DISSERTATION

Fakultät für Sport und Gesundheitswissenschaft

Lehrstuhl und Poliklinik für Prävention, Rehabilitation und Sportmedizin

Long-term effects of an inpatient weight-loss program in overweight and obese children and adolescents

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Abbreviations

AGA	Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter
BMI	Body Mass Index
BMI-SDS	BMI Standard Deviation Score
CI	Confidence Interval
EvAKuJ	Evaluation of obesity treatment in children and adolescents
GP	General Practitioner
HDL	High density lipoprotein
hs-CRP	high sensitive C-reactive protein
HOMA-IR	Homeostasis model assessment-insulin resistance
HRQOL	Health-related quality of life
IOTF	International Obesity Task Force
IL-6	Interleukin 6
LDL	Low density lipoprotein
LOGIC	Long-term effects of lifestyle intervention in Obesity and Genetic Influence in Children
MAR	Missing at random
MetS	Metabolic Syndrome
PA	Physical activity
PCOS	Polycystic ovary syndrome
RBP4	Retinol binding protein 4
SCFE	Slipped capital femoral epiphysis
SNP	Single nucleotide polymorphism
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
WHO	World Health Organization

1. INTRODUCTION

1.1. Overweight and obesity in childhood and adolescence

Definition

According to the World Health Organisation (WHO) “overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health” (1).

Classification of overweight and obesity in adults

The Body mass index (BMI) provides a simple measurable parameter to estimate adiposity in adults. It is defined as body weight in kilograms (kg) divided by the square of body height in meters (m) (kg/m^2). The BMI is used to classify overweight and obesity in adults. According to the WHO definition overweight and obesity are defined as a BMI ≥25 kg/m^2 and ≥30 kg/m^2, respectively (1).

Classification of overweight and obesity in children and adolescents

To classify overweight and obesity in children and adolescents (hereafter referred to as children), age- and sex specific differences need to be taken into consideration. Therefore, children with increased body weight are classified as overweight, obese, or severely obese based on age and sex-specific BMI percentiles (2, 3).

According to current German guidelines (“Arbeitsgemeinschaft Adipositas im Kindes und Jugendalter” (AGA)) overweight, moderate obesity and severe obesity are defined as the 90th, 97th and 99.5th age and sex-specific percentile (4) in combination with national reference data, which were developed taking into account the data of 17 studies conducted in different regions all over Germany (5).

Furthermore, there are definitions based on international reference data, which should be used for international comparisons (3, 6). One of these definitions has been proposed by the International Obesity Task Force (IOTF). It is based on percentiles adapted to the definition in adults. The reference population include several data sets from six different countries (United Kingdom, United States of America, Netherlands, Brazil, Singapore and Hong Kong) (2). Very

recently, Cole et al. published extended cut-offs, which are consistent and can be compared directly with rates based on the original cut-offs (3). According to these cut-offs a BMI centile corresponding to BMI at 18 of ≥25 to 30 kg/m^2, ≥30 to 35kg/m^2 and ≥35kg/m^2 is defined as overweight, moderate obesity and severe obesity, respectively (2, 3).

The degree of obesity in children can be additionally described using the least-square means method developed by Cole (7) which normalizes the BMI skewed distribution and expresses BMI as a SDS (Standard Deviation Score), in combination with national reference data (5). The LMS-method is based on the use of Box cox power transformations through the calculation of a skewness parameter. The M and S curves correspond to the median and coefficient of variation in BMI for German children at each age and sex, whereas the L curve allows for the substantial age dependent skewness in the distribution of BMI (2).

$$SDS_{LMS} = \frac{[BMI / M(t)]^{L(t)} - 1}{L(t) \times S(t)}$$

Equation 1: LMS-formula developed by Cole (2, 7)

Prevalence

Childhood overweight and obesity has increased worldwide during the past three decades in most industrial countries (8). A recent review by 2012 reports that the prevalence rates of childhood overweight and obesity are highest in the WHO Americas and eastern Mediterranean regions (30-40%) followed by the European (20-30%) and south-east Asian, western Pacific, and African regions (10-20%). A total of more than 40 million children were estimated to be overweight and obese and more than 90 million were at risk of overweight in 2010 (9).

The German Health Interview and Examination Study for Children and Adolescents (KiGGS) provided national, representative data of overweight and obesity in 17.000 children aged 3 to 17 years. It has been shown that 15% of these children are overweight and 6.3% suffer from obesity. Based on reference

values of the years 1985 to 1990 the prevalence rates for overweight and obesity raised of about 50 and 100%, respectively (10).

Causes

Obesity is a multifactorial syndrome, which is associated with many endogenic and exogenous determinants and risk factors. Overall, weight gain due to an increase in adipose tissue is the result of an imbalance between energy expenditure and energy intake. This balance can be influenced by both physical activity (PA) and caloric intake, which can be dependent on social, psychological and other behavioural factors (8). In addition, genes have been shown to play a fundamental role in the regulation of body weight (8, 11). Apart from very rare monogenetic disorders (12), a genetically determined higher risk for obesity can often be attributed to a polygenetic pattern involving different single nucleotide polymorphisms (SNP's). For instance, variations in the FTO-gene seem to have an effect on the development of early onset obesity. Likewise, a study by Frayling et al. has shown that the A allele of the rs9939609 SNP is associated with an increased risk of overweight (odds ratio 1.18; 95% Confidence Interval (CI) = 1.13 to 1.24) and obesity (odds ratio 1.31; 95% CI = 1.23 to 1.39), increasing the risk by 20-30%. Additionally, the A allele of the rs9939609 SNP has been found to be associated with an increased BMI in 7 year old children and to also determine obesity during puberty and beyond (13). Furthermore loci associated with neuronal pathways (TMEM18, GNPDA2, SH2B1, NEGR1) have recently been identified to be associated with childhood obesity (14). It has to be noted though that these genetic predispositions may only lead to an obesity phenotype in the presence of an obesogenic environment, and therefore this association may be modified by a lifestyle intervention (15, 16) (17).

Consequences

The global increase in childhood overweight and obesity is a serious health concern (8), as it often tracks into adulthood (18) where it is associated with numerous cardiovascular and metabolic risk factors such as hypertension, type 2 diabetes or hyperlipidemia and even cardiovascular disease (19, 20). In

addition, even at young age, overweight and obesity are related with various physical and psychological comorbidities (see Figure 1). For instance, it has been found that overweight and obese children often suffer from elevated blood pressure, dyslipidemia or disorders of glucose metabolism (21) or the Metabolic Syndrome (MetS) (22). Furthermore, obese children often have impaired health-related quality of life (HRQOL) compared to healthy normal weight children. It has been shown that their HRQOL is comparable to that of youths diagnosed with cancer (23). This seems to particularly affect individuals who have been referred to or seek clinical treatment (24, 25) (17, 26).

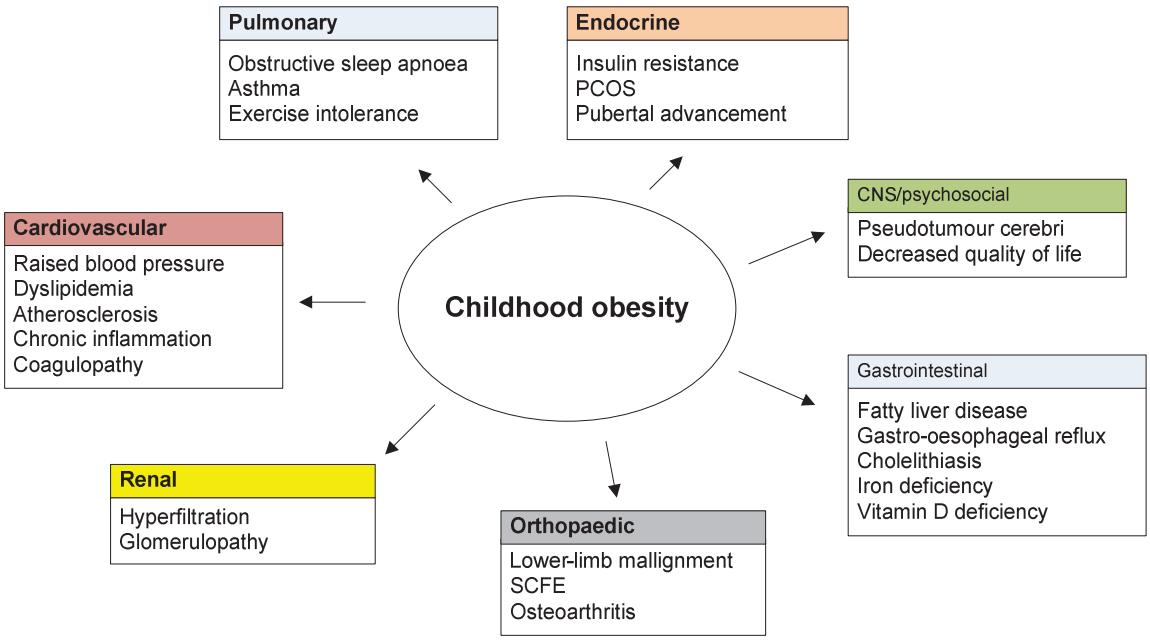

Figure 1: Overview of consequences of childhood obesity (according to (8))
Abbreviations: PCOS=polycystic ovary syndrome, SCFE=slipped capital femoral epiphysis

The economic burden of overweight and obesity for the health care system is high. In Germany the overall costs of obesity in adults (BMI≥30 kg/m²) and the associated complications were putted at 4.2 Mrd. Euros. Ninety percent of these costs were caused by complications and comorbidities such as diabetes mellitus type 2, cardiac infarction, hypertension, or stroke (27). Data on economic costs of childhood obesity are scarce and the results are ambiguous. This might be due to differences in the methodology between different studies and to the fact, that obesity-related comorbidities usually occur later in life and therefore longitudinal surveys are needed (28, 29). Within the KIGGS study, the impact of BMI on utilization of different German healthcare services was

investigated. The authors took into account direct costs, i.e. physician visits, (physical) therapies and hospital days over the last 12 months. Overweight and obese children have shown significantly higher costs for visiting their physician, whereas the difference including all components was not significant. However, the authors conclude that economic implications are already relevant in childhood. Thus obese children need to be classified as priority group for prevention (29).

1.2. The cardiometabolic risk of childhood obesity

Although differences between overweight and obesity are generally recognized, stages of obesity are often described as a single entity. However, there is ample evidence that among obese children there is a wide range of BMI and associated cardiometabolic disturbances. In previous studies, this has been shown for the prevalence of the MetS or its several components (22, 30-32) but also regarding levels of the inflammatory markers c-reactive protein (CRP) and interleukin-6 (IL-6) (22, 33, 34) or adipokines such as leptin (35) and adiponectin (22). This is important because the link between obesity and the development of metabolic and cardiovascular diseases may be seen in obesity-related systemic inflammation (36, 37). Hypertrophy and hyperplasia of the adipose tissue as seen in obesity result in a dysfunction of the adipocytes (38), which increases inflammation and impairs haemostasis, glucose as well as lipid metabolism (36, 37). This is triggered by an alteration of the secretion of the adipokines adiponectin, leptin, retinol binding protein 4 (RBP4) and resistin as well as inflammatory markers such as IL-6, tumor necrosis factor-alpha (TNF-α) and CRP. For example, a decrease in adiponectin and an increase of RBP4 as often found in obese individuals may foster the development of insulin resistance. Furthermore, elevated levels of RBP4, IL-6 and TNF- α increase the inflammatory status by directly stimulating CRP synthesis in the liver (38). In contrast, PA and/or weight-loss seem to have a positive impact on these mechanisms by improving the inflammatory status and reducing insulin resistance (see Figure 2). However, data concerning these mechanisms in children are scarce and results from the existing studies have been inconsistent (38, 39) (40).

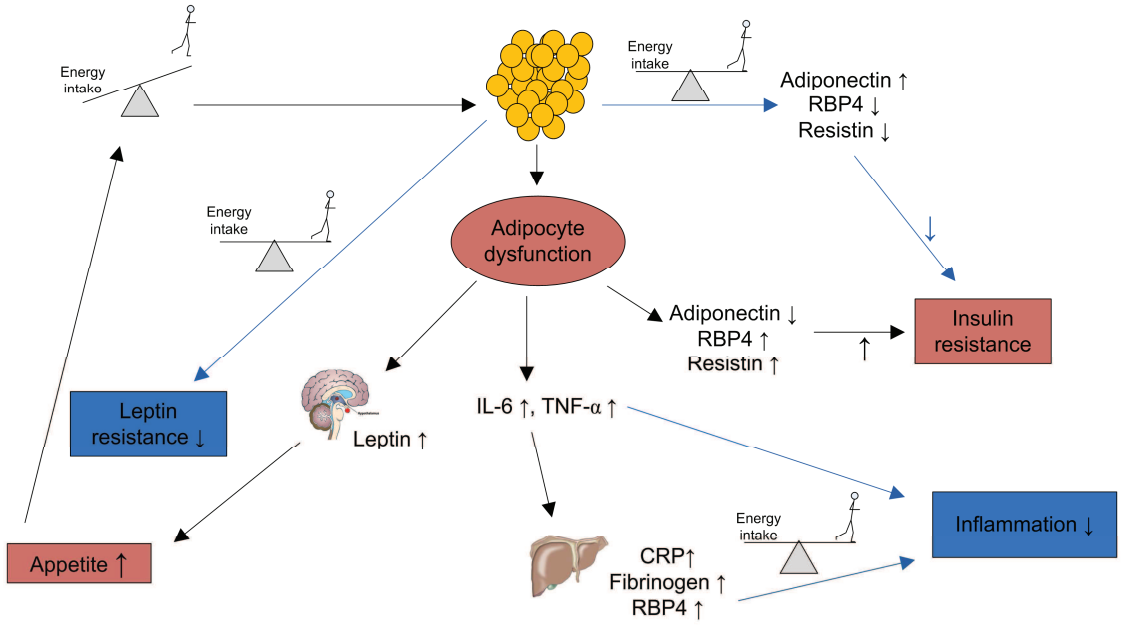

Figure 2: Alterations in selected inflammatory markers and adipokines and their response to lifestyle modifications (according to (38)).
Abbreviations: CRP=C-reactive protein, IL-6=Interleukin-6, TNF-α=Tumor necrosis factor-alpha, RBP4=Retinol binding protein 4

1.3. Lifestyle interventions to treat childhood obesity

Due to the tremendous short and long-term health consequences, current recommendations strongly encourage the treatment of childhood obesity (4). Beyond surgical and pharmacological therapies, there are several forms of lifestyle interventions in the treatment of childhood obesity involving a combination of diet, exercise and/or behaviour modification. These are of great relevance as they focus on changing the behaviour of the children and thus addressing an important key feature in the pathway of the development of overweight and obesity (41).

Lifestyle interventions may be performed in an outpatient or an inpatient setting (e.g. residential or weight-loss camps), or by a combination of both. However, the effectiveness of these types of programs remains uncertain (42). In a recent review by Kelly and Kirschenbaum the average decrease in percent overweight[1] within inpatient treatment across 11 studies was reported 23.9% from pre to post-intervention and 20.6% from pre-intervention to follow-up, whereas the effect on percent overweight was 8.5% and 8.9% for outpatient programs,

[1] Percent overweight has been calculated as ((reported BMI/50th%ile BMI)-1)*100

respectively (43). Within the EvAKuJ study (Evaluation of obesity treatment in children and adolescents study) the short and long-term effects of different German childhood obesity programs were assessed (44). The authors reported that five out of 48 programs included took place in an inpatient setting (n=875 patients), whereas all others were carried out in an outpatient setting (n=1,041 patients). Children participating in inpatient programs achieved a mean reduction in BMI-SDS of -0.36 during the treatment and of -0.17 during the observational follow-up 1-2 years after termination of the treatment, whereas this was -0.18 and -0.21 for outpatient programs, respectively (44). In summary, the results of inpatient versus outpatient programs are equivocal especially regarding long-term effectiveness.

Furthermore, as presented above, very few inpatient treatment programs have been evaluated, and these studies are heterogeneous regarding their study design and overall quality. For instance, the treatment duration ranges from 10 days to 10 months and only 29% of the studies included a follow-up period. The range in follow-up duration also varies dramatically (4 months to 4.6 years) and about half (46%) of the studies performed a follow-up after less than 1 year (43, 45, 46). A study by Braet and van Winckel is the only one with a follow-up period of more than 3 years from the start of the intervention, however, they have not carried out blood analyses and the sample size of their inpatient treatment group was rather low (47).

The results of these studies emphasize that inpatient treatment might be the most effective strategy for children to loose body weight in the short-term and there is a substantial need for intervention studies with considerably longer duration of follow-up and a standardized protocol of the intervention and analyses (17).

2. OBJECTIVES

The current state of research shows that the prevalence of childhood obesity has increased in the past years. This is a great health concern for both the individuals themselves and the health care system. So far, the knowledge about the transition of the cardiometabolic risk from different stages of obesity, i.e. moderate to severe obesity, is scarce. However, to demonstrate the clinical consequences of severe obesity is highly relevant as it will increase the awareness of people working in the field of paediatric healthcare and highlight the need of effective treatment strategies to prevent the occurrences of severe obesity.

On the other hand it is absolutely essential to evaluate existing treatment programs. Inpatient lifestyle programs might be a very effective strategy for children to loose body weight in the short-term. However, there is a substantial need of the evaluation of long-term effects to finally be able to optimize such treatment concepts and succeed in decreasing the prevalence rates of childhood obesity and improving children's health status sustainably.

The purpose of this dissertation is to (1) characterize children and adolescents starting an inpatient program regarding their cardiometabolic risk profile in association with their obesity status and to (2) evaluate long-term changes in BMI, health-related quality of life and physical activity after an inpatient weight-loss program in overweight and obese children and adolescents.

The hypotheses are that severely obese children have a more unfavourable cardiometabolic risk profile compared to moderately obese children and that an inpatient weight-loss program positively impact BMI, HRQOL and PA over the long-term (24 months).

This dissertation includes two published manuscripts and one accepted manuscript. All manuscripts are published or submitted in peer reviewed, international journals. Melanie Heitkamp, b. Rank played the leading role in drafting and writing every included manuscript.

Manuscript 1: "*Long-term effects of an inpatient weight-loss program in obese children and the role of genetic predisposition-rationale and design of the LOGIC-trial" (17)*

All analyses and publications, which are part of this dissertation, were conducted within the LOGIC-trial (**L**ong-term effects of lifestyle intervention in **O**besity and **G**enetic **I**nfluence in **C**hildren). The manuscript describes the rationale and design of the LOGIC-trial.

Manuscript 2 "*The cardiometabolic risk of moderate and severe obesity in children and adolecents" (40)*

The aim of this analysis was to compare the cardiometabolic risk profile between moderately obese (n=197) and severely obese (n=266) children starting an inpatient weight-loss program.

Manuscript 3: "***Health-related quality of life and physical activity in children and adolescents two years after an inpatient weight-loss program" (26)***

The aim of this analysis was to investigate (1) changes in BMI, HRQOL and PA 24 months after an inpatient weight-loss program, and (2) examine associations between changes in HRQOL and changes in both BMI and PA. The study includes 707 overweight and obese children starting an inpatient weight-loss treatment at baseline, of whom 381 completed a 24 month follow-up.

3. METHODS

All analyses and publications, which are included in this dissertation, were conducted within the LOGIC-trial (Long-term effects of lifestyle intervention in Obesity and Genetic Influence in Children) (17). This study runs since 2006 in collaboration between the Department of Prevention, Rehabilitation and Sports Medicine, Technical University of Munich and the Rehabilitation clinic Klinik Schönsicht in Berchtesgaden, Germany.

3.1. The LOGIC trial

The LOGIC trial is a prospective cohort study involving overweight and obese children participating in an inpatient weight-loss program. It is conducted to investigate the determinants for short, middle and long-term weight-loss and weight maintenance after an inpatient weight-loss program in children. The study includes a short-term inpatient weight-loss program complemented by a long-term observational follow-up over 10 years. Measurements include anthropometric, cardiometabolic and genetic parameters as well as assessment of PA and fitness, dietary habits and HRQOL.

Primary endpoint of the LOGIC-trial

The associations between polymorphisms in adiposity relevant genes (e.g. FTO, MC4R, TMEM-18) on the changes in BMI and BMI-SDS after a controlled lifestyle intervention (4 to 6 weeks) in overweight and obese children and adolescents.

Secondary endpoints of the LOGIC-trial

The short (4 to 6 weeks), middle (6 to 12 months) and long-term (2, 5 and 10 years) effects of the intervention on the below-listed parameters and their associations with polymorphisms in adiposity-relevant genes (e.g. FTO, MC4R, TMEM-18):

- anthropometric parameters
- parameters of lipid and glucose metabolism
- adipokines and inflammatory markers

• physical fitness
• PA
• dietary behavior and intake
• HRQOL

Participants

Participants of the LOGIC-trial are 6 to 19 year old overweight and obese children, who are referred to the rehabilitation center Klinik Schönischt in Berchtesgaden, Germany by their local paediatrician to have inpatient weight-loss treatment. The clinic is specialized on childhood obesity and about 200 children with the primary diagnosis overweight/ obesity are being treated here annually. Children are admitted to the clinic on a biweekly basis and recruited consecutively by scientists from the Department of Prevention, Rehabilitation and Sports Medicine, Technical University of Munich. In case they fulfil the inclusion criteria (see Table 1), assent and informed consent for study participation are obtained from the children and their accompanying legal guardians. The study is conducted according to the declaration of Helsinki (Seoul, 2008) and approved by the ethics committee of the Faculty of Medicine of the Technische Universität München, Germany (1354/05).

Table 1: Inclusion and exclusion criteria for participation in the LOGIC-trial

	Inclusion criteria	**Exclusion criteria**
Eligibility criteria for attending the inpatient weight-loss program at the *Klinik Schönsicht*	Overweight (BMI 90.-97th percentile), obese (BMI 97.-99.5th percentile) or severely obese (BMI >99.5th percentile) (4, 5) Repeated failure to accomplish weight-loss in outpatient therapies	Considerable mental or physical disability Severe personality disorders Suicidal behavior Drug addiction
Eligibility criteria for LOGIC-trial participation	Written informed consent by participant and a legal guardian	Obesogenic diseases and disorders such as the Prader-Willi Syndrome, Cushing Syndrome Early withdrawal from the inpatient program (<3 weeks)

Recruitment process

Recruitment for this collaborative study began in January 2006 with the aim to include a total of 1,500 participants by 2013. Figure 3 shows the flow chart of the recruitment and the measurement process. Examinations are performed at the start (Visit 1) and at the end of the intervention at the clinic (generally after 4 to 6 weeks; Visit 2). Follow-up examinations are performed at 6 months (Visit 3), 1 year (Visit 4), 2 years (Visit 5), 5 years (Visit 6) and 10 years (Visit 7) after the start of the intervention by either local paediatricians or general practitioners (GP).

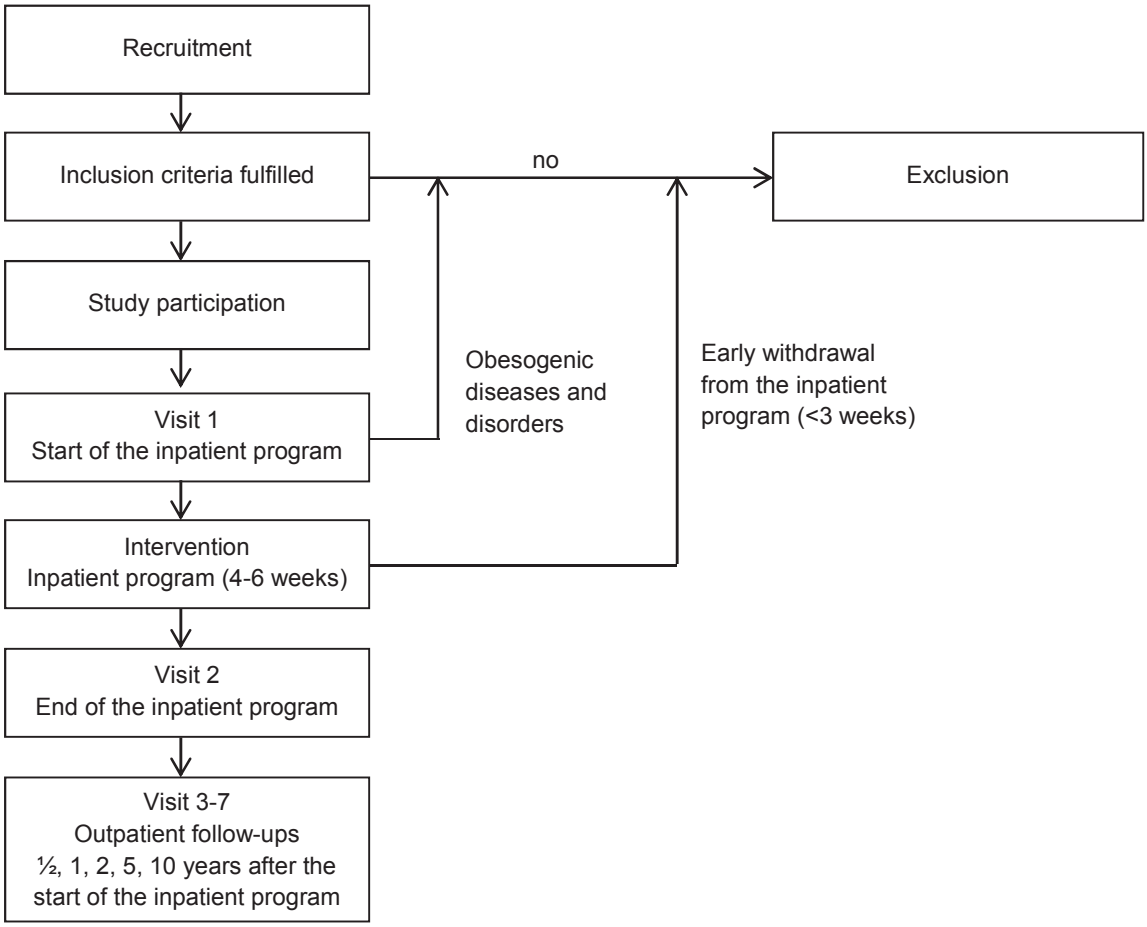

Figure 3: Study flow chart of the LOGIC-trial

Intervention

The rehabilitation clinic is primarily focused on inpatient treatment for childhood overweight and obesity which typically lasts for 4 to 6 weeks. The duration of the stay depends on health insurance allowance and the severity of obesity.

Typically the children are referred to the clinic for 4 weeks and in case of severe obesity or comorbidities they have the opportunity to extend the program. The standardized multimodal program focuses on a calorie-restricted balanced diet, an increase in PA and behavioural counselling. It is conducted by an interdisciplinary team of paediatricians, exercise physiologists, dieticians, psychologists and pedagogues according to German guidelines for inpatient weight-loss programs (AGA) (4). The children are offered an optimized balanced diet prepared according to current guidelines (30%, 15% and 55% of the total energy content from fat, proteins and carbohydrates, respectively), with an allowed energy intake of 1,250-1,800 kcal per day, depending on height and sex (48) (Table 2).

Table 2: Calculation of the allowed energy intake based on body height and sex

Boys		**Girls**	
Height [cm]	**Energy intake per day [kcal]**	**Height [cm]**	**Energy intake per day [kcal]**
≤ 145	1250	≤ 155	1250
146 - 170	1500	156 - 180	1500
≥ 171	1800	≥ 181	1800

The components of the intervention program are shown in Table 3. In brief, the children are required to participate in theoretical and practical lessons on healthy eating, PA and behaviour change skills based on the cognitive-behavioural theory. The exercise therapy consists of approximately 10 hours of organised PA per week, in addition to 6 hours of recreational exercise.

Table 3: Components of the inpatient weight-loss program

Intervention component	Items	Description	Aims	Frequency/Dose
Structured physical activity (10 hrs/ week)	Therapeutic sports	Different types of outdoor activities such as ascending stairs, road running and cross country runs etc.	Endurance training according to individual abilities	2x/week à 60 min
	Swimming	Lane swimming ~1.000m	Endurance training; Learning/improving swimming technique	1x/week à 50min plus the 6km walk to the pool (~3km downhill, 3km uphill)
	Group sports	Different physical activities (e.g. ball games, dancing and gymnastics)	Focus on playing and having fun	1x/week à 45-90min
	Postural training	Strength training: gymnastics, dumbbells, stretch bands, etc.	Strength training to achieve or maintain good posture	1x/week à 45min
	Hiking	10-12 km hikes in the mountains	Endurance training with nature experience	1x/week à 3hrs
Non structured physical activity (~6 hrs/week)	‚Fun- Walk'	Walking to the town centre (~1km downhill, 1km uphill); Time for individual activities	Endurance training, having fun	1x/week à 2hrs (in total)
	Excursions	Various excursions and activities like playing miniature golf, sightseeing, table tennis tournaments, etc.	Having fun, group activities to improve social skills	Dimension of physical activity varies; within 4 weeks of intervention, it accounts for 6 hrs/week
Obesity patient training courses (16 sessions within 4 weeks)	Psychotherapy	• Developing rules for healthy eating behavior • Rigid versus flexible dieting • Recognition of signs of both hunger and satiety • Learning to enjoy food as well as to cope with difficult situations • Developing motivation for participating in regular physical activity	Improving self-esteem and body perception, prevention of relapse.	5 session within 4 weeks à 45min
		Individual sessions if the children suffer from psychosomatic, psycho-vegetative and/or psychological diseases	Treating individual psychological problems	1-3 individual sessions à 45min/week
	Nutritional lessons	Teaching children to choose the appropriate (amount of) food according to their personal needs	Enabling the children to prepare healthy food for themselves	5 sessions within 4 weeks à 45min

	Physical education	Improving knowledge on energy balance, effects and limitations of physical activity, measures of self-control and good posture	Increase knowledge of the effects of physical activity to support adherence to the regular physical activity recommendations	4 sessions within 4 weeks à 45min
	Medical education	Improving knowledge on medical background of overweight and obesity (normal/ideal weight, BMI, comorbidities etc.)	Increase knowledge of the medical consequences of overweight and obesity and promote a realistic goal setting	2 sessions within 4 weeks à 45min
Social competence	Training sessions	• Training for conflict resolution, communication, ability to offer and receive criticism, body language, self-assurance, empathy etc. • Role playing • Concentration training	• Development of emotional-cognitive abilities • Development of occupational skills • Reflecting on and improving social behavior skills	1x/week à 45min
Nutrition	Cooking	Cooking as a creative activity and a positive group experience	Transfer of theoretical knowledge into practice	1x/week, 2hrs
	Lessons for grocery shopping	• Learning how to read packaging labels correctly (e.g. sample sizes, nutritional information) • Learning how to make educated nutritional decisions about potentially misleading products (e.g. 'organic')	Enabling the children to judge different food products correctly	1x/week, 90min
Parents	Supportive training	Parents receive background information on obesity and advice about how to best support their child. In addition, they are requested to take their child to subsequent outpatient psychological treatment. They also receive special handouts about healthy living, including nutrition, physical activity, media consumption etc.	Improving parental support of the children after conclusion of the inpatient program	Two conversations with the physician (at the start and the end of intervention. In special cases, parents are contacted by telephone)
School	Theoretical lessons	German, English and Mathematics	Keeping the children current with the appropriate educational curriculum	Groups 3 and 4: 5x/week à 45min Groups 1 and 2: 6x/week à 45min

3.2. Measurements

An overview of all measurements at the different time points (Visits 1-7), which are conducted within the LOGIC-trial, is presented in Table 4.

Table 4: Overview of the data collection from visit 1 to visit 7

Setting	**Inpatient intervention**		**Outpatient follow-ups**			**(In/)outpatient follow-ups**	
VISIT	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**	**VISIT 6**	**VISIT 7**
Time point	**Intervention start**	**Intervention end**	**1/2y Fu**	**1 y Fu**	**2 y Fu**	**5 y Fu**	**10 y Fu**
Physical examination							
Anthropometry*	+	+	+	+	+	+	+
Pubertal stage (Tanner)	+		+	+	+	+	+
Comorbidities/ Medication	+	+	+	+	+	+	+
Genetic and blood parameters							
Collection of EDTA (DNA)	+						
All blood parameters**	+	+				(+)	(+)
HDL, LDL, total cholesterol, triglycerides, glucose	+	+				+	+
Physical fitness and activity							
Physical fitness (ergometry)	+	+				(+)	(+)
6-Minutes running test	+	+				(+)	(+)
Pedometer***	+					(+)	(+)
Questionnaires (filled in by children)							
Quality of life (KINDL)	+	+	+	+	+	+	+
Diet/ Dietary intake	+	+	+	+	+	+	+
Physical activity	+	+	+	+	+	+	+
Questionnaire (filled in by parents)							
Family background	+						

*Body weight, Body height, Waist circumference, Blood pressure;
** High density lipoprotein (HDL), Low densitiy Lipoprotein (LDL), Total cholesterol, Triglycerides, Glucose, Proinsulin, Insulin, Uric acid, Thyroid stimulating hormone (TSH)-basal, Adiponectin, Leptin, Retinol binding protein 4 (RBP4), Resistin, High-sensitive C-reactive protein (hsCRP), Interleukin-6 (IL-6), Tumor necrosis factor-alpha (TNFα).
*** subgroup-analysis

During the inpatient treatment, the physical examination is performed on the day of admission and on the day of discharge. Blood samples are taken on the third day after admission to the clinic and 3 days before discharge (except for DNA samples, which are taken only at baseline). Physical fitness testing is performed and questionnaires are filled in on the first weekend after admission to the clinic and 1 to 2 days before discharge. In case children extend the treatment, all examinations are being conducted after 6 weeks. Questionnaires are filled in without supervision.

Follow-up (Visits 3 to 5)

Prior to the first follow-up examination, which takes place 6 months after the start of the program (Visit 3), study investigators contact the GPs by telephone to inform them about the study procedures and to obtain agreement on carrying out the upcoming follow-up examinations. The GPs are asked to complete and return a standardized examination sheet including anthropometric measurements (body weight, height and waist circumference), blood pressure as well as the Tanner stage. In addition, study investigators contact the children prior to each visit (6 months, 1 year and 2 years after the start of the intervention) to remind them of the upcoming examination and to enquire about possible address changes. The children are requested to complete the questionnaires, previously sent by post, and to return them using the provided prepaid envelope as well as to visit their GP for the follow-up examination. If both the questionnaires and the examination sheet are returned to the study centre, the children will receive an allowance of 10 Euros (17).

All measurements, which are relevant for the analyses, which are included in this dissertation, are described in the following section in more detail.

Physical examination

Body height was measured barefoot to the nearest 0.5 cm by a rigid stadiometer. Body weight was measured with minimal clothing to the nearest 0.1 kg by a digital scale (Visit 1 and 2: Tanita BC-420 P MA Profi, Tanita Europe B.V., Hoofddorp, The Netherlands; Visits 3-7: calibrated scale). Waist circumference was measured on bare skin by tape to the nearest 0.1 cm midway between the lower rib margin and the iliac crest in standing position after normal exhalation with a non-stretchable tape measure. Blood pressure was measured at the right brachial artery in the fossa cubitalis after the children have been resting for 5 min in supine position by using a validated protocol (49). Identification of pubertal development was defined according to Marshall and Tanner. The children were divided into infantile/prepubertal (Tanner I), pubertal (Tanner II and III), and late pubertal (Tanner ≥IV) (50, 51). Trained medical staff according to standardized procedures conducted all examinations and assessments.

Blood samples

Blood sampling was performed following a ≥10-hour overnight fast. Blood samples were taken by venipuncture of an antecubital vein in either sitting or lying position using vacuum tubes. Samples were stored at -80℃ until analyzed. Plasma glucose was measured with the hexokinase method (COBAS INTEGRA 800; Roche Diagnostics GmbH, Mannheim, Germany). Low density lipoprotein (LDL)-cholesterol and high density lipoprotein (HDL)-cholesterol were measured by the homogenous enzymatic colorimetric method. Total cholesterol was measured by the cholesterol oxidase esterase and peroxidase method and triglycerides by the enzymatic endpoint method (COBAS INTEGRA 6000 C; Roche Diagnostics GmbH, Mannheim, Germany). Serum levels of proinsulin, insulin, leptin, and adiponectin were measured by enzyme-linked immunosorbent assay (ELISA) (Mercodia, Uppsala, Sweden). The inter-assay coefficients of variation were 6.2%, 6.7%, 9.8%, and 11.9%, respectively. Resistin concentrations were measured with a commercial ELISA kit (BioVendor, Heidelberg, Germany), resulting in an inter-assay coefficient of variation of 6.1%. Serum levels of IL-6 and TNF-α were determined as previously described using commercially available ELISA (52). The inter-assay coefficients of variation were 15.6% and 17.3%, respectively. Concentrations of CRP were measured by a high-sensitivity latex-enhanced nephelometric assay with a BN II analyzer (Dade Behring, Marburg, Germany) as described in detail previously (53). The interassay coefficients of variation were 4.0%. All analyses were run in a blinded fashion. The insulin resistance index from fasting plasma insulin and plasma glucose levels was estimated using the homeostasis model assessment-insulin resistance (HOMA-IR) (54) as follows:

$$\text{HOMA-IR} = \frac{\text{Fasting plasma insulin (µl/ml) x fasting plasma glucose (mmol/l)}}{22.5}$$

Equation 2: Calculation of the Homeostasis model assessment-insulin resistance (HOMA-IR)

Current literature does not provide guidelines as to cut-off points for increased concentrations of leptin, adiponectin, or resistin in children.

Health-related quality of life

The German KINDL®-questionnaire (55) was used to assess HRQOL including six domains: “physical well-being”, “emotional well-being”, “self-esteem”, “friends”, “family” and “school”. To obtain a total HRQOL-score (“overall HRQOL”), the average of the domain scores was calculated. Potential scores for all domains range from 0 to 100, with higher values representing better HRQOL. Reliability and validity of this questionnaire is sufficient, with a Cronbach’s $\alpha>0.70$ and a correlation coefficient of $r=0.70$ obtained with instruments measuring similar concepts in previous research (55).

Physical activity

PA was assessed by a self-report questionnaire. The PA questionnaire has been adapted to the MOMO questionnaire, which has been previously validated (56, 57). Level of PA was assessed using a single question: “On how many days last week have you been active for at least 60 minutes?” with possible scores ranging from 0-7 days. This question has been previously validated for use in young people and been shown to be reliable (intraclass correlation 0.77) and significantly correlated with accelerometer data ($r=0.40$) (57). Furthermore, children were asked if they were currently member of a sports club.

Classification of overweight and obesity

According to cut-offs by the IOTF, participants were classified as normal weight (percentiles corresponding to BMI >18.5 to 25 kg/m^2 at age 18), overweight (percentiles corresponding to BMI ≥25 to 30 kg/m^2 at age 18), moderately obese (percentiles corresponding to BMI ≥30 to 35kg/m^2 at age 18) and severely obese (percentiles corresponding to BMI ≥35kg/m^2 at age 18) (2, 3). The degree of obesity was additionally described using the least-square means method developed by Cole (7) which normalizes the BMI skewed distribution and expresses BMI as a SDS, in combination with national reference data (5).

Definition of the Metabolic Syndrome

According to current guidelines of the International Diabetes Federation (58) MetS was defined as a waist circumference above the 90th percentile (59) for

children from 6 to 16 years of age and as ≥94cm in males and ≥80cm in females above the age of 16 years, plus any 2 of the following factors: either systolic or diastolic blood pressure ≥130 mmHg or ≥85 mmHg or treatment with antihypertensive medication, triglyceride levels ≥150 mg/dL, HDL-cholesterol levels <40mg/dL, and fasting plasma glucose levels ≥100 mg/dL or treatment for diabetes. Because there is no standard definition of MetS in children, the analyses were conducted using 2 additional definitions applied in earlier studies (60) and based on modified adult criteria of the National Cholesterol Education Program-Adult Treatment Panel III (61). The definition of Cook et al. (62) includes ≥3 of the following factors: waist circumference ≥90th percentile, either systolic or diastolic blood pressure ≥90th percentile, triglyceride levels ≥110 mg/dL, HDL-cholesterol levels ≤40 mg/dL, and fasting plasma glucose levels ≥110. The definition of de Ferranti et al. (63) includes ≥3 of the following factors: waist circumference >75th percentile, systolic blood pressure >90th percentile, triglyceride levels ≥100 mg/dL, HDL-cholesterol levels <50 mg/d (except in boys aged 15 to 19 years (<45 mg/dL)), and fasting plasma glucose levels ≥110 mg/dL.

3.3. Statistical analyses

Cross-sectional analysis (Manuscript 2)

Quantitative data are shown as means and Standard Deviations (or in the cases of skewed data, medians and Interquartile Ranges). Absolute and relative frequencies are shown for categorical data. Two-sample t-tests were performed to determine group differences of means of continuous variables (in cases of skewed distributions, Mann–Whitney U-tests were conducted). Presented are 95% CI for differences in mean or median, the latter determined using the Hodges–Lehmann estimator, respectively. Because some variables differed significantly between boys and girls, the analyses were also performed stratified by sex. Fisher exact test was used to compare qualitative outcomes between severe and moderate obesity. Relationships between the variables representing glucose metabolism and the other cardiometabolic risk factors were examined by Spearman rank correlation coefficient. Relative differences between the

groups were calculated with moderate obesity as the reference group. As age and puberty are known to have an effect on relevant blood tests (e.g., insulin (64), leptin (65) and blood lipids (66)) as well as the degree of obesity, linear regression models were fit including obesity group, age, and Tanner stage as independent variables and relevant quantitative measures as dependent variables to determine the association of obesity level with measures of interest controlling for age and puberty status. All statistical tests were two-sided at a 5% significance level. Statistical analyses were carried out using the statistical software package PASW Statistics 18 (40).

Longitudinal analysis (Manuscript 3)

Descriptive statistics were first provided to summarize both demographics and study outcomes measured at each visit. Longitudinal data analyses were carried out using repeated measures mixed models to evaluate changes in HRQOL, BMI and PA from baseline to each follow up visit, adjusting for the baseline outcome, age and sex. The regression model has accounted for both repeated measurements on the same participant as well as unequal numbers of observations due to attrition over time. More specifically it used all observed data collected over time, with the missing information having no effect on other measures from that same participant. The random effect provides valid inferences when data are missing at random (MAR), which is a general assumption considered in most scenarios for analysis.

Multiple linear regression models were also used to assess the association of long-term changes (at 24 months) in PA and BMI on long-term changes of HRQOL, adjusting for baseline HRQOL measure, age, and sex. For regression analysis including long-term weight changes BMI was used instead of BMI-SDS as recommended by Cole et al. (67). Statistical tests appropriate to categorical and continuous variables were conducted to assess their associations.

All statistical tests were two-sided at a 5% significance level. The Tukey-Kramer method (68) was used to adjust for multiple comparisons as appropriate. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc. Cary NC) (26).

4. DISCUSSION

The hypotheses of this dissertation are that severely obese children have a more unfavourable cardiometabolic risk profile compared to moderately obese children and that an inpatient weight-loss program positively impact BMI, HRQOL and PA over the long-term (24 months).

The results of the cross-sectional analyses underscore the substantial effect of severe obesity on the health of children starting an inpatient program. These findings highlight the importance of the transition from moderate to severe obesity and point towards the need of effective treatment strategies.
Even it is a crucial requirement to optimize existing treatment strategies, the knowledge about the effectiveness of weight-loss programs in children and adolescents is sparse, particularly regarding long-term outcomes.
We found that the positive initial effects on BMI of an inpatient weight-loss program, which was conducted according to current German guidelines largely diminished over 24 months. A great amount of the children were not successful in reducing or maintaining their BMI over the long-term and the benefits on PA were observed for twelve and six months only. However, we found a significant improvement of HRQOL and particularly self-esteem up to 24 months after the completion of treatment.

4.1. The cardiometabolic risk of severe obesity-the need for effective treatment strategies

The results of the cross-sectional analysis showed that means for insulin and HOMA-IR were approximately 40-50% higher in individuals with severe (n=266) compared with moderate obesity (n=197). This demonstrates early signs of insulin resistance, which is one of the most important risk factors for MetS (69). The prevalence of MetS was three times higher in those with severe compared with moderate obesity according to all of the definitions used. This is in line with a study assessing children from Italy, which showed prevalence of 31% in the severely obese (n = 74) compared with 12% in the moderately obese children (n = 117) (3). A previous study by Weiss et al. (22) including children from North America, reported relatively high prevalence but smaller differences between

the obesity groups and 50% of severely obese (n = 195) and 39% of moderately obese children (n = 244) were considered having MetS. Both studies included on average 12 year old children, used obesity groups based on population or cohort specific z-scores and defined risk factors using BMI instead of waist-circumference as well as cut-offs for blood pressure and fasting lipid levels based on population specific z-scores. In addition, in these studies impaired glucose tolerance using an oral glucose tolerance test rather than elevated glucose levels was considered for classification of MetS. In our analysis fasting glucose levels were mainly in the normal range. The comparisons between different approaches to define paediatric MetS in the current analysis illustrate that using the International Diabetes Federation criteria lead to relatively low prevalence rates and that the results can vary widely between different populations and, importantly, depending on the respective definitions. However, the differences between the obesity groups remain similar.

In the current analysis, the greatest group differences were found for levels of leptin and hsCRP, which were about 1.5-fold higher in those with severe compared with moderate obesity. These differences are of clinical relevance because leptin is not only involved in insulin signalling, lipid metabolism, vascular function, and blood pressure regulation, but also directly affects the development of atherosclerosis (70, 71) and CRP has shown to be elevated even in the early phase of atherosclerosis (72). The potential involvement of the adipokines in the development of insulin resistance (70, 73) is supported by our data showing correlations between HOMA-IR and both levels of leptin and adiponectin. Although both IL-6 and TNF-α are known to be associated and also involved in systemic inflammatory status by directly stimulating CRP synthesis in the liver (38), we found a significant difference of 40% between the 2 obesity groups for IL-6, but no difference for TNF-α. IL-6 seems to be the main inducer of hepatic production of CRP, whereas TNF-α appears to have more local rather than systemic effects (74), which might explain both the lack of group differences, and often inconsistent results regarding this inflammatory marker (36).

There are some important limitations, which have to be considered regarding the interpretation of the results. Insulin resistance was not determined using oral

glucose tolerance testing, which is more sensitive to detect insulin resistance. An inclusion of functional measures of early atherosclerosis (e.g., endothelial dysfunction or intima media thickness) could have yielded further information of the effects on the vascular system dependent on the cardiometabolic and inflammatory profile. The children of the current study were referred to a specialized obesity treatment program. Therefore, the results may only be applicable to patients seeking medical weight management and may not be generalizable for the entire paediatric population.

It has to be considered that there is still no consensus on the definition of severe obesity and widely accepted international criteria are still required to distinguish between obese and severely obese children. Every definition system has its limitations and the results of prevalence rates will be different depending in the methods. For instance, the use of German reference values (4, 5) results in different prevalence rates of obesity than the international IOTF definition (3), which as used for our cross-sectional analysis. In our analysis, 59% of males and 55% of females being defined as BMI ≥35kg/m^2 according to the IOTF definition, whereas 57% of males and 68% of females were ≥99.5th percentile based on German reference values. Thus, it has to be noted that particularly the prevalence of severe obesity in girls may be underestimated in the international compared to the national approach (40).

4.2. Long-term effects of an inpatient weight-loss program

Changes in Body Mass Index

Mean body weight and BMI of the 707 participants at the start of treatment was 90.5±23.9 kg, and 33.5±6.1 kg/m^2, respectively. One half of the children were classified as severely obese at the start of the program according to international criteria (2, 3). During the weight-loss program every participant was successful in losing body weight and mean BMI was 11% lower at discharge compared to baseline (-3.8 kg/m^2; 95% CI -3.85 to -3.76; $p<0.001$). This finding is promising, especially when considering that the treatment was non-pharmacological and of relatively short duration (4-6 weeks). For instance, the BMI reduction of the current study was about 31% greater compared to

similar studies investigating inpatient treatment programs of comparable duration (43).

Regarding the follow-up period there was a steadily increase in BMI. BMI was significant lower than baseline at all follow-up time points, and at 24 months it was still 0.5 kg/m^2 (95% CI. -0.92 to -0.02; p=0.04; n=307) lower than baseline. For BMI-SDS, there was found an improvement of ≥0.25 at six and 12 months, which is considered sufficient to reduce metabolic risk in children (75). However, with a mean reduction in BMI-SDS of 0.2, this was not achieved at 24 months. All over, the magnitude of the difference of BMI was small and a quarter of the participants were still severely obese after 24 months. These results emphasize that weight control over time is still a very challenging issue.

To the best of our knowledge, there are only two previous studies reporting on long-term effects after inpatient weight-loss treatment (≥24 months). In one study (76) the effect of a 10 months inpatient weight-loss program with follow-up measurements after 24 months evaluated. The authors observed a decrease in per cent-overweight by 29%. Braet and Van Winckel (47) investigated the effect of 10-day inpatient treatment with follow-up measurements after 4.6 years. They reported a decrease in per cent-overweight by 12%. For comparison, in the current analysis the reduction in per cent-overweight over 24 months was approximately 8%. It should be noted, however, that there are important differences in design between studies, i.e. a longer period of inpatient treatment (10 months vs. 4-6 weeks) (76) and a considerably higher BMI reduction during treatment (-8.6 kg/m^2 vs. -3.8 kg/m^2). Braet and Van Winckel (47) offered ten days of inpatient treatment, but had additional monthly outpatient cognitive behaviour therapy for one year following discharge. It is likely that their observed effect decreases some time after termination of outpatient treatment which is indicated by another study including outpatient care (77) (26, 78).

Changes in health-related quality of life

In agreement with previous studies (23, 25, 55), baseline HRQOL of this clinical sample of overweight and obese participants was impaired. The mean values of overall HRQOL were seven points lower compared to a reference sample of more than 6,000 11-17 year old German children and adolescents (79). Also in

line with previous studies, overall HRQOL and all domains improved immediately after participation in a weight-loss program of relatively short duration (55, 80) and most of the domains improved over the medium-term (12 months) (81). At 24 months, there were still significant (albeit small) improvements in overall HRQOL and most domains compared to baseline. The greatest improvements were observed for self-esteem. For this domain, the mean value at 24 months was only 1.2 points lower than the representative German sample (79). This is a very important finding, as improvement in self-esteem in children has been suggested to prevent the development of emotional and social problems later in life (82). Similar improvements in self-esteem have been found following inpatient treatment of much greater duration (10 months) in previous research (76), which suggests that our shorter duration treatment may be just as efficacious in this regard. Unexpectedly, the family domain scores decreased at follow-up so that values at six, 12 and 24 months were all below baseline. Similar results were also observed by Jozefiak and co-workers, who suggested that such changes may be development-conditioned and age-dependent. In their study, more than 1,000 healthy school children were observed over six months. The grade eight students (aged 12-14 years) reported a greater decrease in HRQOL compared to the grade six students (aged 10-12 years) in the domains family and school, and in overall HRQOL. The authors concluded that this might be caused by greater autonomy during early adolescence and puberty (83). In our study, age was not a significant confounder for long-term changes in HRQOL. Within the inpatient program the children gain knowledge about healthy living and learn how to change their behaviour, with little or no parental involvement. Therefore, one further potential explanation for the decrease in the family domain scores may be deficient parental support in the implementation of health principles into the home environment (26).

Changes in physical activity

The largest improvement of PA occurred during inpatient treatment, with the effects attenuating over time. By 24 months, PA was not significantly different from baseline.

There are only few studies, which have evaluated PA levels following weight-loss treatment including follow-ups of six to 12 months. For instance, Adam et al. (84) investigated PA behaviour of eight to 15 year old obese children who participated in a study including inpatient treatment for six weeks followed by outpatient treatment for 10.5 months. At follow-up which took place six months after baseline, no difference was observed in the self-reported number of days per week on which children engaged in PA for at least 20 minutes between the intervention and the control group. However, the number of participants reporting regular PA increased in the intervention but not the control group (84). Hoffmeister et al. investigated the effect of various inpatient and outpatient rehabilitation programs in Germany on the PA behaviour of children aged eight to 17 years old following treatment. They also found no significant difference between baseline and a follow-up 12 months after termination of the intervention in the days per week being physically active of at least 60 minutes (44). Larger effects were observed in a study by van Egmond-Fröhlich et al, who observed self-reported weekly PA time and leisure time activity of obese nine to 16 year-olds to be approximately 30% and 50% higher at the 12-month follow-up compared to the start of six weeks of inpatient treatment (85). However, this study included outpatient counselling up to 12 months after baseline, which was web-based or offered by a GP. This study emphasises that a combination of inpatient and outpatient treatment might be a successful strategy for long-term behavioural change (78).

Associations between long-term changes in health-related quality of life, body mass index and physical activity

The results of the current analysis indicate that changes in PA levels were positively associated with the changes in overall HRQOL and the domains friends and physical well-being, while changes in BMI were not associated with any of the HRQOL domains. However, the study design does not allow for inference of causality, and without a concurrent control group to compare with, this before-after analysis may be confounded by other factors which influence the relationship between PA levels and HRQOL. For example, children who have a lower HRQOL due to comorbid diseases might be not able to engage in

as much in PA as do healthier obese children. Additionally, both HRQOL and PA are self-reported measurements while BMI is not. Thus the self-reported data might be subjected to the same perception bias to respond in a socially desirable way.

An important strength of this longitudinal analysis is the long follow-up period of 24 months. Other studies in this area are mostly cross-sectional or have short follow-up durations of a maximum of one year (81). All anthropometrical measurements were taken by either a nurse or a GP, which has obvious advantages compared to self-reports (86). HRQOL was assessed by a well-validated obesity and child specific questionnaire, which was originally developed for German children and adolescents, but is also available and validated in English.

However, this analysis also has some important limitations, which need to be considered. The LOGIC-trial is not a randomized controlled trial as it was felt to be ethically questionable to randomize treatment-seeking overweight and obese individuals into a no treatment or wait-list control. Thus, the results cannot give evidence about the direction of the causality. Moreover, it is difficult to control for the effect of developmental factors on changes in HRQOL and PA. Nevertheless, significant changes were evident after adjustment for age. PA was assessed by questionnaire, although objective measurement (e.g. accelerometers) would have been the superior method. However, logistical issues prevented the use of an objective method in this study. The most important limitation is that the long-term outcome of half of the original sample of more than 700 participants is unknown due to the relatively high loss to follow-up. Fifty-four percent of the baseline sample sent back questionnaires and/or examination sheets at 24 months. This may be due to the objective and therefore more time consuming data assessment at the children's GP as well as the wide spread of participants residing over Germany, Austria, Belgium and France which made follow-up of non-responders difficult. Dropout rates of similar studies including a follow-up after paediatric obesity intervention range from 10% (self-reported BMI, n=122, two year follow-up) (76) to 47% (participants returned to study centre, n=194, 10 months follow-up) (87). An important consideration of the loss to follow up is that participants who withdraw

from the study may differ in important ways from individuals who participate on the follow-up procedures, e.g. may experience poorer outcomes on quality of life, body composition or related health behaviours (26).

4.3. Conclusion

The outcomes of the cross-sectional analysis underscore the deleterious effect of severe obesity on health of children and highlight the importance of the transition from moderate to severe obesity. These findings will hopefully increase awareness of the especially high risk of severe obesity and the need to prevent the occurrences of it and for enrolment in intensified obesity treatment programs for those with established severe obesity.

However, to reasonably improve the treatment of childhood obesity, existing weight-loss programs need to be evaluated. The findings of the longitudinal analysis confirm that inpatient weight-loss programs are effective in the short term regarding weight-loss as well as improvements in HRQOL and PA. Furthermore, HRQOL of our sample, and particularly self-esteem remained improved over the long-term after the completion of 4-6 weeks of inpatient weight-loss treatment. However, the results indicate that weight control and behaviour change over time is still a very challenging issue and cost-effective after-care strategies, e.g. in an outpatient setting need to be urgently developed and applied that help to improve the long-term effectiveness of inpatient treatment in children. Thereby, lifestyle factors such as PA need to be considered, as they seem to impact the improvement of HRQOL rather than weight changes over time.

5. ABSTRACTS

Manuscript 1: "*Long-term effects of an inpatient weight-loss program in obese children and the role of genetic predisposition-rationale and design of the LOGIC-trial" (17)*.

This manuscript describes the rationale and design of the LOGIC-trial (**L**ong-term effects of lifestyle intervention in **O**besity and **G**enetic **I**nfluence in **C**hildren). The purpose of this study is to evaluate the short, middle and long-term effects of an inpatient weight-loss program for children and adolescents and to investigate the likely determinants of weight changes, whereby the primary focus lies on the potential role of differences in polymorphisms of adiposity-relevant genes. The study involves overweight and obese children and adolescents aged 6 to 19 years, who participate in an inpatient weight-loss program for 4 to 6 weeks. It started in 2006 and it is planned to include 1,500 participants by 2013. The intervention focuses on diet, physical activity and behavior therapy. Measurements are taken at the start and the end of the intervention and comprise blood analyses (DNA, lipid and glucose metabolism, adipokines and inflammatory markers), anthropometry (body weight, height and waist circumference), blood pressure, pubertal stage, and exercise capacity. Physical activity, dietary habits, quality of life, and family background are assessed by questionnaires. Follow-up assessments are performed 6 months, 1, 2, 5 and 10 years after the intervention. Apart from illustrating the short, middle and long-term effects of an inpatient weight-loss program, this study will contribute to a better understanding of inter-individual differences in the regulation of body weight, taking into account the role of genetic predisposition and lifestyle factors.

Melanie Heitkamp has written, submitted and revised the manuscript. She is active investigator of the study and coordinates the study since 2009. She has recruited about 700 study participants and she has followed up the children at different follow-up time points between 2008 and 2013.

Manuscript 2 "*The cardiometabolic risk of moderate and severe obesity in children and adolecents" (40)*

The aim of this cross-sectional analysis was to compare the cardiometabolic risk profile between moderately obese and severely obese children and adolescents participating at the LOGIC-trial. The analysis involved 463 obese 6- to 19-year-olds who were referred to an inpatient weight-loss program. Anthropometric data were assessed and fasting blood samples were analyzed for lipid and glucose metabolism, adipokines, and inflammatory markers. Moderately obese individuals (percentiles corresponding to body mass index ≥30 to 35 kg/m2 at age 18 years; n=197) and severely obese individuals (percentiles corresponding to body mass index ≥35 kg/m2 at age 18 years; n=266) were defined by sex and age-specific cut-offs according to the International Obesity Task Force.

The results of the analyses indicated that the prevalence of the MetS was three times higher in severely obese individuals compared with those who are moderately obese. Mean values for proinsulin, insulin, homeostatic model assessment-insulin resistance, triglycerides, and interleukin-6 were 30%-50% higher in severe obesity compared with moderate obesity. Concentrations of leptin and high-sensitive C-reactive protein were about 1.5-fold higher, adiponectin levels were 12% lower, and resistin levels 10% higher in severely obese individuals compared with moderately obese (all $p<0.001$). These data show that severely obese individuals have a markedly more unfavourable cardiometabolic risk profile than those who are moderately obese. The results underscore the substantial effect of severe obesity on health and highlights that these children need to receive particular attention regarding obesity treatment.

Melanie Heitkamp has written, submitted and revised the manuscript. She has the idea of the research question. She has recruited a large amount of the children, who were included in these analyses. She conducted the statistical analyses in collaboration with the Institute for Medical Statistics and Epidemiology, Klinikum rechts der Isar, Technische Universität München.

Manuscript 3: "***Health-related quality of life and physical activity in children and adolescents two years after an inpatient weight-loss program" (26)***

The aim of this prospective longitudinal analysis was to investigate changes in health-related quality of life (HRQOL) of children and adolescents 24 months after an inpatient weight-loss program, and examine concurrent changes in body mass index (BMI) and physical activity (PA). The analysis included 707 overweight and obese 14±2 year olds (57% girls) participating in a 4-6week inpatient weight-loss program, of whom 381 completed a 24 month follow-up. HRQOL, PA and BMI were assessed at baseline, discharge, and six, 12 and 24 months after starting therapy. Longitudinal analyses were conducted using repeated measures mixed models, adjusted for age, sex and baseline outcome and accounted for attrition over time. The results showed that, at 24 months, overall HRQOL indicated significant improvements relative to baseline (3 points on a 0-100 scale; 95% CI. 1.68 to 4.47; $p<0.001$). Of the six HRQOL domains, the greatest improvement was observed for self-esteem (11 points; 95% CI. 8.40 to 13.14; $p<0.001$). BMI was 0.5 kg/m2 lower than baseline (95% CI. -0.92 to -0.02; $p=0.04$). Long-term changes in PA explained 30% of the variation in overall HRQOL ($p=0.01$), while change in BMI was not associated with change in HRQOL. The results of these analyses indicate that in this sample of overweight and obese children and adolescents, HRQOL and particularly self-esteem remained improved up to 24 months after the completion of the inpatient weight-loss treatment. However, the small improvement of BMI over the long-term emphasize that weight control over time is still a very challenging issue and underlines the need of optimizing existing therapy programs. Furthermore, the results of the study indicate the potential role of PA in improving HRQOL without a substantial change in body composition. This highlights the importance of considering lifestyle behaviours such as PA, as well as weight reduction, in paediatric obesity treatment.

Melanie Heitkamp has written, submitted and revised the manuscript. She has recruited a large amount of the included children. She was substantially involved in data collection, interpretation and analyses.

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7. ADDENDUM

Manuskripte:

(1) Rank M, Siegrist M, Wilks DC, Haller B, Wolfarth B, Langhof H, Halle M: Long-term effects of an inpatient weight-loss program in obese children and the role of genetic predisposition - Rationale and design of the LOGIC-trial. **BMC Pediatr**, 2012, Mar 19;12 (1):30.

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BMC Pediatrics

STUDY PROTOCOL Open Access

Long-term effects of an inpatient weight-loss program in obese children and the role of genetic predisposition-rationale and design of the LOGIC-trial

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Abstract

Background: The prevalence of childhood obesity has increased worldwide, which is a serious concern as obesity is associated with many negative immediate and long-term health consequences. Therefore, the treatment of overweight and obesity in children and adolescents is strongly recommended. Inpatient weight-loss programs have shown to be effective particularly regarding short-term weight-loss, whilst little is known both on the long-term effects of this treatment and the determinants of successful weight-loss and subsequent weight maintenance. The purpose of this study is to evaluate the short, middle and long-term effects of an inpatient weight-loss program for children and adolescents and to investigate the likely determinants of weight changes, whereby the primary focus lies on the potential role of differences in polymorphisms of adiposity-relevant genes.

Methods/Design: The study involves overweight and obese children and adolescents aged 6 to 19 years, who participate in an inpatient weight-loss program for 4 to 6 weeks. It started in 2006 and it is planned to include 1,500 participants by 2013. The intervention focuses on diet, physical activity and behavior therapy. Measurements are taken at the start and the end of the intervention and comprise blood analyses (DNA, lipid and glucose metabolism, adipokines and inflammatory markers), anthropometry (body weight, height and waist circumference), blood pressure, pubertal stage, and exercise capacity. Physical activity, dietary habits, quality of life, and family background are assessed by questionnaires. Follow-up assessments are performed 6 months, 1, 2, 5 and 10 years after the intervention: Children will complete the same questionnaires at all time points and visit their general practitioner for examination of anthropometric parameters, blood pressure and assessment of pubertal stage. At the 5 and 10 year follow-ups, blood parameters and exercise capacity will be additionally measured.

Discussion: Apart from illustrating the short, middle and long-term effects of an inpatient weight-loss program, this study will contribute to a better understanding of inter-individual differences in the regulation of body weight, taking into account the role of genetic predisposition and lifestyle factors.

Trial Registration: NCT01067157.

Keywords: Lifestyle intervention, Polymorphism, Follow-up, Adipokines, Inflammation, Fitness

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Background

The global increase in childhood overweight and obesity is a serious health concern [1], as it often tracks into adulthood [2] where it is associated with numerous cardiovascular and metabolic risk factors such as hypertension, type 2 diabetes or hyperlipidemia and even cardiovascular disease [3,4]. In addition, even at young age, overweight and obesity are related with various physical and psychological comorbidities. For instance, it has been found that overweight and obese children and adolescents often suffer from elevated blood pressure, dyslipidemia or disorders of glucose metabolism [5], and have a lower quality of life compared to healthy normal weight children [6].

Obesity and inflammation

The link between adiposity and the development of metabolic and cardiovascular diseases may be seen in obesity-related systemic inflammation [7,8]. Hypertrophy and hyperplasia of the adipose tissue as seen in obesity result in a dysfunction of the adipocytes [9], which increases inflammation and impairs hemostasis, glucose as well as lipid metabolism [7,8]. This is triggered by an alteration of the secretion of the adipokines adiponectin, leptin, retinol binding protein 4 (RBP4) and resistin as well as inflammatory markers such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP). For example, a decrease in adiponectin and an increase of RBP4 as often found in obese individuals may foster the development of insulin resistance. Furthermore, elevated levels of RBP4, IL-6 and TNF-α increase the inflammatory status by directly stimulating CRP synthesis in the liver [9].

In contrast, physical activity and/or weight-loss seem to have a positive impact on these mechanisms by improving the inflammatory status and reducing insulin resistance. However, data concerning these mechanisms in children are scarce and results from the existing studies have been inconsistent [9,10]. In addition, simultaneous measurements of adipokines, inflammatory markers, and cardiovascular risk factors of obese children before and after a short-term lifestyle intervention and at a long-term follow-up during late adolescence or adulthood have not been performed before.

The role of genes

Weight gain due to an increase in adipose tissue is the result of an imbalance between energy expenditure and energy intake. This balance can be influenced by both physical activity and caloric intake, which can be dependent on social, psychological and other behavioral factors. In addition, genes have been shown to play a fundamental role in the regulation of body weight [1,11]. Apart from very rare monogenetic disorders [12], a genetically determined higher risk for obesity can often be attributed to a polygenetic pattern involving different single nucleotide polymorphisms (SNP's). For instance, variations in the *FTO*-gene seem to have an effect on the development of early onset obesity. Likewise, a study by Frayling et al. has shown that a single-nucleotide polymorphism of the SNP *rs9939609*A allele is associated with an increased risk of overweight (odds ratio 1.18; 95% CI = 1.13 to 1.24) and obesity (odds ratio 1.31; 95% CI = 1.23 to 1.39), increasing the risk by 20-30%. Additionally, the A allele of the *rs9939609 SNP* has been found to be associated with an increased body mass index (BMI) in 7 year old children and to also determine obesity during puberty and beyond [13]. Furthermore loci associated with neuronal pathways (*TMEM18, GNPDA2, SH2B1, NEGR1*) have recently been identified to be associated with childhood obesity [14]. It has to be noted though that these genetic predispositions may only lead to an obesity phenotype in the presence of an obesogenic environment, and therefore this association may be modified by a lifestyle intervention [15,16].

Lifestyle interventions to treat childhood obesity

Due to the tremendous short and long-term health consequences, current recommendations strongly encourage the treatment of childhood obesity, which may be performed in an outpatient or an inpatient setting (e.g. residential or weight-loss camps), or by a combination of both. However, the effectiveness of these types of programs remains uncertain [17]. In a recent review by Kelly and Kirschenbaum the average decrease in percent overweight within inpatient treatment across 11 studies was reported 23.9% from pre to post-intervention and 20.6% from pre-intervention to follow-up, whereas the effect on percent overweight was 8.5% and 8.9% for outpatient programs, respectively [18]. Within the EvAKuJ-study (Evaluation of obesity treatment in children and adolescents study) the short and long-term effects of different German childhood-obesity programs were assessed [19]. The authors reported that five out of 48 programs included took place in an inpatient setting (875 patients), whereas all others were carried out in an outpatient setting (1,041 patients). Children participating in inpatient programs achieved a mean reduction in BMI-SDS (BMI standard deviation score [20,21]) of -0.36 during the treatment and of -0.17 during the observational follow-up 1-2 years after termination of the treatment, whereas this was -0.18 and -0.21 for outpatient programs, respectively [19]. In summary, the results of inpatient versus outpatient programs are equivocal especially regarding long-term effectiveness.

Furthermore, as presented above, very few inpatient treatment programs have been evaluated, and these studies are heterogeneous regarding their study design and overall quality. For instance, the treatment duration ranges from 10 days to 10 months and only 29% of the studies included a follow-up period. The range in follow-up duration also varies dramatically (4 months to 4.6 years) and about half (46%) of the studies performed a follow-up after less than 1 year [18,22,23]. A study by Braet and van Winckel is the only one with a follow-up period of more than 3 years from the start of the intervention, however, they have not carried out blood analyses and the sample size of their inpatient treatment group was rather low [24].

These results emphasize that inpatient treatment might be the most effective strategy for children to loose body weight in the short-term, but that there is a substantial need for intervention studies with considerably longer duration of follow-up and a standardized protocol of the intervention and analyses. In addition, only very few studies have reported on the influence of lifestyle intervention in obese children whilst considering genetic predisposition [25-30].

Methods/Design

Objectives

To investigate the determinants for short, middle and long-term weight-loss and weight maintenance, a prospective cohort study involving overweight and obese children and adolescents (hereafter referred to as 'children') is being conducted, which includes a short-term inpatient weight-loss program complemented by a long-term observational follow-up over 10 years. Measurements include anthropometric, cardiometabolic and genetic parameters as well as assessment of physical activity and fitness, dietary habits and quality of life.

Primary endpoint

The associations between polymorphisms in adiposity-relevant genes (e.g. *FTO, MC4R, TMEM-18*) on the changes in BMI and BMI-SDS after a controlled lifestyle intervention (4 to 6 weeks) in overweight and obese children and adolescents.

Secondary endpoints

The short (4 to 6 weeks), middle (6 to 12 months) and long-term (2, 5 and 10 years) effects of the intervention on the below-listed parameters and their associations with polymorphisms in adiposity-relevant genes (*e.g. FTO, MC4R, TMEM-18*):

- anthropometric parameters
- parameters of lipid and glucose metabolism
- adipokines and inflammatory markers
- physical fitness
- physical activity
- dietary behavior and intake
- health-related quality of life

Participants

Participants of the LOGIC-trial (**L**ong-term effects of lifestyle intervention in **O**besity and **G**enetic **I**nfluence in **C**hildren) are 6 to 19 year old overweight and obese children, who are referred to the rehabilitation center *Klinik Schönischt* in Berchtesgaden, Germany by their local pediatrician to have inpatient weight-loss treatment. The clinic is specialized on childhood obesity and about 200 children with the primary diagnosis overweight/obesity are being treated here annually.

Children are admitted to the clinic on a biweekly basis and recruited consecutively by scientists from the *Department of Prevention, Rehabilitation and Sports Medicine, Technical University of Munich*. In case they fulfill the inclusion criteria (see Table 1), assent and informed consent for study participation are obtained from the children and their accompanying legal guardians.

The study is conducted according to the declaration of Helsinki (Seoul, 2008) and approved by the ethics committee of the Faculty of Medicine of the Technische Universität München, Germany (1354/05).

Recruitment process

Recruitment for this collaborative study began in January 2006 with the aim to include a total of 1,500 participants by 2013. Figure 1 shows the flow chart of the recruitment and the measurement process.

Table 1 Inclusion and exclusion criteria for participation in the LOGIC-trial

	Inclusion criteria	Exclusion criteria
Eligibility criteria for attending the inpatient weight-loss program at the *Klinik Schönsicht*	Overweight (BMI 90.-97th percentile), obese (BMI 97.-99.5th percentile) or severely obese (BMI > 99.5th percentile) Repeated failure to accomplish weight-loss in outpatient therapies	Considerable mental or physical disability Severe personality disorders Suicidal behavior Drug addiction
Eligibility criteria for LOGIC-trial participation	Written informed consent by participant and a legal guardian	Obesogenic diseases and disorders such as the Prader-Willi Syndrome, Cushing Syndrome Early withdrawal from the inpatient program (< 3 weeks)

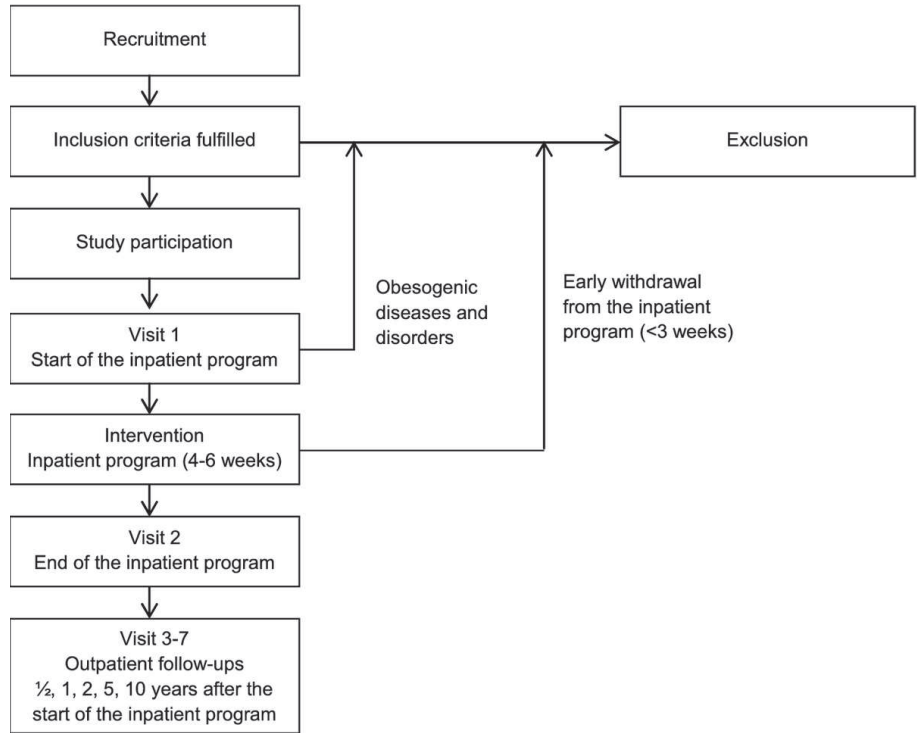

Figure 1 Study flow chart of the LOGIC-trial.

Examinations are performed at the start (Visit 1) and at the end of the intervention (generally after 4 to 6 weeks; Visit 2) at the clinic. Follow-up examinations are performed at 6 months (Visit 3), 1 year (Visit 4), 2 years (Visit 5), 5 years (Visit 6) and 10 years (Visit 7) after the start of the intervention by either local pediatricians or general practitioners (Figure 1).

Intervention

The rehabilitation clinic is primarily focused on inpatient treatment for childhood overweight and obesity which typically lasts for 4 to 6 weeks. The duration of the stay depends on health insurance allowance and the severity of obesity. Typically the children are referred to the clinic for 4 weeks and in case of severe obesity or comorbidities they have the opportunity to extend the program. The standardized multimodal program focuses on a calorie restricted balanced diet, an increase in physical activity and behavioral counseling. It is conducted by an interdisciplinary team of pediatricians, exercise physiologists, dieticians, psychologists and pedagogues according to German guidelines for inpatient weight-loss programs (AGA, Arbeitsgemeinschaft Adipositasim Kindes- und Jugendalter) [31].

The children are offered an optimized balanced diet prepared according to current guidelines (30%, 15% and 55% of the total energy content from fat, proteins and carbohydrates, respectively), with an allowed energy intake of 1,250-1,800 kcal[a] per day, depending on height and sex (Table 2) [32]. The components of the intervention program are shown in Table 3. In brief, the children are required to participate in theoretical and practical lessons on healthy eating, physical activity and behavior change skills based on the cognitive-behavioral theory. The exercise therapy consists of approximately 10 h of organised physical activity per week,[b] in addition to 6 hours of recreational exercise.

Measurements

An overview of all measurements at the different time points (Visits 1-7) is presented in Table 4. During the inpatient treatment, the physical examination is performed on the day of admission and on the day of discharge. Blood samples are taken on the third day after admission to the clinic and 3 days before discharge (except for DNA samples, which are taken only at baseline). Physical fitness testing is performed and questionnaires are filled in on the first weekend after admission to the clinic and 1 to 2 days before discharge. In case children extend the treatment, all examinations are being conducted after 6 weeks. Questionnaires are filled in without supervision.

Physical examination

Body height is measured barefoot to the nearest 0.5 cm by a rigid stadiometer. Body weight is measured with

Table 2 Calculation of the allowed energy intake based on body height and sex

Boys		Girls	
Height [cm]	Energy intake per day [kcal]	Height [cm]	Energy intake per day [kcal]
≤ 145	1250	≤ 155	1250
146-170	1500	156-180	1500
≥ 171	1800	≥ 181	1800

minimal clothing to the nearest 0.1 kg by a digital scale (Visit 1 and 2: *Tanita BC-420 P MA Profi, Tanita Europe B.V.*, Hoofddorp, The Netherlands; Visits 3-7: calibrated scale). Waist circumference is measured on bare skin by tape to the nearest 0.1 cm midway between the lower rib margin and the iliac crest in standing position after normal exhalation with a non-stretchable tape measure. Blood pressure is measured at the right brachial artery in the fossa cubitalis after the children have been resting for 5 min in supine position by using a validated protocol [33]. Pubertal development is determined according to Marshall and Tanner [34,35]. Data on the medical history are documented including current medication and comorbidities (orthopedic complications, attention deficit (hyperactivity) disorders, thyroidal diseases, asthma, metabolic diseases, psychological diseases, acute diseases). All inpatient examinations and assessments are conducted by trained medical staff according to standardized procedures.

Blood samples

Blood sampling is performed following a 10 hour overnight fast. Samples are taken by venipuncture of an antecubital vein in either a sitting or lying position using vacuum tubes. Both plasma and serum samples are stored at -80°C until analyzed. The following parameters will be analyzed from serum: high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, triglycerides, glucose, proinsulin, insulin, uric acid, TSHbasal, adiponectin, leptin, RBP4, resistin, high sensitive CRP, IL-6 and TNF-α.

Genetic analysis

Genomic DNA for all subjects is stored at -20°C after isolation from EDTA blood following a standard protocol. In a first step several SNPs were selected from HapMap CEU data (release 21 phase II, dbSNP 125) including SNPs with minor allele frequencies > 5% in genes of interest for the phenotypes available (e.g. body weight, physical fitness, risk factor profile). In a first step, genotyping was performed using the *MassARRAY* system with *iPLEX™ Gold* chemistry (*Sequenom*, San Diego, CA, USA). The samples were analyzed in a matrix-assisted laser desorption ionisation time of flight mass spectrometer (*MALDI TOF MS, BrukerDaltonik*, Leipzig, Germany). Further analyses will be performed using state of the art genotyping methods.

Physical activity and cardiovascular fitness

Physical activity is assessed by a questionnaire and by pedometers. Cardiovascular fitness is assessed by both cycle ergometry and a 6-Minutes running test.

The physical activity questionnaire has been adapted to the MOMO questionnaire, which has been previously validated [36,37]. Items of the questionnaire include volume, frequency, duration and intensity of school, sports clubs and/or leisure time activities, motivation to be physically active [38] as well as questions on sedentary time (screen time and homework). Between 2008 and 2010 all study participants were asked to wear a pedometer (*OMRON Walking Style Pro)* all day for 2 to 4 weeks during their inpatient stay at the clinic. They also completed a physical activity diary for these days.

Exercise testing is performed stepwise on a cycle ergometer (*Jaeger ERGOSTESTER 900*) to the participants' volitional exhaustion. Absolute or relative exercise capacity (Watt, Watt/kg) is used as a measure of cardiovascular fitness. Since 2008 the study participants have been taking part in a 6 min running test. For this test, which takes place on a straight outdoor sports ground, the children are asked to walk or run as far as possible within 6 min. The covered distance is documented in metres.

Diet

For the assessment of dietary intake, a food frequency recall is used, which has been validated previously in a survey [39].

Quality of life

To assess quality of life, the validated German KINDL^{R}-questionnaire [40,41] with six dimensions ("physical well-being", "emotional well-being", "self-esteem", "friends", "family" and "everyday functioning (school)") is being used. The subscales of these six dimensions are combined to a total score. Furthermore, an additional sub-scale, developed specifically to assess the quality of life of overweight children, is being used, which consists of a filter question and six items. The reliability and validity of this questionnaire have been described elsewhere [41].

In addition, a standardized questionnaire that is supposed to be completed by the parents on the day of admission is being used to obtain demographic information as well as obesity-related health history of first degree family members.

Table 3 Components of the inpatient weight-loss program

Intervention component	Items	Description	Aims	Frequency/Dose
Structured physical activity (10 h/week)	Therapeutic sports	Different types of outdoor activities such as ascending stairs, road running and cross country runs etc.	Endurance training according to individual abilities	2x/week à 60 min
	Swimming	Lane swimming ~1.000 m	Endurance training; Learning/improving swimming technique	1x/week à 50 min plus the 6 km walk to the pool (~3 km downhill, 3 km uphill)
	Group sports	Different physical activities (e.g. ball games, dancing and gymnastics)	Focus on playing and having fun	1x/week à 45-90 min
	Postural training	Strength training: gymnastics, dumbbells, stretch bands, etc.	Strength training to achieve or maintain good posture	1x/week à 45 min
	Hiking	10-12 km hikes in the mountains	Endurance training with nature experience	1x/week à 3 h
Non structured physical activity (~6 h/week)	'Fun- Walk'	Walking to the town centre (~1 km downhill, 1 km uphill); Time for individual activities	Endurance training, having fun	1x/week à 2 h (in total)
	Excursions	Various excursions and activities like playing miniature golf, sightseeing, table tennis tournaments, etc.	Having fun, group activities to improve social skills	Dimension of physical activity varies; within 4 weeks of intervention, it accounts for 6 h/ week
Obesity patient training courses (16 sessions within 4 weeks)	Psychotherapy	• Developing rules for healthy eating behavior • Rigid versus flexible dieting	Improving self-esteem and body perception, prevention of relapse.	5 session within 4 weeks à 45 min
		• Recognition of signs of both hunger and satiety • Learning to enjoy food as well as to cope with difficult situations		
		• Developing motivation for participating in regular physical activity		
		Individual sessions if the children suffer from psychosomatic, psycho-vegetative and/or psychological diseases	Treating individual psychological problems	1-3 individual sessions à 45 min/ week
	Nutritional lessons	Teaching children to choose the appropriate (amount of) food according to their personal needs	Enabling the children to prepare healthy food for themselves	5 sessions within 4 weeks à 45 min
	Physical education	Improving knowledge on energy balance, effects and limitations of physical activity, measures of self-control and good posture	Increase knowledge of the effects of physical activity to support adherence to the regular physical activity recommendations	4 sessions within 4 weeks à 45 min
	Medical education	Improving knowledge on medical background of overweight and obesity (normal/ideal weight, BMI, comorbidities etc.)	Increase knowledge of the medical consequences of overweight and obesity and promote a realistic goal setting	2 sessions within 4 weeks à 45 min
Social competence	Training sessions	• Training for conflict resolution, communication, ability to offer and receive criticism, body language, self-assurance, empathy etc. • Role playing • Concentration training	• Development of emotional-cognitive abilities • Development of occupational skills • Reflecting on and improving social behavior skills	1x/week à 45 min
Nutrition	Cooking	Cooking as a creative activity and a positive group experience	Transfer of theoretical knowledge into practice	1x/week, 2 h
	Lessons for grocery shopping	• Learning how to read packaging labels correctly (e.g. sample sizes, nutritional information) • Learning how to make educated nutritional decisions about potentially misleading products (e.g. 'organic')	Enabling the children to judge different food products correctly	1x/week, 90 min

Table 3 Components of the inpatient weight-loss program *(Continued)*

Parents	Supportive training	Parents receive background information on obesity and advice about how to best support their child. In addition, they are requested to take their child to subsequent outpatient psychological treatment. They also receive special handouts about healthy living, including nutrition, physical activity, media consumption etc.	Improving parental support of the children after conclusion of the inpatient program	Two conversations with the physician (at the start and the end of intervention. In special cases, parents are contacted by telephone)
School	Theoretical lessons	German, English and Mathematics	Keeping the children current with the appropriate educational curriculum	Groups 3 and 4: 5x/week à 45 min Groups 1 and 2: 6x/week à 45 min

Follow-up (Visits 3 to 7)

Visits 3, 4 and 5

Prior to the first follow-up examination, which takes place 6 months after the start of the program (Visit 3), study investigators contact the general practitioners by telephone to inform them about the study procedures and to obtain agreement on carrying out the upcoming follow-up examinations. The general practitioners are asked to complete and return a standardized examination sheet including anthropometric measurements (body weight, height and waist circumference), blood pressure and Tanner stage as well as comorbidities and the current use of medication.

In addition, study investigators contact the children prior to each visit (6 months, 1 year and 2 years after the start of the intervention) to remind them of the upcoming examination and to enquire about possible address changes. The children are requested to complete the questionnaires, previously sent by post, and to return them using the provided prepaid envelope as well as to visit their general practitioner for the follow-up examination. If both the questionnaires and the

Table 4 Overview of the data collection from visit 1 to visit 7

Setting	**Inpatient intervention**		**Outpatient follow-ups**			**(In/)outpatient follow-ups**	
VISIT	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**	**VISIT 6**	**VISIT 7**
Time point	**Intervention start**	**Intervention end**	**1/2 y**	**1 y**	**2 y**	**5 y**	**10 y**
Physical examination							
Anthropometry*	+	+	+	+	+	+	+
Pubertal stage (Tanner)	+		+	+	+	+	+
Comorbidities/Medication	+	+	+	+	+	+	+
Genetic and blood parameters							
Collection of EDTA	+						
All blood parameters**	+	+				(+)	(+)
HDL, LDL, total cholesterol, triglycerides, glucose	+	+				+	+
Physical fitness and activity							
Physical fitness (ergometry)	+	+				(+)	(+)
6-Minutes running test	+	+				(+)	(+)
Pedometer***	+					(+)	(+)
Questionnaires (filled in by children)							
Quality of life (KINDL)	+	+	+	+	+	+	+
Diet/Dietary intake	+	+	+	+	+	+	+
Physical activity	+	+	+	+	+	+	+
Questionnaire (filled in by parents)							
Family background	+						

*body weight, body height, waist circumference, blood pressure.

**HDL, LDL, total cholesterol, triglycerides, glucose, proinsulin, insulin, uric acid, TSHbasal, adiponectin, leptin, RBP-4, resistin, high sensitive CRP, IL-6, TNFα.

***subgroup analysis.

examination sheet are returned to the study centre, the children will receive an allowance of 10 Euros.

Visits 6 and 7

For the 5 and 10 year follow-up examinations, the children are invited to visit the study centre at the *Department of Prevention, Rehabilitation and Sports Medicine, Technical University of Munich*, where the same measurements as at baseline (Visit 1) are planned to be obtained (except for DNA and family history). Children, who are not able to visit the study centre, have blood samples taken by their general practitioner in addition to the basic examination as carried out for the previous follow-up examinations. The blood parameters analysed are fasting HDL, LDL, total cholesterol, triglycerides and glucose. The allowance for each of this visit is 20 Euros.

At all visits, children whose documents have not been returned to the study center are contacted by telephone, repeatedly if necessary, in order to collect the missing documents. If children wish to withdraw from the study in spite of efforts to motivate them to continue participating, study investigators fill out an official drop out sheet.

Statistical considerations

Associations between polymorphisms in adiposity-relevant genes (*FTO, MC4R, TMEM-18*) and changes in BMI(-SDS) from the start to the end of the intervention, will be assessed using analysis of covariance (ANCOVA) models comparing mean changes in BMI(-SDS) between the two groups of homozygous and the group of heterozygous children adjusted for age, sex and baseline weight. A two-sided level of significance of $\alpha = 0.05$ will be used. For pairwise group comparisons, two-sample t-tests will be conducted using a Bonferroni-adjusted level of significance of $\alpha^* = 0.0167$.

Middle and long-term associations between genes and measures of interest such as weight change, physical fitness and physical activity will analogously be analysed in an explorative manner. Linear regression models including all relevant genes plus baseline weight, age and sex will be fit into estimate predictive models for the expected short and long-term weight changes. Predictive accuracy of the models and most relevant genes will be assessed using re-sampling methods (e.g. bootstrap) [42]. To estimate the influence of genes on relevant measures over time, a mixed model will be fit to account for multiple measures in the same participants. Missing values will be replaced using multiple imputation methods based on observed values with varying assumptions. Differences in the results obtained by different imputation strategies will be reported and discussed.

With a sample size of 1,500 children the study is sufficiently powered to detect significant differences in all pairwise comparisons between allele groups on an adjusted two-sided level of significance of $\alpha^* = 0.0167$, if the true difference in means is at least half of the common standard deviation translating to an effect size of 0.5 (power > 90% for each pairwise comparison). The sample size calculation is based on the assumption that the distribution of alleles leading to the smallest subgroups will be 70%, 25% and 5%, hence the smallest sample sizes for pairwise comparisons will be 375 versus 75 children. Sample size estimation was conducted for a two-sample t-test with unequal group sizes using the software nQuery (Version 7.0).

Discussion

This manuscript provides an outline of the rationale and the design of the LOGIC-trial, which is the first study that evaluates the short, middle and long-term effects of an inpatient weight-loss program in association with genetic factors in a large group of children and adolescents (aimed sample size n = 1,500) and includes follow-up measurements over 10 years. Hence, this study will allow the investigation of important determinants of successful weight-loss, particularly the role of a specific genetic predisposition. To achieve this, a large amount of data is being collected, on anthropometry, blood parameters (adipokines and inflammatory markers), physical fitness, physical activity and quality of life.

To our knowledge, only 24 evaluated inpatient programmes have been published, of which merely 14 carried out follow-up assessments. In all studies but one the follow-up periods lasted no longer than three years. No study has ever carried out follow-up measurements after more than five years following an inpatient weight-loss program [18,22-24]. Therefore, our study is unique particularly regarding the 5 and 10 year follow-up measurements and allows investigating the tracking of the effects of an inpatient lifestyle intervention from childhood to adolescence and adulthood. In addition, the large sample size of 1,500 children allows a thorough investigation of the genetic questions of interest. The question of genetic predisposition is particularly interesting regarding obesity and weight change, as obesity is considered as a polygenic syndrome with various SNPs involved. To date, however, the impact of the SNP's on the individual responses to obesity treatment in children is still unclear. The studies that have shown an influence of genetic factors on changes in body weight induced by a lifestyle intervention in children [25-30] had relatively small sample sizes (n = 236 to n = 519) and have shown inconsistent results. A clear advantage of the LOGIC-trial protocol is the inclusion of adipokines and inflammatory markers, as well as objective measures of physical fitness, which will allow investigations of the associations between changes in body weight,

inflammation and physical fitness. These investigations are of particular relevance in light of potentially important links between these parameters as indicated by a recent review [7]. Some studies have shown relevant associations between adipokines and weight-loss induced by lifestyle interventions [43-46], whereas particularly the results concerning the associations between adipokines and physical fitness are equivocal. This can be explained by the small sample sizes and different outpatient study settings [47-51]. A further strength of the LOGIC-trial is that all anthropometrical parameters are taken by either a nurse or a general practitioner. This avoids the underestimation of body weight that is often observed in self-reports [52]. The inpatient setting is standardised in that participants are living in a controlled environment with similar dietary and exercise conditions and intervention. Such a controlled setting is particularly important for the investigation of the influence of genetic factors, which can be strongly confounded by environmental conditions [15].

Our study has a few limitations, which cannot be completely avoided in this real-life setting. This is an observational study and not a randomized controlled trial. In a randomized design with a 10 year follow-up time it would be ethically questionable to randomize children into an inpatient weight-loss programme and a control group, as the children from the control group would not be allowed to take part in the lifestyle intervention during that time. In addition, the primary intention of this study is to investigate the inter-individual variability of the effects of the intervention depending on the children's genotypes, which does not necessarily require a control group. For cross-sectional analyses, we use an age-matched sample of normal weight children of a school-based intervention study [53] as well a cohort of young athletes, who are recruited at the *Department of Prevention, Rehabilitation and Sports Medicine, Technical University of Munich.*

As we recruit a selected cohort of children who take part in a specialized obesity program it has to be considered that data from clinical samples may not be representative for general populations. Furthermore, although we do have objective physical activity measurements during the intervention, long-term physical activity is assessed by questionnaires. It has been planned this way as we require a standardised physical activity assessment method that can be carried out by all participants for every follow-up measurement during this 10 year time period. Considering the inclusion of 1,500 children and in total seven measurement time points, objective physical activity measurements would have been almost impossible. Similar to the physical activity, nutritional behavior and intake is assessed by questionnaire. Again, more objective measurements such as dietary records would have been optimal but logistically difficult to integrate. In order to maintain high the compliance of the participants we tried to develop and carry out follow-up examinations that are valid, practical and not too time consuming. Therefore we are not using a detailed food frequency questionnaire.

In summary, this is the first lifestyle intervention study with a detailed assessment of short, middle and long-term weight changes, physical fitness, cardiometabolic risk factors including both inflammatory markers and adipokines in a large cohort of overweight and obese children. Apart from elucidating the short-term effects of this supervised weight-loss program, this study will provide the outstanding opportunity to investigate the tracking of the immediate effects of a lifestyle intervention on body weight and the cardiometabolic risk profile from childhood into adolescence and adulthood under consideration of the influence of genetic predisposition. This will contribute to a better understanding of inter-individual differences in the regulation of body weight and thus may lead to an optimization of personalized treatment strategies for childhood obesity.

Endnotes

[a]Based on clinic internal considerations this has been changed from 1,200-1,800 to 1,250-1,800 kcal per day in the year 2010.

[b]Based on clinic internal considerations this has been changed from 11 to 10 h per day in the year 2011.

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Authors' contributions

MR has drafted the manuscript. DW has been substantially involved in writing the manuscript. Both are active investigators of the study on site as well as in the analysis center. MH, BW, MS and HL have conducted the study design. In addition, BW was responsible for the design and implementation of the genetic analysis in the study. HL has been coordinator at the *Kinik Schönsicht*. MH, MS, HL, MR and DW have

coordinated the study. MH is senior principle investigator. BH has been in charge of the statistical analyses. All authors have critically read and approved the final manuscript. The trial has been registered under clinicaltrials.gov NCT01067157.

Competing interests
The authors declare that they have no competing interests.

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The Cardio-Metabolic Risk of Moderate and Severe Obesity in Children and Adolescents

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Objective To compare the cardio-metabolic risk profile between moderately obese and severely obese children and adolescents.

Study design Cross-sectional study involving 463 obese 6- to 19-year-olds who were referred to an inpatient weight-loss program. Anthropometric data were assessed and fasting blood samples were analyzed for lipid and glucose metabolism, adipokines, and inflammatory markers. Moderately obese individuals (percentiles corresponding to body mass index ≥30 to 35 kg/m^2 at age 18 years) and severely obese individuals (percentiles corresponding to body mass index ≥35 kg/m^2 at age 18 years) were defined by sex and age-specific cut-offs according to the International Obesity Task Force.

Results The prevalence of the metabolic syndrome was three times higher in severely obese individuals compared with those who are moderately obese. Mean values for proinsulin, insulin, homeostatic model assessment-insulin resistance, triglycerides, and interleukin-6 were 30%-50% higher in severe obesity compared with moderate obesity. Concentrations of leptin and high-sensitive C-reactive protein were about 1.5-fold higher, adiponectin levels were 12% lower, and resistin levels 10% higher in severely obese individuals compared with moderately obese (all $P < .001$).

Conclusion Severely obese individuals have a markedly more unfavorable cardio-metabolic risk profile than those who are moderately obese. The results of this study underscore the substantial effect of severe obesity on health and highlights that these children need to receive particular attention regarding obesity treatment. *(J Pediatr 2013;163:137-42)*.

See editorial, p 6 and related article, p 143

Children and adolescents with increased body weight are classified as overweight, obese, or severely obese based on age and sex-specific body mass index (BMI) percentiles.[1] Although differences between overweight and obesity are generally recognized, stages of obesity are often described as a single entity. However, there is ample evidence that among obese children there is a wide range of BMI and associated cardio-metabolic disturbances. In previous studies, this has been shown for the prevalence of the metabolic syndrome (MetS) or its several components,[2-5] but also regarding levels of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6),[2,6,7] or adipokines such as leptin[8] and adiponectin.[2] This is important because markers of low-grade inflammation represent a potential link between obesity and metabolic disturbances or systemic vascular complications, such as early atherosclerosis or even premature cardiovascular diseases.[9,10]

The current study includes a detailed analysis of cardio-metabolic data from a large cohort of obese children and adolescents before being enrolled in an inpatient weight-loss program. It was hypothesized that those who are severely obese have a more unfavorable cardio-metabolic risk profile than moderately obese individuals,[1,11] including markers of glucose and lipid metabolism, inflammation, and adipokines. As insulin resistance represents one of the key components of MetS and is associated with a systemic inflammatory state,[12] we also analyzed the relationship between insulin resistance and other risk factors such as blood lipids, blood pressure, adipokines, and inflammatory markers.

BMI	Body mass index
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
HDL	High density lipoprotein
HOMA-IR	Homeostasis model assessment-insulin resistance
IL-6	Interleukin-6
LDL	Low density lipoprotein
MetS	Metabolic syndrome
TNF-α	Tumor-necrosis-factor-alpha

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Methods

Participants of this cross-sectional study were 6 to 19 years old, moderately or severely obese, and were to take part in an inpatient weight-loss program. They were recruited as part of the Long-term effects of lifestyle intervention in Obesity and Genetic Influence in Children (LOGIC) trial, which has been described in detail elsewhere.[13] Children who suffered from secondary obesity, syndromal disorders, or monogenetic diseases, such as Prader-Willi syndrome, were excluded (n = 5). The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of the School of Medicine of the Technische Universität München, Germany.

All clinical examinations were conducted by trained medical staff according to standardized procedures. Body height was measured barefoot to the nearest 0.5 cm by a rigid scale. Body weight was measured with minimal clothing to the nearest 0.1 kg by a digital scale (Tanita BC-420 P MA Profi; Tanita Europe B.V., Hoofddorp, The Netherlands). BMI was calculated as the individual's body weight in kilograms divided by the square of body height in meters. According to cut-offs by the International Obesity Task Force, participants were classified as moderately obese (percentiles corresponding to BMI ≥30 to 35 kg/m^2 at age 18 years) and severely obese (percentiles corresponding to BMI ≥35 kg/m^2 at age 18 years).[1,11] The degree of obesity was additionally described using the least-square means method developed by Cole,[14] which normalizes the BMI skewed distribution and expresses BMI as a SDS, in combination with national reference data.[15] Waist circumference was measured by tape measure to the nearest 0.1 cm midway between the lower rib margin and the iliac crest in a standing position after normal exhalation. Blood pressure was measured at the right brachial artery with an appropriate size cuff using the Riva-Rocci method. The average of 2 readings on 2 different days was used for the analysis. Age and sex-specific percentiles were calculated to define an above-normal waist circumference, and hypertension based on national reference data.[16,17] Identification of pubertal development was defined according to Marshall and Tanner. The children were divided into infantile/prepubertal (Tanner I), pubertal (Tanner II and III), and late pubertal (Tanner ≥IV).[18]

Blood sampling was performed following a ≥10-hour overnight fast. Blood samples were taken by venipuncture of an antecubital vein in either sitting or lying position using vacuum tubes. Samples were stored at −80°C until analyzed. Plasma glucose was measured with the hexokinase method (COBAS INTEGRA 800; Roche Diagnostics GmbH, Mannheim, Germany). Low density lipoprotein (LDL)-cholesterol and high density lipoprotein (HDL)-cholesterol were measured by the homogenous enzymatic colorimetric method. Total cholesterol was measured by the cholesterol oxidase esterase and peroxidase method and triglycerides by the enzymatic endpoint method (COBAS INTEGRA 6000 C; Roche Diagnostics GmbH, Mannheim, Germany). Serum levels of proinsulin, insulin, leptin, and adiponectin were measured by enzyme-linked immunosorbent assay (ELISA) (Mercodia, Uppsala, Sweden). The inter-assay coefficients of variation were 6.2%, 6.7%, 9.8%, and 11.9%, respectively. Resistin concentrations were measured with a commercial ELISA kit (BioVendor, Heidelberg, Germany), resulting in an inter-assay coefficient of variation of 6.1%. Serum levels of IL-6 and tumor-necrosis-factor-alpha (TNF-α) were determined as previously described using commercially available ELISA.[19] The inter-assay coefficients of variation were 15.6% and 17.3%, respectively. Concentrations of CRP were measured by a high-sensitivity latex-enhanced nephelometric assay with a BN II analyzer (Dade Behring, Marburg, Germany) as described in detail previously.[20] The inter-assay coefficients of variation were 4.0%. All analyses were run in a blinded fashion.

The insulin resistance index from fasting plasma insulin and plasma glucose levels was estimated using the homeostasis model assessment-insulin resistance (HOMA-IR),[21] as follows:

$$\text{HOMA-IR} = \text{fasting plasma insulin } (\mu\text{L/mL}) \times \text{fasting plasma glucose } (\text{mmol/L})/22.5.$$

Current literature does not provide guidelines as to cut-off points for increased concentrations of leptin, adiponectin, or resistin in children.

According to current guidelines of the International Diabetes Federation,[22] MetS was defined as a waist circumference above the 90th percentile[17] for children from 6 to 16 years of age and as ≥94 cm in males and ≥80 cm in females above the age of 16 years, plus any 2 of the following factors: either systolic or diastolic blood pressure ≥130 mmHg or ≥85 mmHg or treatment with antihypertensive medication, triglyceride levels ≥150 mg/dL, HDL-cholesterol levels <40 mg/dL, and fasting plasma glucose levels ≥100 mg/dL or treatment for diabetes. Because there is no standard definition of MetS in children, the analyses were conducted using 2 additional definitions applied in earlier studies,[23] and based on modified adult criteria of the National Cholesterol Education Program-Adult Treatment Panel III.[24] The definition of Cook et al[25] includes ≥3 of the following factors: waist circumference ≥90th percentile, either systolic or diastolic blood pressure ≥90th percentile, triglyceride levels ≥110 mg/dL, HDL cholesterol levels ≤40 mg/dL, and fasting plasma glucose levels ≥110. The definition of de Ferranti et al[26] includes ≥3 of the following factors: waist circumference >75th percentile, systolic blood pressure >90th percentile, triglycerides ≥100 mg/dL, HDL <50 mg/d (except in boys aged 15 to 19 years [<45 mg/dL]), and fasting plasma glucose ≥110 mg/dL.

Statistical Analyses

Quantitative data are shown as means and SD (or in the cases of skewed data, medians and IQRs). Absolute and relative frequencies are shown for categorical data.

Table I. Comparison of blood pressure and measures of lipid metabolism between MO and SO

	MO	SO		
	Mean (SD)	Mean (SD)	95% CI	*P*
BP sys (mmHg)				
Male	124 (11)	135 (14)	6.7 to 13.6	<.001
Female	122 (8)	128 (10)	4.2 to 8.8	<.001
BP dia (mmHg)				
Male	78 (7)	84 (9)	4.7 to 9.2	<.001
Female	77 (6)	82 (7)	3.6 to 6.8	<.001
Total cholesterol (mg/dL)				
Male	154.7 (31.5)	161.7 (35.4)	2.5 to 16.5	.147
Female	153.9 (31.0)	155.5 (29.2)	−6.0 to 9.2	.679
LDL (mg/dL)				
Male	98.8 (32.7)	110.0 (36.5)	1.3 to 21.1	.026
Female	97.6 (32.9)	102.6 (30.1)	−3.1 to 13.0	.229
HDL (mg/dL)				
Male	55.1 (12.9)	44.2 (10.4)	−14.2 to −7.4	<.001
Female	53.1 (13.3)	47.0 (10.5)	−9.2 to −3.0	<.001
Triglycerides (mg/dL)				
Male	53.7 (27.4)	71.9 (31.3)	9.8 to 26.6	<.001
Female	59.8 (20.9)	77.0 (29.7)	10.9 to 23.4	<.001

BP dia, diastolic blood pressure; *BP sys*, systolic blood pressure; *MO*, moderately obese; *SO*, severely obese.
Data are shown as mean and SD. Group comparisons were performed using two-sample *t* tests. Presented are 95% CI for mean differences.

Two-sample t-tests were performed to determine group differences of means of continuous variables (in cases of skewed distributions, Mann–Whitney U-tests were conducted). Presented are 95% CI for differences in mean or median, the latter determined using the Hodges–Lehmann estimator, respectively. Because some variables differed significantly between boys and girls, the analyses were also performed stratified by sex. Fisher exact test was used to compare qualitative outcomes between severe and moderate obesity. Relationships between the variables representing glucose metabolism and the other cardio-metabolic risk factors were examined by Spearman rank correlation coefficient. Relative differences between the groups were calculated with moderate obesity as the reference group. As age and puberty are known to have an effect on relevant blood tests (eg, insulin,[27] leptin,[28] and blood lipids[29]) as well as the degree of obesity, linear regression models were fit including obesity group, age, and Tanner stage as independent variables and relevant quantitative measures as dependent variables to determine the association of obesity level with measures of interest controlling for age and puberty status. All tests were performed on a 2-sided level of significance of $\alpha = 0.05$.

Results

There were 266 severely obese (111 male) and 197 moderately obese (90 male) participants with a mean age of 13.9 ± 2.3 years. Severely obese individuals were significantly older than moderately obese (14.1 ± 2.4 vs 13.6 ± 2.1 years; $P = .036$). Comparing the means of anthropometric data between severe versus moderate obesity, body weight was 103.4 ± 22.9 kg versus 80.3 ± 14.4 kg, BMI 37.8 ± 5.2 kg/m^2 versus 30.2 ± 2.4 kg/m^2, BMI-SDS 3.2 ± 0.4 versus 2.4 ± 2.2, and waist circumference 118.9 ± 13.7 cm versus 102.4 ± 9.5 cm (all $P < .001$). Of the 380 participants with pubertal assessment (there was no significant difference in the examined variables between children with and without Tanner stage assessment), 14 were pre-pubertal (infantile or Tanner 1), 124 were in stage Tanner II or III, and 242 in Tanner IV or V. Three percent of severely obese individuals were prepubertal, 29% were in Tanner stage II or III and 68% in Tanner stage IV or V, whereas this was 4%, 38%, and 58% for moderately obese individuals, respectively.

When adjusting for age or Tanner stage, the interpretation of statistical test results comparing the two obesity groups did not change.

Comparisons between moderately and severely obese participants regarding blood pressure, measure of lipids and glucose metabolism as well as adipokines and inflammatory markers are shown in Tables I-III. Correlation analyses revealed moderate positive associations between HOMA-IR and triglycerides (r = 0.50) as well as HOMA-IR and leptin levels (r = 0.48). Weak positive correlations were

Table II. Comparison of measures of glucose metabolism between MO and SO

	MO		SO			
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	95% CI*	*P*
Glucose (mg/dL)						
Male	70.2 (8.3)	71.0 (65.0-75.0)	71.5 (7.5)	72.0 (67.0-76.0)	−3.0 to 1.0	.480
Female	71.9 (7.1)	71.0 (68.0-76.0)	75.5 (24.1)	74.0 (68.0-78.0)	−4.0 to 0.0	.051
Proinsulin (pmol/L)						
Male	7.0 (4.8)	6.4 (3.9-8.6)	9.4 (5.4)	8.5 (5.9-11.8)	−3.4 to −1.1	.001
Female	8.2 (6.2)	6.4 (4.3-9.4)	10.5 (5.8)	9.5 (6.5-13.0)	−3.7 to −1.4	<.001
Insulin (mU/L)						
Male	8.7 (5.3)	7.4 (5.8-10.1)	12.0 (5.9)	10.5 (7.9-14.2)	−4.2 to −1.8	<.001
Female	10.1 (5.0)	9.3 (6.6-12.9)	14.6 (6.4)	13.4 (9.8-17.5)	−5.3 to −2.7	<.001
HOMA-IR						
Male	1.5 (1.0)	1.3 (1.0-1.8)	2.2 (1.2)	2.0 (1.4-2.7)	−0.8 to −0.3	<.001
Female	1.8 (1.1)	1.7 (1.1-2.2)	2.7 (1.4)	2.4 (1.8-3.2)	−1.0 to −0.5	<.001

MO, moderate obesity; *SO*, severe obesity.
Data are shown as mean and SD, median, and IQR. Because of skewed distributions, the Mann–Whitney U-test has been conducted for group comparisons.
*CI for differences of medians.

Table III. Comparison of inflammatory markers and adipokines between MO and SO

	MO		SO			
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	95% CI*	*P*
IL-6 (pg/mL)						
Male	1.4 (2.5)	0.9 (0.6-1.3)	1.7 (1.4)	1.3 (0.9-1.8)	−0.6 to −0.3	<.001
Female	1.3 (1.8)	0.9 (0.6-1.4)	1.8 (3.0)	1.3 (0.9-2.0)	−0.5 to −0.2	<.001
TNF-α (pg/mL)						
Male	2.3 (1.7)	1.9 (1.4-2.7)	2.5 (1.9)	2.2 (1.5-3.0)	−0.4 to 0.1	.224
Female	2.4 (1.9)	1.9 (1.3-2.8)	2.4 (1.9)	1.9 (1.4-2.6)	−0.3 to 0.2	.722
hsCRP (mg/L)						
Male	4.0 (8.7)	1.7 (0.8-4.1)	4.7 (5.0)	3.0 (1.7-5.5)	−1.7 to −0.4	=.001
Female	2.4 (2.2)	1.7 (0.7-3.4)	5.4 (7.3)	3.3 (1.6-6.8)	−2.3 to −0.8	<.001
Adiponectin (μg/mL)						
Male	9.7 (2.9)	9.2 (7.6-11.5)	8.3 (2.5)	8.0 (6.5-9.6)	0.5 to 2.1	=.001
Female	9.9 (2.5)	9.8 (8.1-11.2)	8.9 (3.4)	8.4 (7.0-10.4)	0.6 to 1.9	<.001
Leptin (ng/mL)						
Male	20.4 (14.3)	16.0 (11.1-27.6)	35.0 (20.7)	28.7 (19.9-46.6)	−16.3 to −7.9	<.001
Female	35.7 (16.5)	33.5 (27.4-42.9)	61.1 (24.2)	56.8 (43.3-76.3)	−28.4 to −18.9	<.001
Resistin (ng/mL)						
Male	6.0 (2.5)	5.6 (3.8-8.1)	6.5 (2.2)	6.4 (4.8-7.5)	−1.2 to −0.2	.121
Female	6.5 (2.8)	6.1 (4.7-7.7)	7.3 (3.0)	6.7 (5.3-8.9)	−1.4 to −0.1	.018

hsCRP, high-sensitive CRP.
Data are shown as mean and SD, median, and IQR. Because of skewed distributions, the Mann–Whitney U-test has been conducted for group comparisons.
*CI for differences of medians.

observed between HOMA-IR and IL-6 (r = 0.24) as well as HOMA-IR and both systolic (r = 0.27) and diastolic blood pressure (r = 0.23). Weak negative correlations were found between HOMA-IR and both levels of HDL-cholesterol (r = −0.36) and adiponectin (r = −0.26; all $P < .001$).

The rates of MetS and its several risk factors considering the different definitions are shown in the **Figure**. Complete MetS risk factors were available in 94% of the participants. All of them had an enlarged waist circumference according to the criteria of MetS definitions used. In the total group, the participants who had MetS were significantly older compared with those without MetS ($P < .001$).

Discussion

The current study illustrates that more than one stage of obesity has to be recognized in obese children and adolescents regarding the potential influence of the cardio-metabolic risk

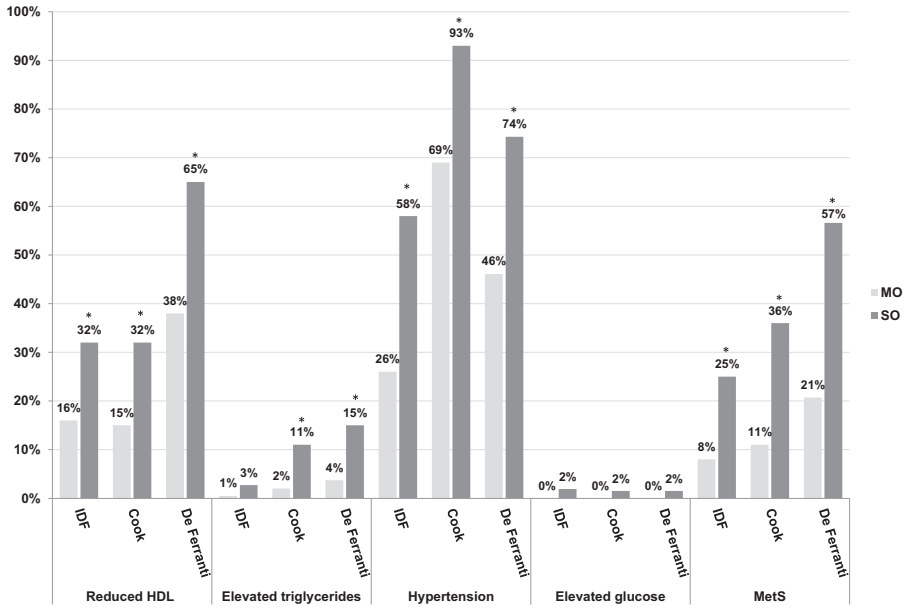

Figure. Prevalence of MetS and its components in moderate and severe obesity using the definition by the International Diabetes Federation of Zimmet et al[22] and modified National Cholesterol Education Program-Adult Treatment Panel III criteria by Cook et al[25] and de Ferranti et al[26]; *$P < .001$. *IDF*, International Diabetes Federation.

profile including adipokines and inflammatory markers. Our data revealed that individuals with severe obesity have a significantly more unfavorable cardio-metabolic risk profile than those with moderate obesity.

Means for insulin and HOMA-IR were approximately 40-50% higher in individuals with severe compared with moderate obesity. This demonstrates early signs of insulin resistance, which is one of the most important risk factors for MetS.[12]

The prevalence of MetS was three times higher in those with severe compared with moderate obesity according to all of the definitions used. This is in line with a study assessing children from Italy, which showed prevalence of 31% in the severely obese (n = 74) compared with 12% in the moderately obese children (n = 117).[3] A previous study by Weiss et al,[2] including children from North America, reported relatively high prevalence but smaller differences between the obesity groups and 50% of severely obese (n = 195) and 39% of moderately obese children (n = 244) were considered having MetS. Both studies included on average 12 year old children, used obesity groups based on population or cohort specific z-scores and defined risk factors using BMI instead of waist circumference as well as cut-offs for blood pressure and fasting lipid levels based on population specific z-scores. In addition, in these studies impaired glucose tolerance using an oral glucose tolerance test rather than elevated glucose levels was considered for classification of MetS. In our study fasting glucose levels were mainly in the normal range.

The comparisons between different approaches to define pediatric MetS in the current study illustrate that using the International Diabetes Federation criteria lead to relatively low prevalence rates and that the results can vary widely between different populations and, importantly, depending on the respective definitions. However, the differences between the obesity groups remain similar.

In the current study, the greatest group differences were found for levels of leptin and high-sensitive CRP, which were about 1.5-fold higher in those with severe compared with moderate obesity. These differences are of clinical relevance because leptin is not only involved in insulin signaling, lipid metabolism, vascular function, and blood pressure regulation, but also directly affects the development of atherosclerosis[30,31] and CRP has shown to be elevated even in the early phase of atherosclerosis.[32] The potential involvement of the adipokines in the development of insulin resistance[30,33] is supported by our data showing correlations between HOMA-IR and both levels of leptin and adiponectin. Although both IL-6 and TNF-α are known to be associated and also involved in systemic inflammatory status by directly stimulating CRP synthesis in the liver,[34] we found a significant difference of 40% between the 2 obesity groups for IL-6, but no difference for TNF-α. IL-6 seems to be the main inducer of hepatic production of CRP, whereas TNF-α appears to have more local rather than systemic effects,[35] which might explain both the lack of group differences and often inconsistent results regarding this inflammatory marker.[36]

One important limitation of this study is that insulin resistance was not determined using oral glucose tolerance testing, which is more sensitive to detect insulin resistance. An inclusion of functional measures of early atherosclerosis (eg, endothelial dysfunction or intima media thickness) could have yielded further information of the effects on the vascular system dependent on the cardio-metabolic and inflammatory profile. The children of the current study were referred to a specialized obesity treatment program. Therefore, the results may only be applicable to patients seeking medical weight management and may not be generalizable for the entire pediatric population.

These data underscore the deleterious effect of severe obesity on health of children and adolescents and highlight the importance of the transition from moderate to severe obesity. We hope these findings will increase awareness of the especially high risk of severe obesity and the need to prevent the occurrences of it and for enrolment in intensified obesity treatment programs for those with established severe obesity. ■

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Health-Related Quality of Life and Physical Activity in Children and Adolescents 2 Years after an Inpatient Weight-Loss Program

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Objectives To investigate changes in health-related quality of life (HRQOL), body mass index (BMI), physical activity, and sedentary behavior at 24 months after an inpatient weight-loss program and to examine correlations between changes in HRQOL and BMI or physical activity.

Study design This prospective study included 707 overweight and obese individuals (mean age, 14 ± 2 years; 57% girls) participating in a 4- to 6-week inpatient weight-loss program, 381 of whom completed a 24-month follow-up. HRQOL, physical activity, sedentary behavior, and BMI were assessed at baseline, at discharge, and at 6, 12, and 24 months after starting therapy. Longitudinal analyses were conducted using repeated-measures mixed models, adjusted for age, sex, and baseline outcome and accounting for attrition over time.

Results All variables improved over treatment and 6-month follow-up ($P < .05$). At 24 months, overall HRQOL indicated improvements relative to baseline (3 points on a scale of 0-100; 95% CI, 1.68-4.47; $P < .001$). Of the 6 HRQOL domains, the greatest improvement was observed for self-esteem (11 points; 95% CI, 8.40-13.14; $P < .001$). BMI was 0.5 kg/m^2 lower than at baseline (95% CI, −0.92 to −0.02; $P = .04$). Long-term changes in physical activity explained 30% of the variation in overall HRQOL ($P = .01$), and change in BMI was not associated with a change in HRQOL.

Conclusions This inpatient weight-loss program was associated with positive changes in HRQOL over the long term, with particular improvements in self-esteem. The results indicate the potential role of physical activity in improving HRQOL without a substantial change in body composition. *(J Pediatr 2014;165:732-7)*.

The prevalence of pediatric obesity has increased worldwide. Along with having a greater risk of cardiovascular disease,[1] obese children and adolescents often have impaired health-related quality of life (HRQOL),[2-4] comparable with that of youths diagnosed with cancer.[2] This seems to especially affect individuals who have been referred to or seek clinical treatment.[5,6]

HRQOL is an important indicator of an individual's own experience of his or her chronic condition, as well as overall psychosocial health and function. Thus, the assessment of HRQOL as a multidimensional construct including physical well-being, emotional well-being, social interactions, and performance in daily life is an essential criterion for the evaluation of pediatric obesity treatment strategies.[7] Previous studies have indicated that inpatient weight-loss programs induce short- and medium-term improvements in HRQOL in children and adolescents.[8-13] However, there are no studies investigating the effects of pediatric inpatient weight-loss programs on HRQOL for more than 1 year after therapy.

Although the negative relationship between body weight and HRQOL is well known, less is known about the other factors that can influence HRQOL in obese children over the long term.[4] One potential contributor to this relationship may be the level of physical activity, which has been shown to improve HRQOL in a dose-dependent manner in overweight and obese adults independent of weight changes.[14] Furthermore, physical activity has been suggested to positively affect HRQOL and psychosocial variables in normal weight[15-18] and overweight/obese children and adolescents.[19]

The aims of the present study were to investigate changes in HRQOL, body mass index (BMI), physical activity level, and sedentary behavior over the course of 24 months after completion of a 4- to 6-week inpatient weight-loss program and to explore the influence of both changes in physical activity level and BMI on HRQOL 24 months after program completion.

BMI	Body mass index
HRQOL	Health-related quality of life
LOGIC	Long-Term Effects of a Lifestyle Intervention in Obesity and Genetic Influence in Children
V	Visit

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Methods

Participants in the prospective Long-Term Effects of a Lifestyle Intervention in Obesity and Genetic Influence in Children (LOGIC) trial were overweight and obese 7- to 20-year-olds who were consecutively referred to the Schoensicht rehabilitation clinic in Berchtesgaden, Germany for inpatient weight-loss treatment between 2006 and 2009. Exclusion criteria for the LOGIC trial were secondary obesity, monogenetic diseases such as Prader-Willi syndrome, and early withdrawal from the inpatient program (<3 weeks). Participants came to the clinic every 2 weeks and were recruited monthly.

All children and adolescents and their parents provided written informed consent for study participation. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, Technische Universitaet Muenchen, Munich, Germany (1354/05).

The weight-loss program and follow-up procedures have been described in detail previously.[20] In brief, the standardized nonpharmacologic weight-loss program was conducted for 4-6 weeks, depending on health insurance allowances and the severity of obesity. Children were assigned to 1 of 4 treatment groups differing by sex and age (<15 or ≥15 years) or developmental stage and consisting of approximately 8-12 participants. The program focused on a calorie-restricted diet, adequate physical activity, and behavior therapy and was conducted according to German guidelines for inpatient weight-loss programs.[21] Energy intake was limited to 1200-1800 kcal per day, depending on height and sex including 30% total energy from fat, 15% from proteins, and 55% from carbohydrates. The exercise therapy consisted of approximately 10 hours of supervised physical activity per week (ie, ball games, swimming, hiking, and strength and posture training) in addition to 6 hours of recreational exercise. The children received theoretical and practical lessons on healthy eating, physical activity, and behavior change skills based on cognitive behavioral theory. These lessons were intended to support the children's adherence to physical activity recommendations after returning home. In addition, therapists and physicians recommended participation in organized physical activity (eg, sports clubs) after the children returned home.

Before the first follow-up examination (6 months after the start of the program), study investigators contacted the children's general practitioners to inform them of the study procedures and to obtain agreement on carrying out the upcoming follow-up examinations using a standardized examination sheet. In addition, before each visit, participants were contacted to remind them of the upcoming examination and to enquire about possible changes of address. They were requested to complete and return a questionnaire (sent by mail) and to visit their general practitioners. To maximize compliance, the families were contacted regularly.

All measurements were conducted at the start (visit [V] 1; V1) and the end (V2) of the inpatient weight-loss program in the clinic by trained medical staff and at 6 months (V3), 12 months (V4), and 24 months (V5) after the start of the program by the children's general practitioners, according to standardized procedures. In the clinic (V1 and V2), height was measured with the children in underwear to the nearest 0.5 cm using a rigid stadiometer, and weight was measured to the nearest 0.1 kg using a digital scale (Tanita BC-420 P MA Profi; Tanita Europe, Amsterdam, The Netherlands). For the subsequent assessments of height and weight (V3-V5), the general practitioners followed standardized measurement procedures.

BMI was calculated as body weight in kilograms divided by the square of body height in meters. Based on age- and sex-specific cutoffs by the International Obesity Task Force, participants were classified as normal weight (percentiles corresponding to BMI >18.5-25 kg/m^2 at age 18 years), overweight (percentiles corresponding to BMI ≥25-30 kg/m^2 at age 18), moderately obese (percentiles corresponding to BMI ≥30-35 kg/m^2 at age 18), or severely obese (percentiles corresponding to BMI ≥35 kg/m^2 at age 18).[22,23] In addition, BMI was transformed into a BMI-SDS according to formulas developed by Cole and coworkers using national reference values.[24,25]

Questionnaires were administered to the children by clinic staff (V1 and V2) or mailed to their homes (V3-V5). The German KINDL questionnaire[7] was used to assess HRQOL in 6 domains: physical well-being, emotional well-being, self-esteem, friends, family, and school. An overall HRQOL was obtained by calculating the average of the domain scores. Potential scores for all domains range from 0-100, with higher values representing better HRQOL. The reliability and validity of this questionnaire have proven sufficient, with a Cronbach $\alpha > 0.70$ and a correlation coefficient of $r = 0.70$ obtained with instruments measuring similar concepts in previous research.[7] The level of physical activity was assessed by self-report questionnaire using the question: "On how many days last week have you been active for at least 60 minutes?" with possible scores ranging from 0-7 days. This question has been previously validated for use in young people and been shown to be reliable (intraclass correlation 0.77) and correlated with accelerometer data ($r = 0.40$).[26] In addition, children were asked whether they were currently a member of a sports club. To assess sedentary behavior, the 3 questions with 2 subdomains were asked: "How many hours do you engage in (1) watching television, (2) using the computer, and (3) doing homework on (1a) weekdays and on (1b) weekend days?" Participants chose from 0.5, 1, 2, 3, 4, or >5 hours. The average weekly time (hours) spent in each behavior as well as total weekly sedentary time is reported here.

Statistical Analyses

Descriptive statistics were used to summarize both demographics and study outcomes measured at each visit. Longitudinal data analyses were performed using repeated measures mixed models to evaluate changes in HRQOL,

BMI, physical activity level, and sedentary behavior from baseline (V1) to each follow-up visit (V2-V5), adjusting for baseline outcomes, age, and sex. The regression model accounts for both repeated measurements in the same participant and unequal numbers of observations owing to attrition over time. More specifically it uses all observed data collected over time, with missing information having no effect on other measures from that same participant. The random effect provides valid inferences when data are missing at random; this is a general assumption considered in most scenarios for analysis.

Multiple linear regression models were used to assess the association of long-term changes (at 24 months) in physical activity level and BMI with long-term changes in HRQOL, adjusting for baseline HRQOL, age, and sex. BMI was used instead of BMI-SDS for regression analysis including long-term weight changes, as recommended by Cole et al.[27] Statistical tests appropriate to categorical and continuous variables were conducted to assess for associations.

Statistical analyses were performed using SAS v 9.2 (SAS Institute, Cary North Carolina). All statistical tests were 2-sided at a 5% significance level. The Tukey-Kramer method[28] was used to adjust for multiple comparisons as appropriate.

Results

Between 2006 and 2009, 707 of 1817 (39%) overweight and obese children presenting at the weight-loss clinic participated in the LOGIC trial. Most of those who did not participate arrived at the clinic when study investigators were not on site (n = 864); treatment started biweekly and participants were recruited monthly. Fourteen individuals did not meet the inclusion criteria (5 owing to secondary obesity or monogenetic disease and 9 to therapy duration <3 weeks), and 232 children declined study participation. A total of 707 individuals (57% female; mean age 13.9 ± 2.3 years) were enrolled into the study at baseline. The response rate (ie, return of questionnaire and/or examination sheet) was 68% at the 6-month follow-up (V3), 61% at the 12-month follow-up (V4), and 54% at the 24-month follow-up (V5) (**Figure 1**; available at www.jpeds.com). To characterize potential differences in children who provided data at the 24-month follow-up (ie, responders) with those who did not (ie, lost to follow-up) they were compared regarding age, anthropometric measurements, HRQOL, physical activity level, and sedentary behavior both at baseline (V1) and at the end of treatment (V2). There were no significant group differences, except that at the end of treatment responders had significantly lower absolute BMI values (29.4 vs 30.2 kg/m^2; P = .03). However, change in BMI over the course of treatment (V1-V2) did not differ significantly between responders and those lost to follow-up.

Table I provides a descriptive summary of all variables of interest at all scheduled visits. **Table II** presents changes from baseline to each of the post baseline periods for all variables of interest using adjusted regression models.

In those children who completed a questionnaire (n = 310), the scores for overall HRQOL and 4 out of 6 HRQOL domains improved significantly from baseline to 24 months. The greatest improvement over the long term was observed for the self-esteem domain. The family domain scores decreased after the weight-loss program, and the follow-up values at 24 months were below baseline (**Table II**). **Figure 2** shows the adjusted mean changes in overall HRQOL and each HRQOL domain score at each time point.

At baseline, 73 of the 707 participants (10%) were classified as overweight, 281 (40%) as moderately obese, and 353 (50%) as severely obese. This distribution was 11% (n = 35), 42% (n = 130), and 46% (n = 142), respectively, for the 307 children who returned the examination sheet after 24 months. BMI was significantly lower than baseline at all postbaseline periods including the 24-month follow-up at which BMI was 0.5 kg/m^2 lower compared with baseline

Table I. Descriptive summary of anthropometric variables, HRQOL domains, physical activity level, and sedentary behavior at all scheduled visits

	Pretreatment (V1)			Post-treatment (V2)			6 mo (V3)			12 mo (V4)			24 mo (V5)		
Variables	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Overall HRQOL	646	65.9	12.4	596	70.8	10.9	408	69.8	13.4	330	68.1	13.6	303	68.7	13.6
Physical well-being	656	64.6	18.3	619	66.3	16.5	408	67.8	19.6	332	65.7	19.8	302	65.7	21.0
Emotional well-being	658	73.1	19.3	622	76.0	17.0	410	77.2	17.4	332	75.2	16.9	304	75.7	17.6
Self-esteem	655	47.1	21.8	621	63.0	20.2	411	60.9	21.0	334	55.6	21.1	304	57.3	22.0
Friends	650	70.0	20.2	599	72.3	18.3	409	72.5	19.1	336	73.3	18.9	303	72.8	17.5
Family	655	81.1	18.7	556	86.0	15.2	410	77.1	20.8	336	75.4	20.8	303	76.7	20.8
School	621	58.9	19.4	571	61.3	19.9	396	63.7	19.4	326	62.2	20.2	281	63.5	18.9
Body weight (kg)	707	90.5	23.9	706	80.6	20.6	439	81.6	19.5	404	86.2	20.8	307	92.3	22.2
Body height (cm)	707	163.1	11.4	706	163.5	11.4	439	164.8	10.8	404	166.2	10.1	307	168.7	9.3
BMI (kg/m^2)	707	33.5	6.1	706	29.8	5.3	439	29.7	5.1	404	31.0	5.8	307	32.3	6.4
BMI-SDS	707	2.7	0.6	706	2.3	0.6	439	2.2	0.7	404	2.4	0.7	307	2.5	0.8
Physical activity level (d/wk)	670	2.8	2.2	469	4.7	2.1	408	3.2	2.0	341	3.0	2.0	310	2.9	2.1
Total sedentary behavior (h/wk)	645	36.0	16.8	458	30.1	19.0	408	32.8	15.3	342	34.5	15.9	306	35.9	16.0
Homework (h/wk)	625	7.7	6.9	444	7.2	6.0	401	6.7	5.3	338	7.1	5.8	296	6.8	6.5
Computer (h/wk)	637	11.5	9.9	453	9.9	9.8	407	10.7	9.6	341	12.1	10.0	304	13.6	9.9
Television (h/wk)	641	17.2	9.9	456	13.4	10.5	407	15.5	8.9	341	15.6	9.0	306	15.8	9.7

Table II. Change from baseline* in HRQOL domains, BMI and BMI-SDS, physical activity level, and sedentary behavior across 4 treatment time periods

Variable	Time period	Mean change	Lower 95% CI	Upper 95% CI	*P* value
Overall HRQOL	V 1-2	4.9	4.14	5.62	<.001
	V 1-3	4.1	2.92	5.20	<.001
	V 1-4	2.0	0.71	3.20	.002
	V 1-5	3.1	1.68	4.47	<.001
Physical well-being	V 1-2	1.4	0.15	2.61	.03
	V 1-3	3.1	1.39	4.91	<.001
	V 1-4	0.3	−1.69	2.34	.75
	V 1-5	1.1	−1.08	3.27	.32
Emotional well-being	V 1-2	2.8	1.55	4.12	<.001
	V 1-3	4.1	2.53	5.71	<.001
	V 1-4	1.6	−0.07	3.25	.06
	V 1-5	3.2	1.35	5.06	<.001
Self-esteem	V 1-2	16.4	14.84	17.87	<.001
	V 1-3	14.1	12.12	16.11	<.001
	V 1-4	8.4	6.21	10.57	<.001
	V 1-5	10.8	8.40	13.14	<.001
Family	V 1-2	4.8	3.70	5.95	<.001
	V 1-3	−3.7	−5.56	−1.88	<.001
	V 1-4	−5.6	−7.68	−3.62	<.001
	V 1-5	−4.2	−6.47	−1.96	<.001
Friends	V 1-2	2.3	0.97	3.64	<.001
	V 1-3	3.2	1.44	4.90	<.001
	V 1-4	4.1	2.30	5.97	<.001
	V 1-5	3.6	1.71	5.45	<.001
School	V 1-2	2.0	0.60	3.42	.01
	V 1-3	3.9	2.19	5.60	<.001
	V 1-4	2.1	0.11	4.08	.04
	V 1-5	3.6	1.42	5.74	.001
BMI (kg/m^2)	V 1-2	−3.8	−3.85	−3.67	<.001
	V 1-3	−3.2	−3.45	−3.01	<.001
	V 1-4	−2.0	−2.34	−1.74	<.001
	V 1-5	−0.5	−0.92	−0.02	.04
BMI-SDS	V 1-2	−0.4	−0.46	−0.43	<.001
	V 1-3	−0.4	−0.46	−0.40	<.001
	V 1-4	−0.3	−0.36	−0.28	<.001
	V 1-5	−0.2	−0.24	−0.12	<.001
Physical activity level (d/wk)	V 1-2	1.9	1.70	2.09	<.001
	V 1-3	0.5	0.27	0.65	<.001
	V 1-4	0.2	0.02	0.43	.03
	V 1-5	0.2	−0.05	0.42	.12
Total sedentary behavior (h/wk)	V 1-2	−6.0	−7.6	−4.35	<.001
	V 1-3	−2.9	−4.2	−1.56	<.001
	V 1-4	−1.4	−2.9	0.07	.061
	V 1-5	−0.2	−2.0	1.54	.811
Homework (h/wk)	V 1-2	−0.9	−1.5	−0.36	.001
	V 1-3	−1.3	−1.8	−0.77	<.001
	V 1-4	−0.9	−1.5	−0.27	.005
	V 1-5	−1.3	−2.0	−0.51	<.001
Computer (h/wk)	V 1-2	−1.1	−2.0	−0.43	.003
	V 1-3	−0.1	−0.9	0.69	.765
	V 1-4	1.0	0.1	1.93	.030
	V 1-5	2.3	1.1	3.33	<.001
Television (h/wk)	V 1-2	−3.9	−4.7	−2.99	<.001
	V 1-3	−1.8	−2.5	−1.06	<.001
	V 1-4	−1.7	−2.5	−0.82	<.001
	V 1-5	−1.4	−2.5	−0.38	.008

*Repeated measures mixed models adjusted for age, sex, and the baseline outcome.

(**Table II**). **Figure 3** (available at www.jpeds.com) shows the transition among the percentile groups from baseline to the 24-month follow-up (V5).

Physical activity level and sedentary behavior improved significantly immediately after treatment but by 24 months were not significantly different from baseline (**Table II**). Regarding participation in organized physical activity during the follow-up period, the rate of sports club membership was 50% at 6 months, 47% at 12 months, and 43% at 24 months after the start of the weight-loss program.

Changes in physical activity level were positively associated with changes in HRQOL, adjusting for baseline HRQOL, age, and sex. A change in physical activity level explained 30% of the variation in overall HRQOL, 47% of the variation in the friends domain, and 26% of the variation in the physical well-being domain (all $P < .05$). Changes in BMI were not associated with overall HRQOL or any of the HRQOL domains (**Table III**; available at www.jpeds.com).

Discussion

In agreement with previous studies,[2,6,7] baseline HRQOL was impaired in this clinical sample of overweight and obese children and adolescents. The mean overall HRQOL value was 7 points lower compared with that of a nationally representative sample of more than 6000 11- to 17-year-old German children and adolescents.[29] Also in line with previous studies, overall HRQOL and all domains improved immediately after participation in a weight-loss program of relatively short duration[7,9] and most of the domains were improved over the medium term (12 months).[12]

At 24 months, there were still significant (albeit small) improvements in overall HRQOL and most domains compared with baseline. The greatest improvements were seen in the self-esteem domain. For this domain, the mean value at 24 months was only 1.2 points lower than that of the representative German sample.[29] Improving self-esteem in children and adolescents can help prevent the development of emotional and social problems later in life.[30] Previous research has found similar improvements in self-esteem after inpatient treatment of much longer treatment duration (10 months),[31] suggesting that our shorter duration treatment may be just as efficacious in this regard.

Unexpectedly, family domain scores were decreased at follow-up, with values at 6, 12, and 24 months all below baseline. Similar results were also reported by Jozefiak et al,[32] who suggested that such changes may be development-conditioned and age-dependent. In their study, more than 1000 healthy school children were observed over 6 months. The eighth grade students (aged 12-14 years) reported a greater decrease in HRQOL compared with the sixth grade students (aged 10-12 years) in the family and school domains and in overall HRQOL. The authors concluded that this may be related to the greater autonomy during early adolescence and puberty. In our study, age was not a significant confounder for long-term changes in HRQOL. In the

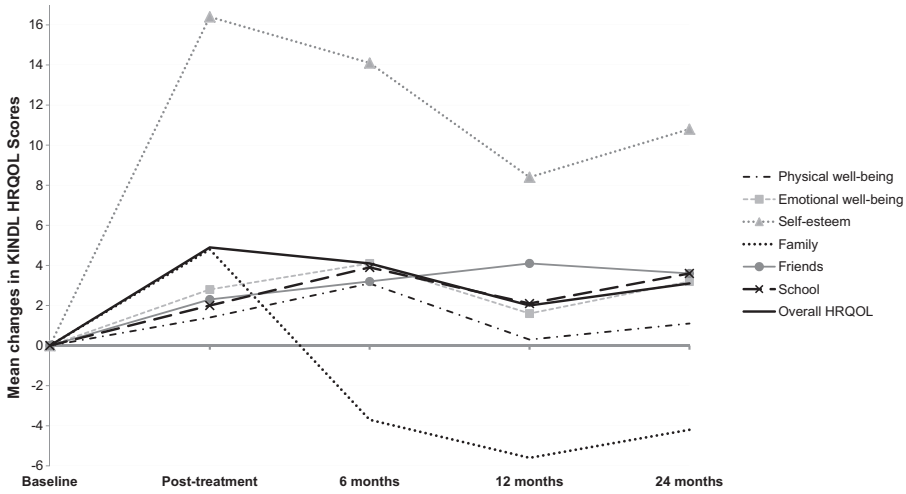

Figure 2. Adjusted mean changes from baseline in HRQOL domains across the 4 time periods (for adjusted changes and their significance see **Table II**).

inpatient program, the children gain knowledge about healthy living and learn how to change their behavior, with little or no parental involvement. A further potential explanation for the decrease in the family domain scores may be deficient parental support in the implementation of health principles into the home environment.

The trajectory of physical activity level and sedentary behavior was similar to that for BMI, in that the greatest improvement occurred during inpatient treatment, with the effects attenuating over time. For BMI, a statistically significant (yet modest) effect remained at 24 months, but neither physical activity level nor sedentary behavior were significantly different at this final time point. Our results indicate that changes in physical activity levels were positively associated with the changes in overall HRQOL and the friends and physical well-being domains, and changes in BMI were not associated with any of the HRQOL domains. Our study design does not allow for an inference of causality (eg, if a higher level of physical activity improves HRQOL or if children with a better HRQOL might have more drive to perform physical activity). Furthermore, we cannot rule out that this before-after analysis is confounded by other factors that influence the relationship between physical activity levels and HRQOL. For example, children with comorbidities might have both a lower HRQOL and not engage in as much physical activity than healthier children. In addition, both HRQOL and physical activity are self-reported measurements, whereas BMI is not, and these self-reports might be subject to perception bias in that children respond in a socially desirable way.

An important strength of this study is the long follow-up period of 24 months. Most previous studies in this field were cross-sectional or had a short follow-up duration, with a maximum of 1 year.[12] Another strength is that the primary outcome variable HRQOL was assessed using a well-validated obesity and child-specific questionnaire that was originally developed for German children and adolescents but is also available and validated in English. A further strength of this study is that all anthropometric measurements were obtained by either a nurse or a general practitioner, which has obvious advantages compared with self-reports.[33]

This study also has some limitations. It was not a randomized controlled trial because such a trial was believed to be ethically questionable by randomizing treatment-seeking overweight and obese individuals into a no-treatment group or wait-list control group. Thus, the results provide no evidence of the direction of causality. Moreover, controlling for the effect of developmental factors on changes in HRQOL was difficult. Nevertheless, significant changes were evident after adjustment for age. For logistical reasons, physical activity level and sedentary time were assessed by questionnaire, although objective measurement (eg, accelerometry) would have been the superior method. There is no information about the validity of the questions on sedentary behavior used in this study. Responses may have been affected by difficulty in recalling the duration of sedentary activities or by social desirability bias. The most important limitation is that the long-term outcome of one-half of the original sample of more than 700 participants is unknown owing to the relatively high loss to follow-up. Only 54% of the baseline sample returned the questionnaires and/or examination sheets at 24 months. This may be related to the objective and more time consuming data assessment at the children's general practitioners, as well as the wide distribution of participants throughout Germany, Austria, Belgium, and France, which hindered follow-up of non-responders. Dropout rates of similar studies including a follow-up after pediatric obesity intervention range from 10% (self-reported BMI, n = 122, 2-year follow-up)[31] to 47% (participants returned to study center, n = 194, 10-month follow-up).[34] An important consideration related to the loss to follow-up is that

participants who withdraw from the study may differ in important ways from those who participate in the follow-up procedures, with, for example, poorer outcomes for HRQOL, body composition, or related health behaviors.

Our results indicate the potential role of physical activity in improving HRQOL without a substantial change in body composition. This highlights the importance of considering lifestyle behaviors such as physical activity, as well as weight reduction, in pediatric obesity treatment. ■

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Table III. The association* of long-term changes in physical activity and BMI on long-term changes of HRQOL domains from baseline to the 24 months follow-up

Variables	Changes	Estimate	*P* value	R^2
Δ Overall HRQOL (n = 208)	Physical activity	0.858	.01	0.301
	BMI	−0.191	.35	
Δ Physical well-being (n = 208)	Physical activity	1.042	.04	0.258
	BMI	0.230	.44	
Δ Emotional well-being (n = 210)	Physical activity	0.751	.10	0.448
	BMI	0.045	.87	
Δ Self-esteem (n = 211)	Physical activity	0.768	.18	0.388
	BMI	−0.664	.06	
Δ Family (n = 208)	Physical activity	0.323	.54	0.326
	BMI	−0.064	.84	
Δ Friends (n = 207)	Physical activity	1.155	.01	0.472
	BMI	−0.291	.27	
Δ School (n = 194)	Physical activity	0.767	.11	0.343
	BMI	−0.177	.55	

*Multiple linear regression models adjusted for age, sex, and HRQOL at baseline.

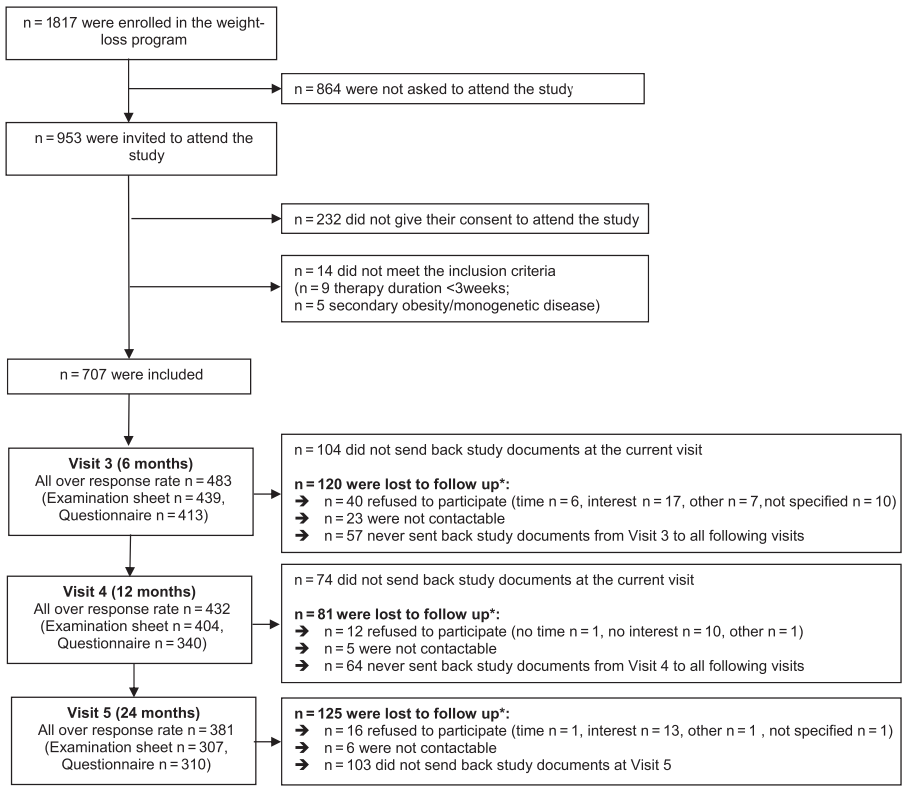

Figure 1. Flow-chart of study recruitment and follow-up. *Children have been considered as lost to follow-up if they did not send back either the examination sheet or the questionnaire.

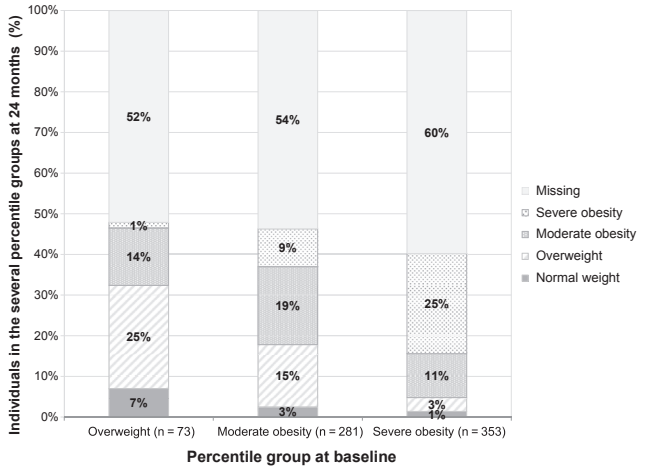

Figure 3. Transition of the study participants between the several percentile groups from baseline to 24-month follow-up.

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