses described in Chapter 5; only 24% had complete cost data available in the last half year of follow-up. Multiple imputation was used to deal with missing data to avoid inefficiency associated with complete-case analyses and to prevent
bias through selective drop-out. Multiple imputation is generally considered to be the most appropriate method to deal with missing data in cost-effectiveness analyses.\textsuperscript{42-43}

Furthermore, the power calculation used to determine participants needed for each treatment group was based on detecting a difference of 0.5 SDS-BMI. Therefore, the study was underpowered to detect relevant cost differences, which was reflected in wide confidence intervals around the cost differences. However, this is a common problem in cost-effectiveness analyses. Moreover, it may be considered unethical to include more participants than needed to show statistically significant differences in clinical effects.\textsuperscript{44}

A final limitation is the use of SDS-BMI as an outcome measure. Neither SDS-BMI nor BMI are optimal outcome measures to examine change in body fatness in children and adolescents. BMI is the most widely used measure to estimate body fatness, but is an indirect measure as it includes lean mass in addition to body fat. Both measures are influenced by the pubertal stage which does not make them optimal for usage in children.\textsuperscript{45} During puberty, changes in body composition and fat distribution occur independently of body weight which results in relatively low correlations between (changes in) SDS-BMI and BMI on the one hand and body fatness on the other. However, SDS-BMI was chosen because it is the most practically applicable measure and often used in other related studies.

Treatment
This study is unique with regard to the intensity, duration and content of the treatments studied. Intensive lifestyle treatment for severely obese children and adolescents is often delivered in ambulatory form. Nonetheless, research suggests that lifestyle treatment for severely obese children and adolescents in ambulatory form is insufficiently effective in the long-term.\textsuperscript{46-47} Therefore, long-term inpatient treatments such as the one evaluated in this study are suggested as the most effective nonsurgical treatment for severely obese children and adolescents.\textsuperscript{12} The total duration of treatment was long with one year, but this did not result in a high attrition rate; only 12 participants (15\%) dropped out of treatment. Not only the children and adolescents were involved in the treatment, but the treatment was family-based with active parental participation. Most effective lifestyle treatments are family-based.\textsuperscript{16-20} Probably due to the fact that children will return to their home environment
after treatment and have to continue learned behavior. Finally, all children were treated in a specialized childhood obesity center with an established history of providing treatment for severely obese children and adolescents and their parents. The professionals at the center are highly experienced in the approach and counseling of these families. The professional counseling, the relationship between the families and the professionals and the treatments that were tailored specifically for severely obese children and adolescents and their parents, may well have contributed to the relatively low attrition rate.

The inpatient period that was part of the treatments studied in this thesis poses a high burden on the participating families. Children were placed in a completely new environment and were away from their families, home, school, and friends for a long period of time, especially in the long-stay group. In addition, parents/caregivers often needed to take time off from work to participate in the treatment resulting in productivity losses. However, since the child returns home again after the intensive inpatient period, we considered it essential that parents/caregivers were included in the treatment as well.
Recommendations for future research and implications for practice and policy

Future research
Several recommendations for future research can be made taking into account the limitations of the current study as mentioned above. Above all, the long-term effects of treatment for severely obese children and adolescents need to be further investigated. Although the follow-up of two years is longer than most studies available on severely obese children and adolescents, it is still not long enough to evaluate the longer-term effects of the treatments on societal costs and health benefits later in life. Long-term follow-up of participants allows for studying the transition from high school to further education or occupation. It is already known that obese children and adolescents are less likely than their thinner counterparts to complete high school and more likely to live in poverty.3

A longer-term study will provide information on participation of severely obese children and adolescents in society as young adults. To estimate the longer-term effects of treatment of severe obesity in children and adolescents, modeling is needed. By using such a model, the tracking of childhood obesity into adulthood and the associated effects on societal costs later in life can be evaluated. Some of the health consequences of obesity, such as diabetes mellitus type 2, cardiovascular disease or cancer, may develop late in life. An empirical study on the impact of treatment of childhood obesity would require large numbers of patients followed over many decades.

Neither SDS-BMI nor BMI are optimal outcome measures to examine change in body fatness in children and adolescents, other ways to measure fat mass directly could be taken into account. Skinfold measures are a possible way to determine fat mass, although not very easily applicable. A dual-energy X-ray absorptiometry (DXA, previously DEXA) scan is primarily used for measuring bone density. It is as simple as lying on a table and getting a full-body X-ray. The DXA scan provides one of the most highly accurate measurements of body composition available, registering fat and lean mass distribution throughout the entire body. When combining outcome measures like (SDS) BMI and DXA scan, weight-loss could be followed both directly and indirectly.
The improvements in generic and weight-related HRQoL observed in Chapter 6 suggest that it may be useful to include generic and weight-related HRQoL as outcome measures when monitoring the effects of lifestyle treatment in severely obese children and adolescents. The findings suggest that the PedsQL 4.0 is a sensitive instrument to measure changes in generic HRQoL in severely obese children and adolescents. In addition, the IWQOL-kids is suitable to gain insight in changes in weight-related HRQoL, which is specifically relevant for severely obese children and adolescents participating in an intensive lifestyle treatment.

**Implications for practice**
The results in Chapter 3 clearly demonstrated that the majority of the severely obese children and adolescents included in this study already had several cardiometabolic risk factors and were at high risk for developing cardiometabolic disease in young adulthood.

These findings stress the importance of early identification and appropriate treatment of severely obese children. The recommended approach to identify and diagnose children with severe obesity is described in the integrated health care standard for obesity.\textsuperscript{15} It is well known that childhood obesity often tracks into adulthood. This is especially important, since childhood obesity also has strong negative health effects in adulthood. Chronic diseases such as cardiovascular disease, diabetes mellitus type 2, several forms of cancer, and stroke are more prevalent in obese adults and comprise a great burden for healthcare, society, and economy.\textsuperscript{48}

Because of the high risk of regaining weight after successful treatment, continuous treatment for severely obese children and adolescents is needed.\textsuperscript{49} The results of this study and also those from Vos et al\textsuperscript{32} show that treatment including return visits after the less intensive treatment phase is associated with better results than treatment without or only a small number of return visits during follow-up as shown by the studies of van der Baan et al and Hofsteenge et al.\textsuperscript{34-35} However, in this study weight increased again in the second year of the study after the follow-up visits ended. To ensure long-term maintenance of weight-loss after intensive treatment, monitoring and periodic intensive return visits seem essential. Hypothetically, if the monthly return visits of two days in this study would be continued from the second half year of treatment to one year after treatment had ended, this would have
led to extra costs of €7878 per participant. Future studies should evaluate whether the costs of such intensive follow-up weigh up against the effects. Inpatient treatment is costly and poses a high burden on the families participating, so preferably this continuous treatment is organized in the home environment making it more feasible and less expensive. When treatment is transferred to the home environment of the child, it is of utmost importance that this transfer is prepared carefully, to ensure that participants are not lost to follow-up and receive the appropriate continuous treatment. Special attention should be paid to the reduction of attrition in the continuous treatment phase.

**Implications for policy**

To be able to provide effective treatment for severely obese children and adolescents, intensive lifestyle treatment should be integrated in a continuous care model with clear role descriptions for all relevant healthcare providers. The integrated health care standard for obesity describes a care model that\(^{15}\) ensures continuous care for this vulnerable group of children can be provided in their home environment.

The results of this study show that the short-stay treatment was cost-effective in comparison with the long-stay treatment. However, it is still unclear whether the treatment is cost-effective in comparison with usual care as well; this is to be examined in future research. So far it is the only viable alternative for bariatric surgery for severely obese children and adolescents in the Netherlands. The evaluation of the cost-effectiveness served as a basis for an advisory report by the National Health Care Institute to the minister of Health, Welfare and Sport. At the moment, the National Health Care Institute is discussing the conditions under which the treatment should remain available and should be reimbursed by healthcare insurance companies.

To diminish the burden for both participants and their families, specialized obesity treatment centers should be set up throughout the country. Treatment could also be made more practical for participants and their family if it were to coincide with regular school vacations. In this way, participants would not have to miss their family and friends, nor school, and parents miss less time from work due to travelling back and forth to the center.
Conclusions

In conclusion, this thesis shows cardiometabolic risk factors were highly prevalent in this group of severely obese children and adolescents who also experienced important limitations in their HRQoL. SDS-BMI decreased statistically significantly in both treatment groups as compared with baseline. For that reason, both treatments can be considered a promising alternative for severely obese children and adolescents who do not respond sufficiently to intensive ambulatory treatment. However, there were no statistically significant differences between the two groups, but the costs in the long stay group were statistically significantly higher than in the short stay group. Therefore, based on the results from the cost-effectiveness analysis, the short-stay treatment can be regarded as cost-effective from the societal perspective in comparison with the long-stay treatment. Finally, the severely obese children and adolescents experienced statistically significant long-term improvements in generic and weight-related HRQoL after the treatment in this study in comparison with baseline. Intensive lifestyle treatment with an inpatient period can therefore be a valuable complement to the existing treatment options for children and adolescents with severe obesity.
References

Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources. In humans, both vitamin D2 and vitamin D3 are converted into several major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3, which is obtained from sunlight-induced synthesis of the skin (9). The two important dietary sources of vitamin D are fatty fish, cod-liver oil, eggs, butter, and fortified dairy products. However, approximately 80% of vitamin D production comes from sunlight exposure. Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D production depends on sunlight-induced synthesis of the skin (9).

Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)2D. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D) for full biological activity. Vitamin D is obtained from sunlight-induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 and vitamin D3. However, vitamin D3 is the more common form of vitamin D in nature and is produced by the skin and comes from animal food sources.

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SUMMARY

NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

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LIST OF PUBLICATIONS

ABOUT THE AUTHOR
Introduction

Childhood obesity has become a major global health challenge over the past thirty years. The prevalence of overweight and obesity has increased substantially in children and adolescents between 1980 and 2013 in both developed and developing countries. Despite a leveling off in the prevalence of childhood obesity, as seen recently in some countries, there is a worrisome increase in the prevalence of severe childhood obesity.

Severe childhood obesity can have negative consequences on both the child’s physical and psychosocial health. Children and adolescents with severe obesity have an increased risk of several chronic diseases such as diabetes mellitus type 2, cardiovascular diseases and musculoskeletal and respiratory problems. In addition to these physical consequences, low self-esteem and behavioral problems are commonly seen in obese children. Severely obese children and adolescents also report an impaired quality of life (QoL), with QoL-scores similar to individuals diagnosed with cancer. The presence of severe obesity in childhood is therefore associated with increased direct costs as a result of increased utilization of healthcare services. Healthcare services include for example the prescription of drugs, emergency room visits, outpatient visits, and inpatient treatment.

To counteract the negative physical-, psychosocial, and economic consequences, it is necessary to treat childhood obesity. Since bariatric surgery is not currently considered an appropriate treatment option for children and adolescents in the Netherlands, intensive lifestyle treatment is the only viable treatment option for the majority of children and adolescents with severe obesity in the Netherlands. When ambulatory treatment is insufficiently effective, treatment with an inpatient period in a specialized childhood obesity center can be indicated.

This thesis describes the results of the Health Effects of Lifestyle Interventions in Obese children and adolescents Study (HELIOS). The overall objective was to evaluate the cost-effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods (two or six months) for severely obese children and adolescents from a societal perspective over a period of two years.
Design of the study

Chapter 2 of this thesis describes the design of HELIOS and the intensive one-year lifestyle treatment in detail. The study was designed as a randomized controlled trial with two active treatment groups. The interventions in this study comprised an intensive one-year lifestyle treatment with an inpatient period of either two months and biweekly return visits during the next four months (short-stay group) or six months (long-stay group). The second half year of the treatment consisted of six monthly return visits in both groups. Both interventions were provided at the same specialized childhood obesity center in Hilversum, the Netherlands. Treatment focused on change of nutrition, physical activity and behavior of the participants and their parents, after which the participants were followed up for another year. The study population consisted of 80 participants (8-19 years) with severe obesity. All participants were referred to the specialized childhood obesity center by their local pediatrician who considered ambulatory obesity treatment to be insufficiently effective for them.

Cardiometabolic risk factors

Chapter 3 describes the demographic characteristics and cardiometabolic risk factors of the study population of severely obese children and adolescents included in HELIOS. Cardiometabolic risk factors were already highly prevalent in this group of severely obese children and adolescents. Participants reported impaired quality of life. However, quality of life was not associated with the prevalence of cardiometabolic risk factors in this group.

Effectiveness of the treatments

Chapter 4 evaluates the effectiveness of two intensive one-year lifestyle treatments with varying inpatient periods (two or six months). The average SDS-BMI (a measurement for the severity of the overweight) decreased statistically significantly after one year of treatment compared with baseline in both groups. A number of cardiometabolic risk factors improved as well. The long-stay treatment resulted in a relatively larger decrease in SDS-BMI than the short-stay treatment, but the difference was not statistically significant. During the waiting list period, SDS-BMI increased in the year prior to the start of treatment, but this was not statistically significant.
Cost-effectiveness of the treatments

Chapter 5 evaluates the cost-effectiveness comparing two intensive one-year lifestyle treatments with varying inpatient periods (two or six months) for severely obese children and adolescents with regard to SDS-BMI and quality-adjusted life-years (QALYs). SDS-BMI decreased in the first six months of treatment, stabilized in the second six months and increased during the second year in both groups. After two years, there was no statistically significant difference in SDS-BMI between both groups, but SDS-BMI was still lower than at baseline in both groups. Costs in the long-stay group were statistically significantly higher than in the short-stay group which was caused mainly by the higher treatment costs in this group. Based on these results, the short-stay treatment is considered cost-effective from the societal perspective in comparison with the long-stay treatment.

Health-related quality of life

In Chapter 6, the changes in health-related quality of life (HRQoL) are reported directly after treatment and at follow-up one year later. Improvements were observed in generic and weight-related HRQoL after participating in an intensive one-year lifestyle treatment in comparison with baseline, even when participants partially regained their weight in the year after treatment. Larger weight-loss was correlated with larger improvements in physical HRQoL domains of all questionnaires.

Discussion

Chapter 7, the final chapter, is a general discussion in which the main findings of this thesis are being summarized, discussed and compared with existing literature. The strengths and limitations of the design and execution of the study, the study population, the data collection and analysis, and the treatment are discussed and the implications thereof for the interpretation of the results. In addition, recommendations for future research and for practice and policy are provided.
Conclusions

In conclusion, this thesis shows cardiometabolic risk factors were highly prevalent in this group of severely obese children and adolescents who also experienced important limitations in their HRQoL. SDS-BMI decreased statistically significantly in both treatment groups as compared with baseline. For that reason, both treatments can be considered a promising alternative for severely obese children and adolescents who do not respond sufficiently to intensive ambulatory treatment. However, there were no statistically significant differences between the two groups, but the costs in the long stay group were statistically significantly higher than in the short stay group. Therefore, based on the results from the cost-effectiveness analysis, the short-stay treatment can be regarded as cost-effective from the societal perspective in comparison with the long-stay treatment. Finally, the severely obese children and adolescents experienced statistically significant long-term improvements in generic and weight-related HRQoL after the treatment in this study in comparison with baseline. Intensive lifestyle treatment with an inpatient period can therefore be a valuable complement to the existing treatment options for children and adolescents with severe obesity.
Introductie

Obesitas bij kinderen en adolescenten is de afgelopen dertig jaar een steeds grotere uitdaging geworden voor de mondiale volksgezondheid. De prevalentie van overgewicht en obesitas is substantieel toegenomen bij kinderen en adolescenten tussen 1980 en 2013 in zowel rijkere als minder rijke landen. Ondanks een stabilisering in de prevalentie van obesitas op kinderleeftijd, zoals recentelijk gezien in sommige landen, is er een zorgelijke stijging in de prevalentie van ernstige obesitas bij kinderen en adolescenten.

Ernstige obesitas bij kinderen en adolescenten kan nadelige gevolgen hebben voor de fysieke en psychosociale gezondheid. Kinderen en adolescenten met ernstige obesitas hebben een verhoogd risico op verschillende chronische ziekten zoals diabetes mellitus type 2, cardiovasculaire ziekten, aandoeningen van het bewegingsapparaat en ademhalingsproblemen. Behalve deze negatieve fysieke gevolgen, gaat ernstige obesitas relatief vaak gepaard met een verminderd zelfvertrouwen en met gedragsproblemen. Ernstig obese kinderen en adolescenten hebben gemiddeld ook een relatief slechte kwaliteit van leven (KvL), met KvL-scores gelijk aan die van kinderen waarbij kanker is gediagnosticeerd. De aanwezigheid van obesitas op kinderleeftijd is daardoor geassocieerd met verhoogde directe kosten als gevolg van verhoogde zorgconsumptie. Voorbeelden van zorgconsumptie zijn voorgeschreven geneesmiddelen, bezoeken aan de eerste hulp, poliklinische afspraken en opname in het ziekenhuis.

Om deze negatieve fysieke en psychosociale gezondheidsproblemen en economische gevolgen zoveel mogelijk te beperken, is het nodig om obesitas op kinderleeftijd te behandelen. Aangezien bariatrische chirurgie op dit moment geen geschikte behandelloptie is voor kinderen en adolescenten in Nederland, is intensieve leefstijlbehandeling de enige echte behandelloptie voor de meerderheid van de kinderen en adolescenten met ernstige obesitas in Nederland. Wanneer ambulante behandeling onvoldoende succesvol is, kan opname in een gespecialiseerd behandelcentrum geïndiceerd zijn.
Dit proefschrift beschrijft de resultaten van de Health Effects of Lifestyle Interventions in Obese children and adolescents Study (HELIOS). Doel van het onderzoek was het evalueren van de kosteneffectiviteit van twee intensieve leefstijlbehandelingen met verschillende opnameperioden (twee of zes maanden) voor ernstig obese kinderen en adolescenten vanuit een maatschappelijk perspectief gedurende een periode van twee jaar.

**Design of de HELIOS studie**

*Hoofdstuk 2* van dit proefschrift beschrijft het design van HELIOS en de intensieve eenjarige leefstijlbehandeling in detail. De studie was ontworpen als een gerandomiseerde gecontroleerde studie met twee actieve behandelgroepen. De interventies in deze studie omvatten een intensieve eenjarige leefstijlbehandeling met een opname van ofwel twee maanden en tweewekelijkse terugkombezoeken gedurende de volgende vier maanden (korte-verblijf groep) of zes maanden (lange-verblijf groep). Het tweede halfjaar van de behandeling bestond bij beide groepen uit zes maandelijkse terugkombezoeken. Beide interventies werden uitgevoerd door hetzelfde gespecialiseerde behandelcentrum voor ernstige kinderobesitas in Hilversum. De behandeling richtte zich op verandering van voeding, lichaamsbeweging en gedrag van de deelnemers evenals dat van hun ouders, waarna de deelnemers nog een jaar gevolgd werden. De studiepopulatie bestond uit 80 deelnemers (8-19 jaar) met ernstige obesitas. Deze kinderen waren verwezen naar deze intensieve vorm van behandeling door hun kinderarts die ambulante therapie voor hen onvoldoende effectief oordeelde.

**Cardiometabole risicofactoren**

In *Hoofdstuk 3* worden de demografische kenmerken en cardiometabole risicofactoren van de studiepopulatie van ernstig obese kinderen en adolescenten in HELIOS beschreven. Cardiometabole risicofactoren waren al zeer frequent aanwezig in deze groep van ernstig obese kinderen en adolescenten. De deelnemers rapporteerden een sterk verminderde kwaliteit van leven. Kwaliteit van leven was bij hen echter niet geassocieerd met de prevalentie van cardiometabole risicofactoren.
Effectiviteit van de behandelingen

In Hoofdstuk 4 wordt de effectiviteit beschreven van de twee intensieve eenjarige leefstijlbehandelingen met verschillende opnameperiodes (twee of zes maanden). De gemiddelde SDS-BMI (een maat voor de ernst van het overgewicht) nam in beide groepen statistisch significant af na een jaar behandeling vergeleken met de beginwaarden. Ook verbeterde het niveau van een aantal cardiovasculaire risicofactoren. De langere opname resulteerde in relatief meer afname in SDS-BMI dan de kortere opname, maar dat verschil was niet statistisch significant. Gedurende de wachtlijstperiode nam de SDS-BMI toe in het jaar voorafgaand aan de start van de behandeling, hoewel deze toename niet statistisch significant was.

Kosteneffectiviteit van de behandelingen

Hoofdstuk 5 beschrijft de kosteneffectiviteit van twee intensieve eenjarige leefstijlbehandelingen met verschillende opnameperiodes (twee of zes maanden) voor ernstig obese kinderen en adolescenten met betrekking tot SDS-BMI en kwaliteits-aangepaste levensjaren (QALYs). De SDS-BMI nam af in het eerste half jaar van behandeling, stabiliseerde in het tweede half jaar en nam toe in het tweede jaar in beide groepen. Na twee jaar was er geen statistisch significant verschil in SDS-BMI tussen beide groepen, maar SDS-BMI was nog altijd lager dan de beginwaarden in beide groepen. Kosten in de lange-verblijf groep waren statistisch significant hoger dan in de korte-verblijf groep wat voornamelijk veroorzaakt werd door de hogere behandelkosten in deze groep. Gebaseerd op deze resultaten wordt de korte-verblijf behandeling beschouwd als kosteneffectief vanuit een maatschappelijk perspectief vergeleken met de lange-verblijf behandeling.

Gezondheids-gerelateerde kwaliteit van leven

In Hoofdstuk 6 worden de veranderingen in de gezondheidsgerelateerde kwaliteit van leven (HRQoL) gerapporteerd na een jaar behandeling en één jaar later. Verbeteringen werden geobserveerd in generieke en gewichtsgerelateerde HRQoL na participatie aan een intensieve eenjarige leefstijlbehandeling in vergelijking met beginwaarden, zelfs wanneer deelnemers
het jaar daarna gedeeltelijk weer aankwamen in gewicht. Groter gewichtsverlies was gecorreleerd met grotere verbeteringen in fysieke HRQoL domeinen van alle vragenlijsten.

**Discussie**

*Hoofdstuk 7*, het laatste hoofdstuk, betreft een algemene discussie waarin de belangrijkste bevindingen van dit proefschrift worden samengevat, bediscussieerd en vergeleken met bestaande literatuur. De sterke en zwakke punten van het design en de uitvoer van de studie, de studiepopulatie, de dataverzameling en –analyse en de behandeling worden besproken en de implicaties daarvan voor de interpretatie van de resultaten. Bovendien worden aanbevelingen gedaan voor toekomstig onderzoek en voor praktijk en beleid.

**Conclusies**

Concluderend laat dit proefschrift zien dat cardiometabole risicofactoren al zeer frequent aanwezig waren in deze groep van ernstig obese kinderen en adolescenten die ook belangrijke beperkingen ervoeren in hun HRQoL. De SDS-BMI nam statistisch significant af in beide behandelgroepen vergeleken met beginwaarden. Om deze reden kunnen beide behandelingen als een veelbelovend alternatief worden gezien voor ernstig obese kinderen en adolescenten die niet voldoende reageren op intensieve ambulante behandeling. Echter, er waren geen statistisch significante verschillen in SDS-BMI tussen de twee groepen, maar de kosten in de lange-verblijf groep waren statistisch significant hoger dan in de korte-verblijf groep. Daarom, gebaseerd op de resultaten van de kosteneffectiviteitsanalyse, kan de korte-verblijf behandeling worden beschouwd als kosteneffectief vanuit een maatschappelijk perspectief in vergelijking met de lange-verblijf behandeling. Bovendien ervoeren de ernstig obese kinderen en adolescenten statistisch significante lange-termijn verbeteringen in generieke en gewichts-gerelateerde HRQoL na behandeling in deze studie vergeleken met beginwaarden. Intensieve leefstijlbehandeling met opname kan dus een waardevolle aanvulling zijn op het behandelaanbod voor kinderen met ernstige obesitas.
Eindelijk is het zover: mijn proefschrift is af en kan naar de drukker! Na jaren van inspanning is dit boekje het resultaat. Graag wil ik de mensen bedanken die hier direct en indirect aan bijgedragen hebben; zonder hen was het me niet gelukt.

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exposure drops dramatically and vitamin D deficiency becomes even more prevalent. Furthermore, time of the day, latitude, altitude, skin colour, ageing, sunscreen use, and air pollution substantially influence vitamin D production. Some foods such as fatty fish, cod-liver oil, eggs, butter, and fortified dairy products also contain vitamin D, but approximately 80% of vitamin D is obtained from sunlight induced synthesis of the skin (9). The two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is the plant and yeast-derived form of vitamin D. Vitamin D3 – the more common form of vitamin D in nature – is produced by the skin and is also derived from animal food sources. In humans, both vitamin D2 and vitamin D3 are converted into several metabolites. In the bloodstream, vitamin D is mainly transported by vitamin D-binding protein. Two metabolic steps are necessary to convert inactive vitamin D into its most active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D) for full biological activity. Vitamin D is transported to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Subsequently, the enzyme 1-α hydroxylase is needed for the conversion of 25(OH)D to the active form 1,25(OH)2D (Figure 1). This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body.

![](image)

**Figure 1:** Synthesis of the active vitamin D metabolite - 1,25(OH)2D

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This process mainly occurs in the kidney and 1,25(OH)2D is circulated throughout the body. 

![Figure 1: Synthesis of the active vitamin D metabolite - 1,25(OH)2D](image)

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**ABOUT THE AUTHOR**

Sabine Makkes was born on March 9th, 1983 in Leiden, the Netherlands. After finishing her pre-university education at Leeuwenhorst, Teylingen College in Noordwijkerhout, she started Biomedical Sciences at the University of Leiden in 2001. After she completed her bachelor, she started working for a large health insurance company and followed a course to learn Spanish in Salamanca, Spain. In the fall of 2006 she began with a premaster in Health Sciences and finished her master in 2008. She worked as a research assistant in statistics at the VU University Amsterdam after graduation and again for several months at the health insurance company. She then commenced her PhD-project in the spring of 2009 at the EMGO+ Institute for Health and Care Research and at the Department of Health Sciences of the VU University Amsterdam on the Health Effects of Lifestyle interventions for severely Obese children and adolescents Study (HELIOS). She completed HELIOS on which this thesis is based in 2014 and has worked at the Dutch Institute for Clinical Auditing (DICA) for some time after she left the VU University Amsterdam.