# Diagnosis and treatment of obese children with insulin resistance

Aa, M.P. van der

# Chapter 1

General introduction on diagnosis and treatment of obese children with insulin resistance

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Nowadays, worldwide more people are overweight or obese than underweight [1]. In 2014, worldwide 10.8% (9.7–12.0) of adult men and 14.9% (13.6-16.1) of adult women were obese, whereas the prevalence of underweight was respectively 8.8% (7.4-10.3) in men and 9.7% (8.3-11.1) in women [1].

Obesity is a condition which is defined as abnormal or excessive body fat accumulation. This condition may impair health, and is of specific concern in view of the increasing prevalence in children [2, 3]. To classify overweight, and thereby obesity, the body mass index (BMI) is used. The BMI is calculated as weight (kg) divided by (height (m))$^2$, with adult cut-off values for overweight and obesity of respectively ≥25 kg/m$^2$ and ≥30 kg/m$^2$ [2]. In children normal growth results in an initial decrease of BMI until the age of 4-5 years, followed by an increase in BMI. Consequently, fixed cut-off values for BMI to classify obesity in children cannot be used, and therefore standard deviation scores (SDS), z-scores, or percentiles are used to the define overweight and obesity [4-6]. These scores are based on the number of standard deviations below or above the median BMI for age and sex of an international population of six large, nationally representative growth studies [4, 5]. Cut-off values used in the Netherlands are BMI-SDS > 1.1 (BMI > p85) for overweight and BMI-SDS > 2.3 (BMI > p95) for obesity [7].

In the 1960's, childhood obesity was very uncommon, with prevalence rates for overweight (BMI > p85) and obesity (BMI > p95) of 4.2-4.6% for children 6-19 years old in the United States [8]. Since that moment, prevalence of childhood obesity is rising. Although prevalence rates from 2007-2012 suggest that the rising prevalence in childhood obesity may have reached a plateau since 2003-2004 [9-11], in 2013-2014 the prevalence was rising again. In 2013-2014 the prevalence rates in children and adolescents 2-17 years old in the US for overweight (BMI > p85) and obesity (BMI > p95) were 33.4 (95%CI 30.9-35.9) % and 17.4 (95%CI 15.2-19.6)%, respectively [3]. In the Netherlands, prevalence of obesity was 0.3% in native boys and 0.5% in native girls aged 2-21 years in 1980. In 2010 however, these prevalence rates for obesity were 1.8% and 2.2% in native boys and girls, respectively, and higher in Moroccan and Turkish descent (6.0% and 8.4% in boys and 7.5% and 8.4% in girls, respectively). These figures should be seen in the context of a prevalence of overweight of 13.3 and 14.9% in native boys and girls, up to 32.5 and 31.7% in boys and girls of Turkish descent [12].

Obesity is most frequently caused by an energy imbalance between intake of calories and calories burned. During the last decades, energy intake shifts towards high-caloric foods containing few vitamins, minerals and other healthy nutrients. At the same time, the energy expended is reduced because of physical activity is reduced

and a sedentary lifestyle is more common [2]. The energy not expended is stored as fat mass. However, there is evidence that more factors contribute to obesity, such as parental obesity, social economic state, maternal nutrition and glucose metabolism during pregnancy and psychological health [13-15]. In 2-4% of the obese children, an endocrine cause (such as hypothyroidism, growth hormone deficiency, Cushing syndrome or hypothalamic obesity), genetic cause (for example leptin deficiency, mutations in POMC or MC4R deficiency) or genetic syndrome (for example Prader-Willi syndrome, Bardet-Biedl and Alstrom syndrome) is found [13, 14, 16-18]. Finally, use of medication, for example anti-epileptic and antipsychotic drugs, can contribute to the development of obesity [18, 19].

### Prognosis and consequences of childhood obesity

Childhood obesity is a strong predictor for obesity in adulthood. Whitaker et al. described in 1997 that 79% of children who were obese at age 10-14 years old, were still obese as young adults (21-29 years) [20]. A systematic review by Singh et al, described rates from 47-83% of obese children becoming obese adults [21]. Odds ratios for obese children to become obese adults varied from OR 1.3 for obese children aged 1-2 years to an OR of 22.3 for obese children aged 10-14 years [20, 22]. In adults who were obese during childhood (age 14-19 years) relative risk for all-cause mortality after 31.5 years of follow up was 1.82 (95% CI 1.48–2.43) in men and 2.03 (95% CI 1.51–2.72) in women [23].

There are multiple consequences affecting almost all organ tracts, of which many will be listed here. Consequences of childhood obesity are both psychosocial and somatic. Psychosocial consequences have a high burden on the quality of life on short-term and long-term. Short-term psychosocial consequences are for example poor self-esteem, being bullied, depression and eating disorders [24, 25]. Low self-esteem was found in 34% of obese girls vs 8% in non-obese girls [26]. Long-term psychosocial effects of obesity include higher risk of depression, oppositional defiant disorder and lower incomes [27-29].

Cardiovascular and metabolic consequences are very common, both on short-term and long-term. The cardiovascular short-term consequences are hypertension, dyslipidemia and endothelial dysfunction [16, 24]. In a cohort of 886 obese children, 42% had dyslipidemia and 32% had hypertension [30]. These short-term consequences, which are risk factors for cardiovascular events such as myocardial infarction and stroke, persist in adulthood when obese children become obese adults [31, 32]. BMI during adolescence was associated with death from cardiovascular disease in a follow up of up to 40 years [33]. The metabolic consequences of childhood obesity are insulin resistance (IR), impaired glucose tolerance, and, in a minority of the obese children, type 2 diabetes mellitus (T2DM). In adulthood, developing T2DM is more common.

Pulmonary short-term and long-term consequences are sleep apnoea, asthma and exercise intolerance [34-37]. Regarding the digestive tract, short-term and long-term consequences are equal, these include gall-stones [38, 39], constipation [40-42], hepatic steatosis or non-alcoholic fatty liver disease (NAFLD) [38, 43-45] and gastro-oesophageal reflux [46, 47]. Short-term musculosketelal problems are flat feet [48-50], lower limb pain [51-53], malalignment of knees and fractures of fore-arm, humerus and femur [54-56]. Fifty to seventy percent of the patients with slipped femoral capital epiphysis was obese [56, 57]. Long-term consequences are arthrosis of knee and hip in early adulthood [58]. Childhood obesity has consequences for the urogenital tract in boys as hypogonadism occurs and in girls by the occurrence of PCOS, which may cause an irregular menstrual cycle, and on long-term subfertility [16, 24, 59]. PCOS is associated with IR [59-61].

### Insulin resistance in children with obesity

IR is a state in which increased levels of insulin are measured in absence of diabetes mellitus, which results from peripheral tissues being less sensitive to insulin [62]. IR in obesity develops as a result of the excess fat mass. Fat is an endocrine active tissue, which excretes adipocytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and free fatty acids. These adipocytokines induce a chronic inflammatory state [63]. This inflammatory state and the free fatty acid release reduce the muscle glucose uptake, and more insulin is needed to maintain normoglycemia. As a result of this insulin resistance, a compensatory hyperinsulinemia arises. Hyperinsulinemia is correlated with NAFLD [64], hypertriglycidemia [65, 66], hypertension [66] and T2DM [67-69].

Therefore, IR is described to play a key role in the development of metabolic and cardiovascular consequences in obesity [63, 70-72]. Although IR is related to obesity, not all obese children are insulin resistant, and not all insulin resistant children are obese. IR levels increase with the level of overweight [73, 74]. Other factors influencing IR are for example puberty, in which a physiological decrease of ~25-50% in insulin sensitivity was observed, and gender and ethnicity [75-77]. Black, African-American and Mexican American children have higher levels of both fasted insulin and post-glucose load insulin levels than white children, irrespective of their pubertal state [74, 78-81].

As IR is a precursor of T2DM, it can be considered an early marker for those who are at high risk of T2DM. Although the other precursors of T2DM, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are clearly defined by the ADA criteria [82], for IR there is no uniform method and cut off value. As a result, the prevalence of IR reported within the same obese population varies between 40.5% and 80.1% in obese children and adolescents (6-18 years), depending on the definition used [83].

In another study the prevalence of IR in obese children aged 8-10 years was 27.3% or 58.4% depending on the definition used [84].

### Treatment of childhood obesity

Lifestyle intervention is the cornerstone of the treatment of obesity, since lifestyle interventions aim to restore the balance between calories ingested and calories burned. The effectivity of lifestyle interventions for the treatment of obesity in children is studied frequently. A Cochrane review and meta-analysis showed a BMI reduction of -3.04 (95% confidence interval (CI) -3.14 to -2.94) and -3.37 (95% CI -3.38 to -3.17) after 6 and 12 months, respectively in children of 12 years and above. The change in BMI-SDS after 6 and 12 months was respectively -0.14 (95%CI -0.17 to -0.12) and -0.14 (-0.18 to -0.10). In younger children (<12 years) after 6 months a small decrease in BMI-SDS was achieved (-0.06 (95%CI -0.12 to -0.01), which declined after 12 months (-0.04 (-0.12 to 0.04) [85]. However, there is large variation in lifestyle programmes, and drop-out rates are high. The effectivity of lifestyle interventions is largely influenced by the motivation of parents. Parent-only interventions for children with obesity showed a reduction in child BMI [86-88]. Finally, to improve the effect of lifestyle interventions for childhood obesity, the use of smartphones and internet-based programmes was studied. Most studies showed an improved compliance and response, and lower drop-out rates. However, no difference in body weight was found between groups using the smartphones or internet-based programmes and the groups receiving standard care [89-91].

In addition to lifestyle intervention, treatment with pharmacological agents, has been explored in obese children and adolescents. The following pharmacological agents have been evaluated in pediatrics [92, 93]: orlistat which is FDA approved for the treatment of obesity, sibutramine (withdrawn in 2010 because of safety reasons [94]), exenatide, and metformin, registered for treatment of T2DM from the age of ten years. According to a Cochrane systematic review, orlistat has shown an additional reducing effect on the absolute BMI in children and adolescents, yet medication related adverse effects such as gastro-intestinal tract symptoms were observed [85]. A review and meta-analysis on the effect of metformin in obese children and adolescents without T2DM concluded that metformin is moderately effective in reducing BMI and IR in hyperinsulinemic obese children and adolescents on short term use (6 months or less): a reduction in mean BMI of 1.42 kg/m$^2$ and homeostasis model assessment of insulin resistance (HOMA-IR) score by 2.01 [95]. Long-term data are limited to one study of 48 weeks, in which a reduction in BMI of 0.9 kg/m$^2$ was reported in participants receiving metformin versus an increase of 0.2 kg/m$^2$ in the placebo group [96].

Finally, the effect of bariatric surgery for severe obese adolescents (BMI of > 40 kg/m$^2$ or > 35 kg/m$^2$ with associated co-morbidities) has been studied. In three trials, chil-

dren who failed to achieve weight loss with non-invasive treatments were included. Bariatric surgery (most frequently laparoscopic sleeve gastrectomy) resulted in this selected populations in significant changes in BMI compared to lifestyle intervention groups, with a follow up of two to four years. Complications occurred in 4.1-4.4% of the patients [97-99]. Three-year follow up of adolescents who underwent bariatric surgery, showed improvement in weight, cardiometabolic health and weight-related quality of life. Complications included deficiencies in micronutrients [99].

## Objectives of this thesis

Childhood obesity is an increasing problem, with IR as an important consequence. The role of IR in the development of T2DM is clear. Given the lack of a generally accepted definition of IR in children, the exact prevalence and incidence of IR are unclear. Therefore, in **chapter 2**, a literature review on the epidemiology of IR in population based studies in pediatric populations is presented.

In **chapter 3**, the variety in definitions for IR in paediatrics is further investigated. The aim of this study is to review all published definitions for IR in children and to apply these definitions to a population of patients with obesity from a pediatric outpatient clinic. The application of all definitions in this population demonstrates the large heterogeneity in definitions.

The clinical application of IR as a screening measure for children at risk of T2DM is investigated in **chapter 4.** In this study the recommended screening for T2DM using fasted plasma glucose (FPG) is compared to a screening combining FPG with a IR measurement, to investigate whether IR is useful as an additional screening to identify more children at risk for T2DM.

As the recommended screening interval for children at risk for T2DM is 3 years, in **chapter 5**, a follow up study is performed in children at risk for T2DM, to evaluate weight, insulin sensitivity, and progression to T2DM approximately 3 years after being diagnosed with overweight/obesity and IR.

In the second part of this thesis, the effect of long-term treatment with metformin in obese children with IR is presented. **Chapter 6a** presents the study protocol of the randomized controlled double-blind trial (RCT) in which the effect of long-term treatment metformin on BMI and IR was studied. In **Chapter 6b** the results of this RCT are presented.

Since treatment effects from clinical trials might differ from the effects in daily clinical practice, the results of the RCT described in **chapter 6,** are compared to the effects of metformin on BMI in daily clinical practice. The aim of **chapter 7** was to compare the effects of metformin (in addition to a lifestyle intervention programme) on change in

BMI between obese adolescents treated with metformin in daily clinical practice and patients who participated in the above mentioned RCT.

A summary of the conclusions of chapter 2-7 is presented in **chapter 8**. Finally, the future perspectives are discussed.

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