

# Predictors of Metabolic Risk in Childhood Obesity

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## Key Words

Metabolic syndrome · Non-alcoholic fatty liver disease · Pre-diabetes · Longitudinal predictors · Markers

## Abstract

Most of the complications of juvenile obesity are due to metabolic disturbances induced by an excessive accumulation of fat which leads to chronic diseases like type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Finding effective ways of identifying obese paediatric patients who are at increased risk of developing cardiovascular and metabolic complications has been recognised to be a promising strategy to improve prevention of complications of early obesity. Moreover, correctly identifying obese children who are already affected by metabolic co-morbidities should be a clinical priority. According to the state of the art summarised in this review, traditional metabolic variables included in the definitions of metabolic syndrome (MS), pre-diabetes, non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steato-hepatitis and, in obese girls, the presence of polycystic ovary syndrome are the best available longitudinal predictors of CVD and T2DM among obese children and adolescents. In clinical practice, traditional metabolic variables included in the definitions of MS should be assessed in all obese children and adolescents; fasting metabolic vari-

ables have been proposed to identify obese patients likely to be affected by impaired glucose tolerance or T2DM, and ultrasound has proved to be a valid surrogate for biopsy in the diagnosis of NAFLD. Further large longitudinal and cross-sectional studies are needed to improve our chances of identifying obese youth at the highest metabolic risk.

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## Introduction

Early-onset obesity, which has reached pandemic proportions, is associated with increased morbidity and mortality and therefore with a shorter life expectancy [1, 2]. Most of the health-threatening consequences of juvenile obesity are due to metabolic disturbances induced by an excessive accumulation of fat which leads to chronic diseases like type 2 diabetes mellitus (T2DM), hypertension and cardiovascular disease (CVD) [1, 2]. Thus, the prevention of obesity-induced metabolic conditions is a cornerstone of the management of overweight and obesity during childhood [3]. Due to the challenging proportion of children and adolescents affected by obesity in most countries, finding effective ways to identify obese paediatric patients who are at increased risk of developing cardiovascular and metabolic complications has been recog-

nised to be a promising strategy to improve prevention of complications of early obesity and has been a major priority of the research in the field of childhood obesity for several years [4]. Despite the large number of papers published on this subject, our knowledge of risk factors for the progression towards overt obesity-related cardiovascular and metabolic disease from childhood to adulthood is still far from being satisfactory and does not allow for a fully accurate discrimination of obese children and adolescents who are at increased metabolic risk [4]. However, some obesity-related conditions, such as impaired glucose tolerance (IGT), non-alcoholic fatty liver disease (NAFLD) and others, that are common complications of obesity during childhood and adolescence have been recognised to be risk factors for the development of cardiovascular and metabolic disease, such as non-alcoholic steato-hepatitis (NASH), symptomatic atherosclerosis and T2DM, and have been included in the metabolic assessment of the obese child or adolescent in most clinical settings despite their imperfect accuracy in stratifying the risk for adult disease. As the diagnosis of some of these conditions requires invasive and/or non-cost-effective tests, several circulating, imaging or anthropometric markers have been recently proposed as screening tools for these baseline complications of childhood obesity, in order to narrow the number of patients undergoing gold-standard invasive tests. This review critically summarises the current knowledge about both the prospective predictors of cardio-metabolic risk in obese children and adolescents and the markers of the presence of obesity-related metabolic impairment. These markers can be defined as 'cross-sectional predictors', as they do not precede the metabolic impairment but mark its presence. Thus, the term 'predictor' is used with the double meaning of risk factor and marker in the title of this review, which includes two main sections, one concerning predictors of future disease, titled 'Risk Factors', and one concerning predictors of current metabolic impairment, titled 'Markers of Co-Morbidities'.

Articles of potential interest for this review were searched in PubMed using the following term: 'predict\* AND obes\* AND (child\* OR adolescen\*) AND (dyslipidemia OR triglyceride\* OR glucose OR 'type 2 diabetes' OR atherosclerosis OR hypertension OR cholesterol OR hypercholesterolemia OR NAFLD OR NASH OR cardiovascular OR coronary OR stroke OR metabolic)'. A total of 2,185 abstracts were read, and 113 full-text articles were uploaded and examined, 71 of which were retained as references for this review, based on their suitability for the reviewed subject, their scientific quality and their currency.

## Risk Factors

### *The Metabolic Syndrome and Traditional Fasting and Non-Fasting Circulating Risk Factors*

Metabolic syndrome (MS) is by far the most extensively described condition associated with childhood and adolescent obesity and has traditionally been supposed to be a risk factor for adult cardiovascular and metabolic complications. In adolescents as in adults, MS is generally defined as the association of obesity or central obesity with at least 2 other cardiovascular risk factors from among abnormal glucose homeostasis, high systolic and/or diastolic blood pressure, high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) [5–8]. There are several controversies that have fuelled the scientific debate on the utility of assessing MS in children and adolescents, both in the general population and among obese patients [6–8].

A real consensus on the definition of MS for children and adolescents has never been achieved [6, 7]. Several definitions with different cut-off values for the diverse parameters have been proposed, leading to greatly different prevalence estimates and diagnosis inconsistency when tested in the same populations and often showing diagnosis instability during adolescence [8–10]. More importantly, independently of the definition adopted, there is still debate about the utility of MS as a cardiovascular predictor in children and adolescents, as it has not been definitively established whether MS has a legitimate role as a clinical tool to identify adolescents with the highest metabolic and cardiovascular risk [7]. Longitudinal data from the Bogalusa Heart and Cardiovascular Risk in Young Finns studies, which included 1,781 participants aged 9–18 years examined at baseline and 14–27 years later, and longitudinal data from the Tehran Lipid and Glucose Study, which included 1,424 adolescents followed up for 10.4 years, have not shown that MS during childhood and adolescence is any more useful than body mass index (BMI) or the presence of obesity in predicting subclinical atherosclerosis, T2DM or adult MS [11, 12]. However, these studies are population-based and they do not address the question whether among BMI-matched obese children and adolescents the presence of MS may imply a further cardio-metabolic risk besides obesity. The above studies have also highlighted that the presence of MS during adolescence is not predictive of adult MS after adjustment for adult BMI and is not predictive of adult T2DM or increased carotid intima-media thickness (cIMT), a surrogate marker of pre-clinical atherosclerosis, after adjustment for the presence of adult MS. This means, in

other words, that obesity or MS that resolves before adulthood does not imply any worse cardio-metabolic prognosis compared to never experiencing either obesity or MS [12, 13]. Consistently, data on 6,328 subjects from four prospective cohorts pooled together (the Bogalusa, Muscatine, Cardiovascular Risk in Young Finns and Childhood Determinants of Adult Health studies) showed that obese children and adolescents who recover from their obesity have the same risk of presenting adult T2DM, hypertension, dyslipidaemia or increased cIMT as children and adolescents who were never obese [14]. On the other hand, the Bogalusa and Cardiovascular Risk in Young Finns studies showed that while individuals developing MS as adults have a 1.7-fold higher risk of presenting increased adult cIMT than those never experiencing MS, individuals with persistent MS from childhood onwards have a 3.4-fold higher risk of presenting increased adult cIMT, suggesting that childhood MS, unless it resolves, is a real cardiovascular risk factor [13]. Consistently, the Princeton Lipid Research Clinics Follow-up Study, the only available paediatric prospective study assessing real cardiovascular events and not surrogate cardiovascular markers like cIMT, demonstrated that not only do subjects with persistent high blood pressure or high TG from childhood onwards have about a 3-fold higher risk of developing adult T2DM than those with adult onset of these risk factors, but also that subjects with persistent high TG from childhood onwards have about a 5-fold higher risk of developing adult CVD than those with adult onset of hypertriglyceridaemia, thus highlighting the deleterious role of persistent childhood metabolic risk factors in the development of adult cardio-metabolic disease [15]. Although these studies are population-based, thus not focusing on obese youth, they strongly suggest that an obese child with traditional metabolic impairments has an increased metabolic and cardiovascular risk compared to a BMI-matched peer without metabolic impairments. Supporting this hypothesis, cross-sectional studies on obese adolescents have shown that obese individuals with MS or single MS components have higher cIMT and a higher risk of presenting left ventricular hypertrophy than obese counterparts with no impairment [16–18]. Moreover, a short-term longitudinal study of obese Latino children and adolescents showed that persistent MS was associated with higher cIMT compared to subjects without MS [19].

A recent cross-sectional study including 461 overweight adolescents reported that the presence of MS is a less effective predictor of increased cIMT than the sum of the quantitative components of MS [20]. Consistent-

ly, a longitudinal study in 265 adolescents showed that a cluster score using traditional MS as continuous variables tracks better into adulthood than dichotomous MS and is a better predictor of adult MS [21]. Even if the use of quantitative scores has not yet entered routine clinical practice, these data suggest that while assessing the metabolic profile of an obese child or adolescent, severe impairments of metabolic parameters should be considered particularly unfavourable from the point of view of cardiovascular prognosis, even if isolated. Of note, while cardiovascular risk associated with childhood BMI and MS has been shown to be reversible in the case of obesity/MS recovery, childhood low-density lipoprotein (LDL) cholesterol and blood pressure have come to be associated with adult cIMT irrespective of their tracking into adulthood, based on the Cardiovascular Risk in Young Finns Study [22]. Small dense LDL cholesterol particles are particularly atherogenic; recently, the TG/HDL-C ratio has been shown to be a good marker of small dense LDL in overweight and obese children and adolescents and has been associated with increased arterial stiffness in children, adolescents and young adults, regardless of BMI and blood pressure [23, 24]. Thus, the TG/HDL-C ratio should be calculated while assessing the cardiovascular risk of obese paediatric patients. A TG/HDL-C ratio  $\geq 3$  is associated with a markedly higher concentration of small LDL than a TG/HDL-C ratio  $< 3$  [23].

Despite a considerable body of evidence about the associations between traditional metabolic risk factors and adult T2DM, an accurate risk score to identify obese children who are likely to develop T2DM is still lacking. Longitudinal cohorts have shown that the combination of 4 or more MS components during childhood or adolescence is strongly predictive of T2DM during young adulthood, though this criterion has poor sensitivity [25, 26]. The IGT, a traditional pre-diabetic condition, is not a fully accurate predictor of future T2DM. In fact, short-term longitudinal studies have shown that IGT is a strong predictor of T2DM in severely obese African-American adolescents and a moderate predictor in obese white adolescents, in whom it tends to convert to normal glucose tolerance in 75% of cases [27, 28]. Notably, IGT during childhood and adolescence is a cardiovascular risk factor per se, independently of the development of diabetes, as it is associated with an increased rate of cardiovascular events in adults [29], and it has recently been shown to be associated with increased cIMT in youth [20]. Impaired fasting glucose (IFG), which affects 2–5% of obese children and adolescents, is also considered a pre-diabetic

condition [30]. Even if the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study failed to demonstrate any association between baseline IFG and T2DM in young adulthood [11, 30], the Princeton Lipid Research Clinics Follow-up Study showed that IFG was the strongest independent predictor of adult IFG/T2DM from among parental history of T2DM, IFG and cigarette smoking after adjustment for BMI [26]. Another study in pre-adolescent and adolescent girls showed that IFG was a strong independent predictor of IFG/T2DM at 24 years of age, along with weight gain, MS and high insulinaemia [31]. Further longitudinal studies especially designed for populations of obese adolescents at baseline would probably be helpful to clarify the exact significance of isolated IFG in obese individuals during adolescence. Combined IFG and IGT is a condition characterised by profound impairment of both insulin sensitivity and secretion, whose pathophysiology in obese youth largely overlaps with that of overt T2DM [32]. Thus, although longitudinal studies exploring the exact short- and long-term predictive utility of this condition are lacking, it should be considered a strong risk factor for the development of T2DM. As in adults, a 1-hour glucose level >155 mg/dl during an oral glucose tolerance test (OGTT) in obese children and adolescents was shown to be associated with impaired glucose disposition and insulin secretion, thus being a candidate predictor of T2DM for future longitudinal studies [33]. Preliminary data from a pilot longitudinal study show that glycated haemoglobin (HbA1c) in non-diabetic obese adolescents may be a predictor of short-term onset of T2DM, but a validated cut-off is still not available [34].

In summary, in obese adolescents the development of T2DM and CVD is predicted not only by traditional fasting risk factors but also by the presence of IGT, especially among patients of non-European ancestry and in association with IFG.

#### *Anthropometric Risk Factors*

Data from the 1958 British birth cohort have shown that childhood BMI and BMI gain were weak predictors of adult T2DM and CVD risk factors [35]. Consistently, data from the 1985 Australian Health and Fitness Survey showed that BMI, waist circumference (WC), waist-to-height ratio (WtH-r) and the sum of skinfolds are all similarly weak predictors of adult MS score (Spearman correlations around 0.20 and 0.30 for measures at 7–11 and 12–15 years, respectively) [36]. Longitudinal data on predictive properties of anthropometric measures in samples of obese children and adolescents do not exist.

#### *Family History*

T2DM has a high heritability, and children of people with T2DM are at increased risk of developing T2DM [37]. Even if longitudinal studies on the exact predictive value of a family history of T2DM among obese children and adolescents are not available, cross-sectional data demonstrate that obese children and adolescents with a family history of T2DM are more likely to present with glucose dysregulation [38, 39], suggesting an increased risk of adult T2DM in this sub-group of obese paediatric patients. Moreover, a very high percentage (74–100%) of children with T2DM has a family history of T2DM, proving that the absence of family history is a good negative predictor of paediatric-onset T2DM [40]. The predisposition to CVD is also heritable, and cross-sectional data in healthy young adults prove that a family history of coronary heart disease is a risk factor for subclinical atherosclerosis even after adjustment for MS, suggesting that obese youth with a family history of coronary heart disease may have an increased risk of developing CVD [41].

#### *Birth Weight*

Low birth weight is a well-recognised risk factor for the development of T2DM and CVD [42–44]. Even if longitudinal studies specifically exploring the predictive value of low birth weight among obese youth are not available, cross-sectional evidence proves that obese children and adolescents born small for gestational age are more likely to present with insulin resistance and MS compared to their counterparts born normal or large for gestational age, suggesting that a low birth weight is predictive of worse metabolic and cardiovascular status in obese youth [42–44].

#### *Adiposity Rebound*

At a general population level, an early adiposity rebound is a risk factor for adverse adult metabolic outcomes because it associates with childhood obesity and higher adult BMI [45]. This justifies the hypothesis that obese children and adolescents with a history of early adiposity rebound may be at increased metabolic risk because of an increased likelihood of becoming obese adults compared to their obese peers without a history of early adiposity rebound. This should be assessed by longitudinal studies in cohorts of obese children and adolescents.

#### *Other Risk Factors*

Besides traditional circulating, anthropometric and anamnestic paediatric risk factors for adult T2DM and CVD, several others have been emerging as potential predictors of these conditions at a general population level.



Among lifestyle risk factors, infrequent fruit consumption and low physical activity in childhood were associated with accelerated 6-year IMT progression in adulthood in the Cardiovascular Risk in Young Finns Study [22], while a persistently low consumption of fruits and vegetables was associated with increased adult cIMT [22]. However, data from pooled longitudinal analyses using the recently established 7 American Heart Association (AHA) ideal goals (ideal BMI, physical activity and diet, non-smoking, ideal blood pressure, cholesterol and fasting blood glucose) as outcome have shown that the association between childhood diet variables and the number of adult AHA goals disappeared after adjustment for parental smoking and socio-economical status, baseline anthropometry and traditional circulating variables [46]. Data on the predictive value of lifestyle variables in cohorts of obese youth are not available.

The prospective paediatric studies also explored the predictive utility of established CVD-associated polymorphisms in predicting subclinical atherosclerosis during childhood, highlighting the lack of accuracy improvement compared to traditional factors alone [22]. A similar conclusion has been drawn for several 'alternative' circulating biomarkers, like C-reactive protein, adiponectin, leptin, homocysteine and asymmetric dimethylarginine [22], even if high adiponectin has been shown to be protective against adult MS among obese girls [47]. Overall, according to the state of the art, the 2011 AHA statement that 'substantial research is required before non-traditional risk factors can be used to identify [...] cardiovascular disease risk in children and adolescents' [48, 49] still seems to be valid.

Among co-morbidities of childhood and adolescent obesity, polycystic ovary syndrome and low sex hormone-binding globulin in adolescent girls are known to be strong risk factors for severe obesity and MS during early adulthood [50], and NAFLD in obese children and adolescents is known to be associated not only with NASH but also with short-term worsening of glucose homeostasis [51].

## Markers of Co-Morbidities

### *Markers of T2DM and IGT*

According to the American Academy of Pediatrics, all adolescents evaluated for obesity should undergo a fasting plasma glucose (FPG) test [3]. FPG has recently shown good accuracy in detecting OGTT-confirmed cases of T2DM in obese children and adolescents, in contrast to

the 6.5% HbA1c cut-off proposed by the American Diabetes Association as a screening tool for T2DM, which has shown low sensitivity in detecting T2DM cases diagnosed by FPG or OGTT [34]. An HbA1c above 5.8% was associated with 67% sensitivity and 87% specificity for T2DM [34]. Acanthosis nigricans, a well-known marker of insulin resistance and metabolic co-morbidity in obese children, is present in 90% of non-Caucasian children with T2DM; thus, the absence of acanthosis nigricans among non-Caucasian children greatly contributes to excluding the presence of T2DM [40].

Regarding the state of the art on potential fasting screening tools for IGT, high-normal (5.5%) or mildly pre-diabetic (5.7–5.8%) thresholds of HbA1c have shown only moderate accuracy in identifying OGTT-confirmed IGT cases among obese children and adolescents [52–55]. The American Diabetes Association's criteria for selecting children to test for T2DM and criteria specifically designed for screening obese children for IGT in European populations, such as a clinical score issued from a German cohort or the fasting glucose cut-off of 86 mg/dl issued from an Italian cohort [56, 57], have recently shown sub-optimal accuracy in identifying IGT when tested in different populations [58]. Also, a clinical score based on data from a multi-ethnic American cohort showed only moderate accuracy [39]. Recently, fasting TG >103 mg/dl has been proposed as a criterion for identifying obese youth at risk of IGT in a Canadian population [58]. This criterion has recently been validated in a large pooled population of obese Italian children and adolescents, where it showed 67% sensitivity and 68% specificity for IGT [59]. Based on the Italian data, an implemented tool combining TG and FPG has been proposed to identify youth at risk for IGT. The combination of TG ≥100 mg/dl and FPG ≥80 mg/dl had 69% sensitivity and 78% specificity in identifying youth with IGT, which is the highest accuracy ever achieved by a published screening tool for IGT in youth [59]. This screening strategy should be validated abroad before being recommended in the management of obese youth [59].

### *Markers of NAFLD and NASH*

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommends that all obese children older than 3 years have abdominal ultrasounds and hepatic function tests performed to search of NAFLD [60]. While alanine aminotransferase and aspartate aminotransferase are not predictive of this condition, ultrasounds have been shown to be accurate in identifying biopsy-confirmed NAFLD in obese children

and adolescents [61]. However, large-scale abdominal ultrasounds may not be a cost-effective approach. Several circulating biomarkers and composite clinical scores including both clinical and circulating variables have been proposed as screening tools for NAFLD, but none of them proved to have higher accuracy and cost-effectiveness than ultrasounds [62]. Biopsy is also the gold-standard method to diagnose NASH and hepatic fibrosis. Recently, cytokeratin-18 fragment levels as well as a combined score made up of clinical variables and 5 polymorphisms have been proposed to identify obese children with NASH [63, 64]. The paediatric NAFLD fibrosis index and transient elastography have both showed good accuracy in detecting hepatic fibrosis in children with NAFLD [65, 66].

### Markers of MS

Among normal or overweight children, the degree of general or central adiposity, expressed as the Z score of BMI (Z-BMI) and WC or WtH-r, is a good marker of the presence of MS [67, 68]. In contrast, among obese children and adolescents the Z-BMI, WC, WtH-r and skinfold thickness, though showing positive associations with MS and its components, are only moderate predictors of these co-morbidities [38, 69–73]. For example, even though a WtH-r cut-off of 0.6 has been proposed to detect obese children with metabolic impairments [38, 73], data from the National Health and Nutrition Examination Survey provide evidence that a high percentage of subjects affected by metabolic co-morbidities (about 50%) is under this threshold despite a real increased risk associated with a WtH-r >0.6, due to the unsatisfactory accuracy of this criterion [73]. Interestingly, among both normal and obese children and adolescents, traditional surrogate measures of visceral adiposity like WC and WtH-r do not perform better than BMI or Z-BMI as markers of metabolic co-morbidities [68–70]. This can be convincingly explained by recent evidence that during childhood and adolescence, BMI and WC are very highly correlated and have similarly sized associations with intra-abdominal adipose tissue [74, 75]. Thus, in paediatric clinical practice, the use of measures of central adiposity to identify obese patients to test for metabolic variables is not justified, although some authors say the opposite [73]. Consistently, the American Academy of Pediatrics recommends that a metabolic assessment including fasting glucose and lipids and blood pressure measurement be offered to obese children and adolescents regardless of other conditions [3].

Several circulating markers, such as uric acid, alanine aminotransferase, adiponectin, leptin, resistin, retinol binding protein 4, plasminogen activator inhibitor-1 and other inflammatory markers, as well as novel adiposity markers, such as epicardial fat, have been associated with MS, fueling the research on the pathogenesis, long-term prediction and treatment of cardio-metabolic disease [17, 76–80]. However, their clinical advantages as markers of MS have not been assessed, so that their use as screening tools for MS is not justified [17, 76–80].

### Conclusions

According to the state of the art, traditional metabolic variables, pre-diabetes, NAFLD/NASH and, in obese girls, the presence of polycystic ovary syndrome are the best available longitudinal predictors of CVD and T2DM among obese children and adolescents. In clinical practice, traditional metabolic variables included in the definitions of MS should be assessed in all obese children and adolescents; fasting metabolic variables have been proposed to identify obese patients likely to be affected by IGT or T2DM with normal FPG; ultrasound has proved to be a valid surrogate for biopsy in the diagnosis of NAFLD; cytokeratin-18 and some genetic polymorphisms have been proposed to diagnose NASH, and elastography has showed good accuracy in detecting hepatic fibrosis. Further large longitudinal and cross-sectional studies are needed to improve our chances of identifying obese youth at the highest metabolic risk.

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