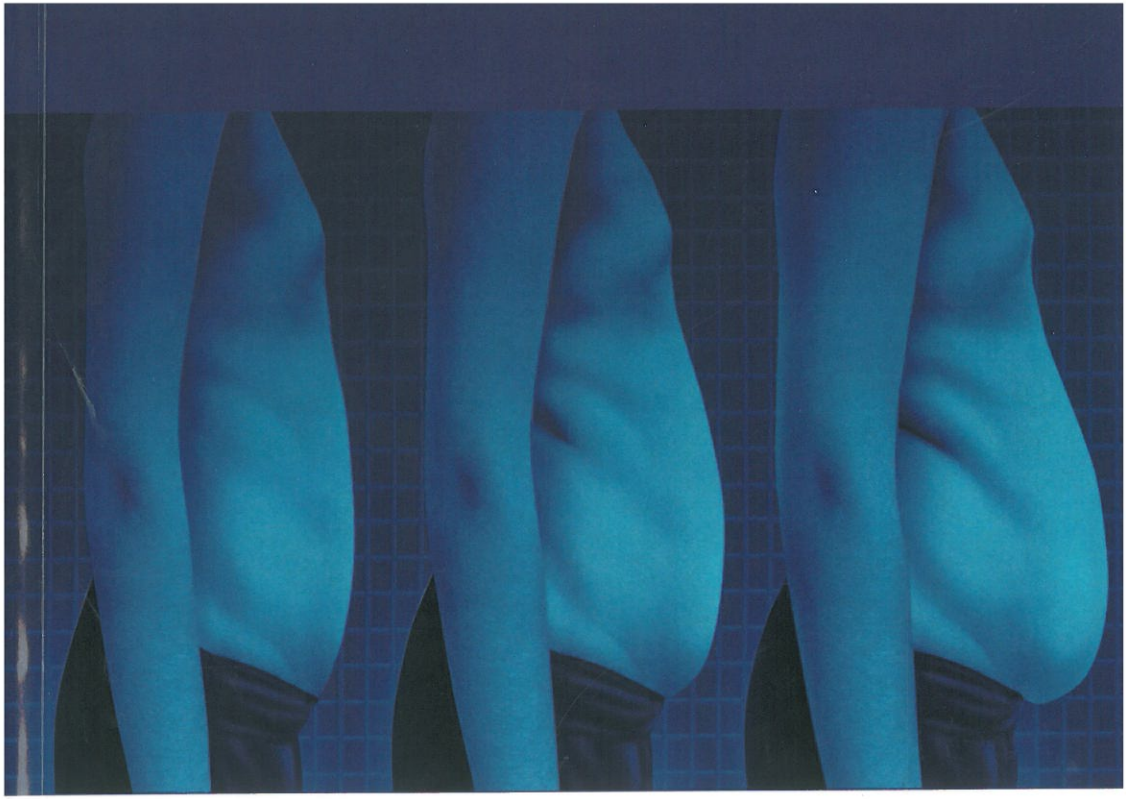

Jorge Bravo

Metabolic Syndrome Paediatric Criteria

The Accuracy of Current Abdominal Obesity Criteria

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List of Abbreviations

AO – Abdominal Obesity

ATP III – Adult Treatment Panel

AF – Aerobic Fitness

AUC – Area Under the Curve

BMI – Body Mass Index

CVD – Cardiovascular Disease

cMSr – Continuous Metabolic Syndrome Risk

DBP – Diastolic Blood Pressure

EYHS – European Youth Heart Study

GLU – Glucose

HDL-C – High Density Lipoprotein-Cholesterol

IDF – International Diabetes Federation

IOFT – International Obesity Task Force

LMS – Lambda-Mu-Sigma

LDL – Low Density Lipoprotein

MS – Metabolic Syndrome

ONAFAF – Observatório Nacional da Actividade Física e da Aptidão Física

OW – Overweight

PA – Physical Activity

PCA – Principal Component Analysis

ROC – Receiver Operating Characteristic

SBP – Systolic Blood Pressure

TG – Triglycerides

Vs - Versus

WC – Waist Circumference

WHO – World Health Organization

Introduction

Lifestyle related diseases and youth

Lifestyle related diseases such as Type II Diabetes, Cancer and Cardiovascular Diseases (CVD) represent the most serious threat against public health in the industrialized western world, and today burden of non-communicable diseases is increasing even in the developing countries (Walt, 2004). Relatively ancient references report inappropriate lifestyle recognized in particular by alcohol intake (Friedenreich, Howe, Miller, & Jain, 1993; Rothman, 1980; Stinson & DeBakey, 1992), smoking (Chao, et al., 2000; Coughlin, Calle, Patel, & Thun, 2000), sedentary behaviour (Helmrich, Ragland, Leung, & Paffenbarger, 1991; Manson, et al., 1991; Sesso, Lee, & Paffenbarger, 1998), and high caloric diet rich in fat (Brunner, 1997; Hu, et al., 1997), has been found to be associated with the reduced health status. Consequently, changed lifestyle habits are addressed as important issues regarding the increased prevalence of non-communicable diseases (Guilbert, 2003; Who & Consultation, 2003).

Although the clinical manifestations of lifestyle related diseases typically are absented until adulthood, bad habits picked up in childhood cannot be considered benign conditions since there are several pathways through which childhood behaviour might influence health status. For instance, a possible direct relationship between lifestyle in childhood and health status in adulthood is being supported by findings from longitudinal studies, where physical activity (PA) and aerobic fitness (AF) during youth has been found to be related to CVD risk factors in adulthood (Boreham, et al., 2002; Thorp, Owen, Neuhaus, & Dunstan, 2011; Twisk, Kemper, & Mechelen, 2002). In addition, CVD and all-cause mortality have been reported to be elevated among adults who were overweight (OW) in childhood irrespective of adult weight (Gunnell, Frankel, Nanchahal, Peters, & Smith, 1998; Must & Strauss, 1999).

Furthermore, lifestyle during childhood may be related to the health status in the same period, which is again an important predictor for health status in adulthood, or lifestyle in childhood might even be related to lifestyle during adult age, which again is directly related to health status in adulthood (Twisk, Kemper, & Mechelen, 2002). An American study, the Pathobiological Determinants of Atherosclerosis in Youth Study, found that approx. 60% of adolescents aged 15 to 19 years had visible changes in the coronary arteries, increasing to 70-80% in men and women aged 30 to 34 years (Stary, 2000; Strong, et al., 1999). More progressive lesions begin to appear around puberty, and are present in about a quarter of the 25- to 35-year-olds (Stary, 2000; Strong, et al., 1999). Similar findings were made by the multinational study, the Pathobiological Determinants of Atherosclerosis in Youth study, which showed the presence of fatty streaks in the coronary arteries of subjects as young as 5 years of age (Fernandez-Britto, Wong, Contreras, Nordet, & Sternby, 1999).

Evidence supporting these theories has been recognized in the literature, where behavioural characteristics in childhood, such as being physically active, has been found to reduce antecedent risk factors for coronary heart diseases (Boreham, Twisk, Savage, Cran, & Strain, 1997; Palve, et al., 2014). Furthermore, major health risk factors like low PA, low AF, OW, smoking, and poor food habits have been found to persist from childhood into adolescence (Clarke & Lauer, 1993; Janz, Dawson, & Mahoney, 2000; Kelder, 1994) and from adolescence into the adult years (Twisk, Kemper, Mechelen, & Post, 1997).

The justification for lifestyle interventions among children and adolescents (apart from smoking) has, however, long been debated. Among other things, it was not known whether the presence of risk factors – or the modification of risk factors – in children and adolescents had any effect on the development of atherosclerotic disease several decades later. It was only in the past ten years that the relationship between lifestyle, risk factors and the development of atherosclerosis in children and adolescents has become clearer, along with the significance of this relationship for the development of disease later in life (Daniels, 2001). The tendency of tracking of

risk factors indicates that successful interventions carried out to reduce lifestyle related disease incidences should be initiated as early as in childhood.

Cardiovascular Disease Risk Factors and the Youth

It was already established about fifty years ago that the likelihood of an individual developing CVD could be predicted by assessing relatively few of the individual's characteristics – also called risk factors (Misra, 2000). Many of these risk factors are interrelated, and several of them have an additive or synergetic effect on the risk.

CVD is a disease of major personal and social economic impact, and today it is considered as a major threat to the public health, especially in the Western world (Walt, 2004). According to the European Heart Network, more than 35% of all deaths in Denmark in 2005 were caused by CVD (Petersen, et al., 2005), and the World Health Organization (WHO) has stated that over a billion people will die from CVD worldwide in the first half of the 21st century (Mackay & Mensah, 2004). Unfortunately, interventions designed to reduce CVD risk in adults have had only limited effect, but some evidence exists that greater success may be achieved with children (Daniels, Pratt, & Hayman, 2011; Simons-Morton, 1991; Webber, et al., 1996).

Cross-sectional studies have shown that a high intake of energy primarily from fat, sugar and fast food and physical inactivity in children and adolescents is associated with OW (Durant, et al., 1993; Fogelholm, Nuutinen, Pasanen, Myoehaenen, & Saeaetelae, 2000; French, Story, & Jeffery, 2001; Gazzaniga & Burns, 1993; Gillis, Kennedy, Gillis, & Bar-Or, 2002; Nguyen, Larson, Johnson, & Goran, 1996; Trost, Kerr, Ward, & Pate, 2001). Inactivity and unhealthy eating habits soon were associated with elevated levels of fat in the blood, elevated insulin levels and high blood pressure (Gutin, et al., 1990; Raitakari, et al., 1997). Approximately 20-30% of OW children have elevated systolic or diastolic blood pressure (Figueroa-Colon, Franklin, Lee, Aldridge, & Alexander, 1997), being verified a marked intensification of the influence of adiposity on blood pressure when children reach the categories of

OW and obese (Tu, et al., 2011). A study of over 13,000 Danish secondary-school pupils showed that both a high body mass index (BMI) and a low level of physical fitness increase the risk of elevated blood pressure, and that the correlation between BMI and blood pressure was closer among adolescents with low levels of fitness (Nielsen & Andersen, 2003).

Another findings have shown that many OW children have increased levels of C-reactive protein in their blood (Ford, et al., 2001). An increased level of this protein is directly linked to the risk of CVD.

One longitudinal study conducted in New Zealand showed that the children and adolescents that spend more time watching television presented higher BMI, serum cholesterol and triglyceride levels, and the poorer was their physical fitness at the age of 26 years; the study did not show, however, an association between television viewing and blood pressure levels (Hancox, Milne, & Poulton, 2004). In a Danish study that had measured physical fitness and PA as well as a number of cardiovascular risk factors (blood pressure, skinfolds, waist circumference (WC), total cholesterol and triglyceride levels and LDL and HDL cholesterol) among 15- to 19-year-old girls and again 8 years later (Hasselstrom, Hansen, Froberg, & Andersen, 2002), revealed that fitness and activity while young were not associated with risk factors in adulthood, but changes in physical fitness from childhood to adulthood was a good predictor of most risk factors in adults and of changes in risk factors from childhood to adulthood. The cohort was characterized by considerable changes in levels of physical fitness in the course of the 8 years the study lasted.

In the American Bogulosa Heart Study, OW during teenage years (13 to 17 years) was associated with higher systolic and diastolic blood pressure, and higher concentrations of total cholesterol, LDL cholesterol, triglyceride, insulin and glucose 12 to 14 years later (Srinivasan, Bao, Wattigney, & Berenson, 1996).

A Dutch study, more precisely the Amsterdam Growth and Health Longitudinal Study (AGHLS), measured physical fitness and PA among 13-year-olds (Twisk, et al.,

2002). After a 20- year tracking period, the study established that good physical fitness in childhood is related to a healthy risk profile among adults (lower fat mass, waist measurement and total cholesterol, though not HDL cholesterol). However, not all longitudinal studies have found an association between lifestyle and/or OW in children and high levels of biological intermediary risk factors in adults. The British Newcastle Thousand Families Study thus failed to report an association between OW among 13-year-olds and the incidence among 50-year-olds of high systolic and diastolic blood pressure, and concentrations of total cholesterol, HDL cholesterol and LDL cholesterol as well as insulin and GLU (Wright, Parker, Lamont, & Craft, 2001).

A recent cross-sectional multicentre study with six research groups performed in Spain (Garcia-Ortiz, et al., 2010) analysed the relationship of PA and dietary pattern to the circadian pattern of blood pressure, central and peripheral blood pressure, pulse wave velocity, carotid intima-media thickness and biological markers of endothelial dysfunction in active and sedentary individuals without arteriosclerotic disease in a 20-80 years old sample. They found that sustained PA and the change from sedentary to active as well as a healthy diet improve circadian pattern, arterial elasticity and carotid intima-media thickness and moreover, the results of their study support interventional approaches that combine physical exercise and diet to delay vascular aging (Garcia-Ortiz, et al., 2010).

Although the established causal links between health status and CVD risk factors not yet have been confirmed in children to the same extend as in adults, both behavioral, physiological, and genetic risk factors for CVD can be identified in children and young people (Andersen, Henckel, & Saltin, 1989; C. Boreham, Savage, Primrose, Cran, & Strain, 1993), and according to autopsy studies evident atherosclerotic lesions are identifiable even in young children (Berenson, et al., 1992; Green & Humphries, 1994; Strong & McGill Jr, 1969). Furthermore, besides being recognized as independent risk factors for CVD mortality in men and woman (Blair, et al., 1996; Calle, Thun, Petrelli, Rodriguez, & Heath, 1999), OW and low cardio respiratory fitness have been found to be related to CVD risk factors, such as elevated blood

pressure and unfavorable blood lipids, at an early stage in children (Andersen, Wedderkopp, Hansen, Cooper, & Froberg, 2003; Freedman, Dietz, Srinivasan, & Berenson, 1999; Katzmarzyk, Malina, & Bouchard, 1999).

A high fat mass – and low PA and low physical fitness – in children and adolescents is often associated with metabolic changes compatible with the metabolic syndrome (MS) – elevated blood pressure and abnormal blood lipids (dyslipidaemia) as well as reduced GLU tolerance and elevated insulin (Andersen, et al., 2003; Bergstrom, Hernell, Persson, & Vessby, 1996; Durant, et al., 1993; Freedman, et al., 1999; Steinberger, Moorehead, Katch, & Rocchini, 1995). These are factors which, when they coexist, significantly increase the risk of heart disease. The syndrome has been observed in children as young as 5 years of age (Young-Hyman, Schlundt, Herman, De Luca, & Counts, 2001).

Abdominal Obesity, Cardiovascular Disease and the Metabolic Syndrome

Third "National Cholesterol Education Program Adult Treatment Panel" (ATP III) defined the MS as the presence of at least three of the following five risk factors in an individual: abdominal obesity (AO), hypertension, hypertriglyceridemia, low HDL cholesterol and fasting high GLU levels. The MS represents an increased risk for CVD and diabetes mellitus (Jessup & Harrell, 2005).

The "International Diabetes Federation" (IDF) definition requires the presence of high WC and two of the remaining risk factors, adopting the ATP cut-offs. For the WC cut-offs, the IDF provided ethnic adjustments(Alberti, Zimmet, & Shaw, 2005).

The MS components were shown not only in adults but also in children and adolescents (Arslanian & Suprasongsin, 1996; Caprio, Bronson, Sherwin, Rife, & Tamborlane, 1996; Jiang, Srinivasan, Webber, Wattigney, & Berenson, 1995), however the agreement in the definition of the MS remains doubtful. Some researchers used the ATP III recommended criteria (possess at least three of the five components)(Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003; Cruz, et al., 2004; Weiss, et al., 2004), whereas others included high fasting insulin levels (Ford &

Giles, 2003).

Such variability with the definition is due to the growth changes produced during childhood and adolescence period (Tfayli & Arslanian, 2007), making difficult the establishment of risk factors specific cut-offs. Variables such as high heart pressure, weight, height and BMI differ between genders and are age-specific. Moreover, OW is differently defined in children and in adults once children are in continuous growth, changing constantly height and weight during childhood making difficult to establish cut-offs for OW and obesity.

Abdominal obesity, considered a key component of the MS, is an example of the difficulty to establish risk levels in children. Despite the recommended cut-offs for WC in adults, the recommendations for children and adolescents remain non-consensual. Some researchers used the BMI z-score to define OW instead an indicator for AO such as WC (Weiss, et al., 2004). However others used the 90th percentile as the cut-off for AO (Cook, et al., 2003).

The IDF, looking for a consensus, developed a practical worldwide definition to identify the youth with high risk for CVD and diabetes mellitus(Alberti, et al., 2005). The consensus established that the ATP III components would be a reasonable basis. Moreover, the consensus agreed that diabetes and insulin resistance have been considered excessively important in previous definitions. Insulin resistance assessment have been considered unpractical, although some MS components, specially WC and triglycerides (TG) were highly correlated to insulin sensitivity (Lemieux, et al., 2000).

Abdominal obesity assessed by WC was considered essential in the MS diagnose due to the strong evidences that correlate the WC with CVD and other MS components. The cut-off selected for WC was the same used by the "European Group for the Study of Insulin Resistance" and lower than the cut-off recommended by ATP III once the data suggest an increase in other CV risk factors in "Europids" (Caucasians original from Europe) when the WC exceed the 94 cm in men and the 80 cm in

women (Eckel, Grundy, & Zimmet, 2005).

A new MS definition emerged recently for children and adolescents using adult's modified criteria. In this definition the IDF recommends that for youth with 16 years old and older should be applied the adult's criteria for all the MS components, whereas for younger than 16 years and older than 6 years the 90th percentile should be used as cut-off for the WC (Zimmet, et al., 2007).

In recent years there has been a growing interest in the constellation of closely related cardiovascular risk factors, emerging the fundamental importance of the MS in identifying individuals at high risk for type II diabetes and CVD. Several expert groups have attempted to produce accurate diagnostic criteria.

The first attempt was produced by the diabetes group of the WHO in 1999 which proposed a definition that could be modified as more information would be obtained (Consultation, 1999). The criteria containing the insulin resistance and impaired GLU tolerance as essential components with at least two of the following: high blood pressure, hypertriglyceridemia and / or low HDL cholesterol, obesity (measured by BMI) and microalbuminuria. The "European Group for the Study of Insulin Resistance" (Balkau & Charles, 1999) then produced a modification of the WHO criteria, excluding people with diabetes needing the presence of hyperinsulinemia. The WC was the measure of obesity with different cut-offs generating considerable confusion and lack of comparability between studies.

Another problem with WHO and ATP III definitions has been its applicability to different ethnic groups, especially in regarding the cut-offs for classifying obesity (WHO, 2004). For example, the risk for type II diabetes is evident at much lower levels of adiposity in Asian populations than in European populations (Tan, Ma, Wai, Chew, & Tai, 2004).

With the current MS definitions, particularly the ATP III definition, a suspiciously low prevalence of MS have been observed in Asian populations (Tan, et al., 2004), suggesting the need for ethnic-specific cut-offs, at least for obesity.

A study conducted with 818 prepubertal children between 3 and 11 years of age suggested that children with a WC above the 90th percentile were more likely to develop multiple risk factors that children with WC below the 90th percentile, especially having an adverse lipid profile and hypertension (Maffeis, Pietrobelli, Grezzani, Provera, & Tatò, 2001). It is important to highlight that previous results were based in a prepubertal population.

Still, there are recognized hormonal, metabolic and psychological changes during adolescence with direct implications for insulin sensitivity, showing to be a phase of instability in the control of cardiovascular risk factors (Tfayli & Arslanian, 2007). We thus believe that the allocation of a single percentile for this stage of the development of young people may be inadequate both for age and gender during adolescence, not compensating for the instability of the metabolic variables influencing cardiovascular risk factors such as the WC.

A European study of 4881 adults showed that individuals with the WC above 94 cm in men and 80 cm in women were 1,5 to 2 times more likely to have one or more CV risk factors compared to individuals who had a WC between (94 – 101 cm in men; 80 – 87 cm in women). Individuals with a WC above these values (101 cm men, 87 cm women) were 2,5 to 4,5 times more likely to have 1 or more CV risk factors. From this study WC cut-offs have been established for the adult population (94 cm men, 80 cm women) (Han, Van Leer, Seidell, & Lean, 1995).

Given the cut-offs for adults recommended by the IDF and considering this as an era of greater stability to study the correlation between body composition and cardiovascular risk factors when compared to prepubertal stage, seems to be adequate the adoption of these cut-offs calculating the corresponding cut-offs to the stages below 16 years, adjusting the cut-off to individual's age and gender through a method suggested by Jolliffe y Jansen (Jolliffe & Janssen, 2007). These researchers suggest the use of *Lambda Mu Sigma* (*LMS*) growth curves method, but by passing the WC curves through the 20-year-old being the cut-offs defined for adults, specific for men

and women, making a subsequent regression curve and determining the specific cut-off point for each age and gender.

The Metabolic Syndrome through a Continuous Score

Current thoughts about inflammatory diseases as CVD and diabetes mellitus are guiding researchers from a Cartesian to a systems biology analysis. Biological systems are complex systems; specifically, they are systems that are spatially and temporally complex, built from a dynamic web of interconnected feedback loops marked by interdependence, pleiotropy and redundancy. Systems biologists attempt to understand how complex biological systems function in light of multiple interconnected pathways (Reaven, 2006). Complex systems have properties that cannot wholly be understood by understanding the parts of the system (Gallagher & Appenzeller, 1999). Understanding each individual risk factor for CVD for example, is not enough to diagnose the disease or to establish an efficient intervention strategy. More than cluster all risk factors for CVD, it's imperial to understand the relationships between them and the variation between individuals that make those factors become a clinic risk for the disease.

One question that is repeatedly asked about the MS is whether its whole is more than its parts. Presumably, the question being asked is whether the syndrome confers a greater risk of CVD than does its component risk factors. The properties of the system are distinct from the properties of the parts, and they depend on the integrity of the whole. This thought is contained in the concept of emergence, which implies that new entities, such as living systems, emerge out of complex combinations of simple units (Ordovas, 2006). It is on this concept that the MS probably embodies more risk than would be embodied by the sum of its risk components.

One argument supporting the view that the CVD risk accompanying the MS is greater than its component parts is the observation that risk factors are multiplicative, because their combined effect on risk is greater than the sum of the risk of individual risk factors. Presumably, risk factors are synergistic in their actions on the arterial

wall. The multiplicative nature of CVD risk factors is well established in epidemiology and presumably is an example of a biologic system.

Even if the risk associated with the MS were to equate to the sum of the component risk factors, the issue remains whether all of the risk components can actually be identified. Because atherogenesis is a chronic condition, it is difficult to define the relative contributions of each of the components of the syndrome.

Through complex systems within the context of metabolic regulation, each piece of the puzzle its crucial for understanding both the risk of outcome and, even more importantly, the causal metabolic basis of the dysregulations and hence the appropriate pathway to successful interventions.

Assessing the relationship of the components of the MS is complex (Ferrannini, 1998; Meigs, 2000). Pathophysiologically, the multiple feedback mechanisms involved in the maintenance of GLU and lipid homeostasis make it difficult to establish which events or attributes lead to the cascade of disorders that characterize the syndrome (Ferrannini, 1998). Statistically strong correlations among variables thought to be central features of the MS complicate establishing independent associations using standard multivariate statistical models (Meigs, 2000). One statistical method of interpreting clustered risk variables is factor analysis (Edwards, et al., 1994; Meigs, 2000). Factor analysis reduces a large number of intercorrelated variables to a smaller subset of underlying "independent" variables (factors) that represent statistically independent and physiologically distinct phenotypes. The overlap reveals underlying commonalities between physiological domains (Meigs, 2000). When there is a single underlying cause for risk variable clustering, factor analysis can identify the dominant factor (Oh, Hong, Sung, & Barrett-Connor, 2004).

However, the variability within an open system leads to a specific broach for research utility, because different combinations of risk factors have different impact in different subjects in different contexts at different times.

Increasing evidence supports the use of a continuous metabolic syndrome risk (cMSr)

score in epidemiological analyses in adults (Wijndaele, et al., 2006) and youth (Eisenmann, Laurson, DuBose, Smith, & Donnelly, 2010; Shafiee, et al., 2013; Viitasalo, et al., 2014), rather than a binary definition (Kahn, Buse, Ferrannini, & Stern, 2005), because dichotomizing continuous outcome variables reduces statistical power to detect associations (Ragland, 1992). Furthermore, CVD and diabetes risk increase progressively with an increasing number of MS risk factors (Klein, Klein, & Lee, 2002), eliminating the need to dichotomize the presence of the syndrome in case of, for example, three or more present risk factors (Kahn, et al., 2005).

The rationale for creating a cMSr score stems mainly from the fact that there is no clear definition of the MS in childhood or adolescence and the prevalence rate is relatively low. A low prevalence rate requires a large sample size in order to conduct association studies. Thus, the ability to show links between exposures (e.g., physical activity, diet, etc.) and the dichotomous outcome (i.e., metabolic syndrome) using logistic regression would limit the power to detect an association (Eisenmann, et al., 2005).

Metabolic syndrome prevalence rates in children and adolescents was reported to be 2% in Turkey (Agirbasli, Cakir, Ozme, & Ciliv, 2006), 9% in Korea (Kim, Park, Kim, & Kim, 2007), 10% in Canadian Quebec (Lambert, et al., 2004), 6.5% in northern Mexico (Rodríguez-Morán, Salazar-Vázquez, Violante, & Guerrero-Romero, 2004), whereas the obesity prevalence was approximated 30-50% (Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003; Dhuper, et al., 2007; Sen, Kandemir, Alikasifoglu, Gonc, & Ozon, 2008). Data from Spanish youth (Schroder, et al., 2014) pointed an OW prevalence of 21.5% in children and of 17.4% in adolescents, whereas the obesity prevalence was of 6.6% in children and 5.2% in adolescents. A Portuguese study compared the OW and obesity prevalence rates according two different diagnose methods, WHO and International Obesity Task Force (IOTF) (Sardinha, et al., 2011). Results reported OW prevalence rates of 17% for girls and 17.7% for boys according to IOFT criteria and 23.1% for girls and 20.4% for girls according to WHO criteria. Obesity prevalence rates were of 4.6% in girls and 5.8% in boys according

IOFT criteria and of 9.6% in girls and 10.3% in boys according to WHO criteria (Sardinha, et al., 2011).

A recent study of the worldwide prevalence of the MS in children and adolescents showed that the prevalence ranged from 1.2-22.6%, being observed rates of up to 60% in the OW and obese youth (Tailor, Peeters, Norat, Vineis, & Romaguera, 2010). Such discrepancy between MS rates and obesity rates leads us to search for a continuous score rather than a dichotomous classification, especially for research use.

Several authors have derived a continuous score to represent the clustering of components of the MS in youth (Andersen, et al., 2006; Bao, Srinivasan, Wattigney, & Berenson, 1994; Batey, et al., 1997; Brage, et al., 2004; DuBose, Eisenmann, & Donnelly, 2007; Eisenmann, Welk, Ihmels, & Dollman, 2007; Eisenmann, Wickel, Welk, & Blair, 2005; Katzmarzyk, Pérusse, et al., 2001). The inclusion of these key components (i.e., GLU, lipids, blood pressure, and adiposity) is supported by the results of factor analysis in children and adolescents (Chen, Srinivasan, Elkasabany, & Berenson, 1999; Dwyer, et al., 2002; Lambert, et al., 2004; Moreno, Pineda, Rodriguez, Fleta, Giner, et al., 2002) which shows the underlying patterns or structure among variables showing high degrees of inter-correlation. Thus, there are common variables that can be used to calculate a MS score.

Being the continuous metabolic syndrome score a statistically more sensitive and less error prone when compared to the dichotomous approach (Brage, et al., 2004; Ragland, 1992), numerous researchers (Andersen, et al., 2006; Bao, Srinivasan, Wattigney, & Berenson, 1994; Batey, et al., 1997; Brage, et al., 2004; DuBose, Eisenmann, & Donnelly, 2007; Eisenmann, et al., 2005; Eisenmann, Welk, Ihmels, & Dollman, 2007; Eisenmann, et al., 2005; Katzmarzyk, et al., 2001; Raitakari, Porkka, Rasanen, Ronnemaa, & Viikari, 1994) have derived a continuous score, including principal component analysis (PCA) (Batey, et al., 1997; Katzmarzyk, et al., 2001), Z-scores (Andersen, et al., 2006; Batey, et al., 1997; Brage, et al., 2004; DuBose, et al., 2007; Eisenmann, et al., 2005; Eisenmann, et al., 2007; Eisenmann, et al., 2005),

and centile rankings (Bao, et al., 1994; Raitakari, et al., 1994).

A recent study (Eisenmann, et al., 2010) showed that a continuous metabolic syndrome score derived from PCA was higher in children with the MS and that the score increased progressively with increasing number of adverse risk factors, validating the cMSr score in children aged 7-9 years old. Moreover, their study suggests the application of such approach to validate and create a continuous metabolic syndrome score for older youth and specific for the study population.

More recently a Finish study combined data from all age groups resulting in 491 children, 1.900 middle-aged man, 614 older women and 555 older man (Viitasalo, et al., 2014). The core features of a MS were assessed and a MS score was calculated using *z*-score for WC, insulin, TG, GLU, HDL-C and blood pressure. Afterwards a confirmatory factor analysis was carried out to investigate whether MS represents a single entity in population samples. The results proved that the MS can be described as a single entity for all age groups and moreover, that the MS score is a valid tool for research, evaluating cardiometabolic risk in different age groups. These researchers also suggested that future research is needed to define cut-off points for risk estimation in clinical practice (Viitasalo, et al., 2014).

Studying the Metabolic Syndrome in Danish Children and Adolescents: The "European Youth Heart Study"

Effective interventions towards increased heath status in early life can only be performed when detailed knowledge of multiple risk factors and their possible predisposers is possessed.

In order to oblige this demand, several large-scale epidemiological studies have been designed and initiated (e.g. The Amsterdam Growth and Health Study, The Bogalusa Health Study, The National Health and Nutrition Examination Survey, The Northern Ireland Young Heart Project, The Danish Youth and Sport Study, and The European Youth Heart Study).

The present work relies on cross sectional data from the Danish part of the European Youth Heart Study (EYHS), a study which first was contemplated in the mid-nineties when a group of European exercise scientists met and decided to investigate possible multiple CVD risk factors in children and young people.

The EYHS is an international multi-centre-study (Figure 1), designed to study the nature, strength and interactions between personal, environmental and lifestyle influences on CVD risk factors in children of differing age, sex, culture and ethnicity.

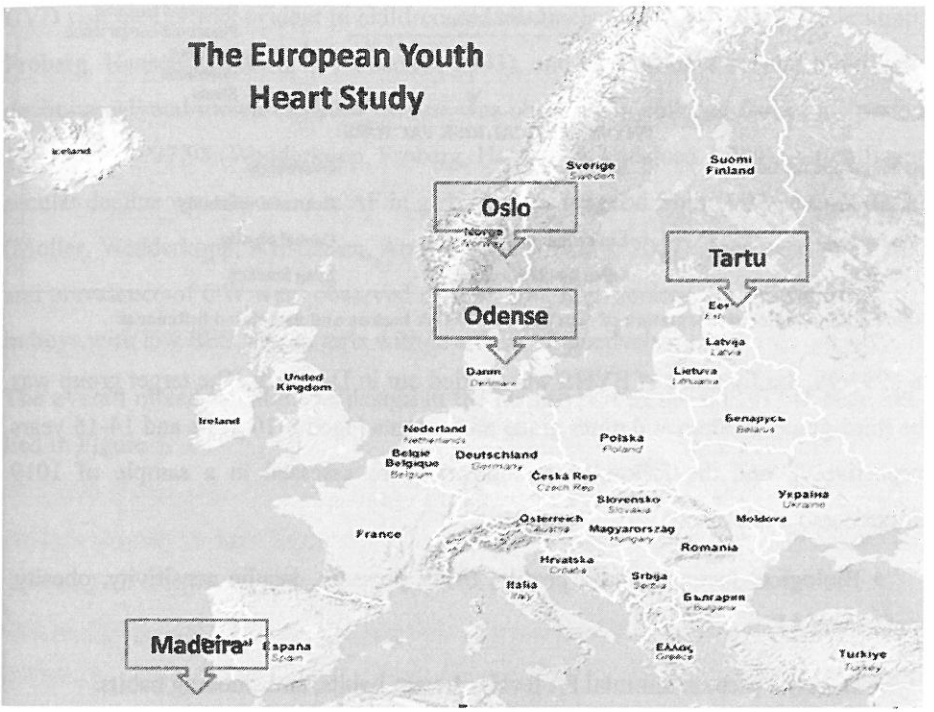

Figure 1 Study locations in the European Youth Heart Study

More than assess the prevalence of CVD risk factors, the EYHS essence is to discover and explain a) the complex relationships between personal, lifestyle, and environmental parameters which influence CVD risk, b) the relationships between these parameters and the physiological CVD risk factors, and c) how these

relationships vary between cultures and ethnic groups, as it is schematically illustrated in Figure 2.

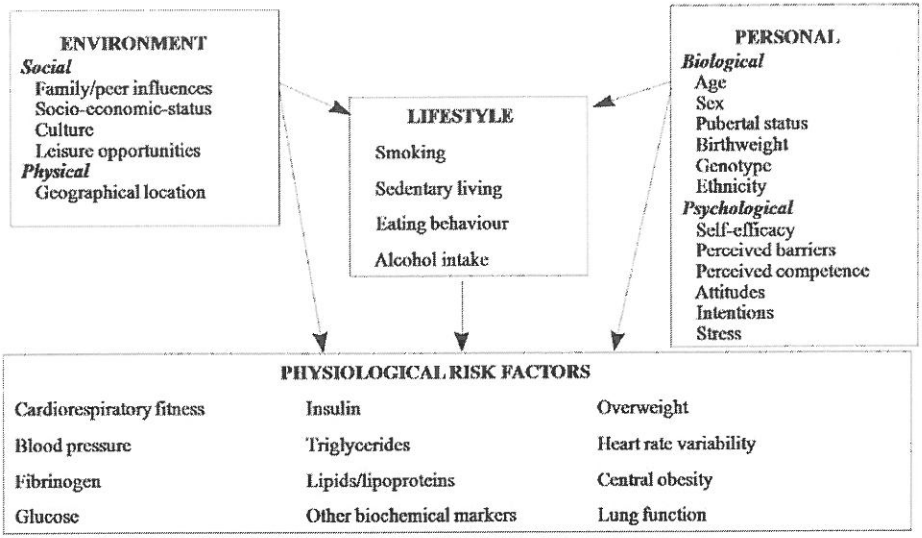

Figure 2 Schematic representation of candidate CVD risk factors and associated influences

In 1997/98, the first part of EYHS was carried out in Denmark. The target group was the third-grade children and ninth grade adolescents (aged 8-10 years and 14-16 years respectively), and the following parameters were assessed in a sample of 1019 children and adolescents:

- Biological factors: s-lipid profile, blood pressure, insulin sensitivity, obesity, and AF.
- Lifestyle factors: habitual PA levels, dietary habits, and smoking habits.
- Personal and environmental factors: Self-perception and socioeconomic issues.
- Genetic factors: Familiar predisposition of CVD.
- Furthermore, the children and adolescents were examined for any back problems (MR-scanning).

Six years later in 2003, the second part of the EYHS was carried out in Denmark. The implementation of EYHS-II has extended the design into a mixed longitudinal design, and today the study is one of the few large cohort studies in Denmark capable of isolating possible age, cohort, and time of measurements effects. Therefore, the EYHS has the potential to provide valuable information in the area of concern, and thereby play an important role especially in the fight against lifestyle related diseases as CVD and Type II diabetes.

Prior main results from the Danish part of the EYHS-I revealed that clustering of CVD risk factors was evident in children and adolescents with low AF (Wedderkopp, Froberg, Hansen, Riddoch, & Andersen, 2003), and in addition a secular trend with declining AF and increasing body fatness was observed in children during the period 1985/86 to 1997/98 (Wedderkopp, Froberg, Hansen, & Andersen, 2004). A significant secular decline was observed in AF in girls overall in period from 1997/98 to 2003/04 (Moller, Wedderkopp, Kristensen, Andersen, & Froberg, 2007). Increased AF, BMI, and prevalence of OW were observed in boys with high socioeconomic status (SES), in boys with low SES, and in girls with low SES, respectively.

The overall mixed longitudinal design in the Danish part of the EYHS has been outlied in Figure 3.

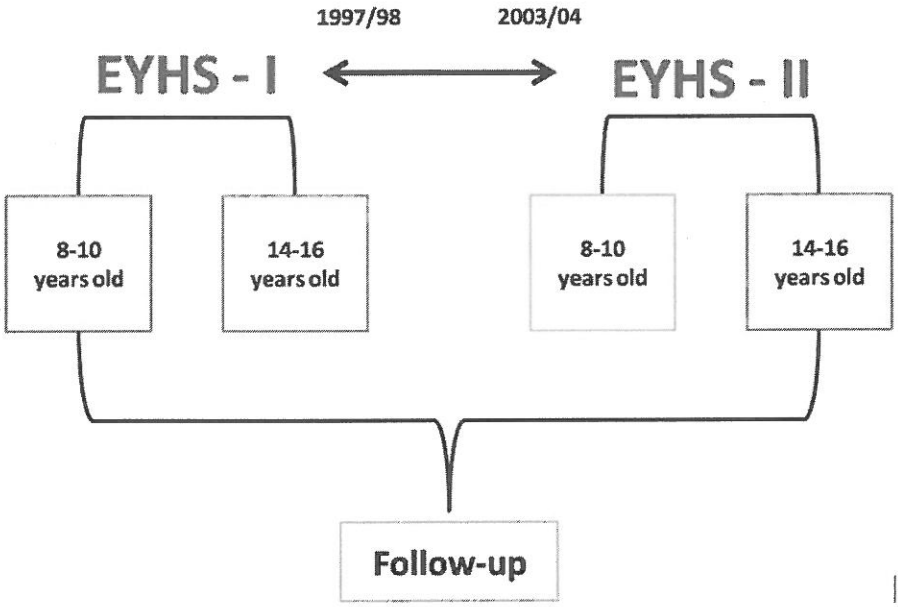

Figure 3 EYHS Design

The Waist Circumference as a Core Component of the Metabolic Syndrome: Recommended Criteria for Children and Adolescents

The childhood obesity epidemic has increased over the past decades in several countries and thus it is an important public health problem (Y. Wang, Chen, Klag, & Caballero, 2006). Several investigations have demonstrated that childhood obesity usually tracks into adulthood, being the risk of OW children becoming OW adults at least twice as high compared with their normal-weight pairs (Singh, Mulder, Twisk, Mechelen, & Chinapaw, 2008).

Body mass index is a general indicator of adiposity that is routinely used to identify OW and obesity in paediatric populations (Cole, Bellizzi, Flegal, & Dietz, 2000; WHO), conversely, BMI does not provide an indication of body fat distribution (Brambilla, et al., 2006) and thus WC has been acknowledged as a better predictor of metabolic risk (Lee, Bacha, Gungor, & Arslanian, 2006; Lee, Bacha, Gungor, &

Arslanian, 2006; Savva, et al., 2000).

Waist circumference is a practical anthropometric measure of AO, both central subcutaneous and visceral fat, and in paediatric populations, it is an independent predictor of insulin resistance, lipid levels, and blood pressure (Flodmark, Sveger, & Nilsson-Ehle, 1994; Hirschler, Aranda, Calcagno Mde, Maccalini, & Jadzinsky, 2005; Lee, Bacha, Gungor, et al., 2006; SoJung Lee, et al., 2006; Mesa, et al., 2006; Moreno, Pineda, Rodriguez, Fleta, Sarria, et al., 2002; Savva, et al., 2000), all components of the MS (Lee, Bacha, & Arslanian, 2006).

The IDF states that obesity is a *sine qua non* condition of the MS both in adult (Alberti, Zimmet, & Shaw, 2006) and paediatric (Zimmet, et al., 2007) populations, and the criteria for AO according to this organization for Caucasian adults was established at WC > 94 cm in men and > 80 cm in women (Alberti, et al., 2006). The early diagnosis of MS in children and adolescents would help to identify those at increased risk (Bao, et al., 1997; Eisenmann, Welk, Wickel, & Blair, 2004; Katzmarzyk, Perusse, et al., 2001). The IDF consensus (Zimmet, et al., 2007) established that below 10 years of age the MS cannot be diagnosed, despite that a strong message should be made regarding obesity, and from 16 years old the criteria is the same as for adults. Consequently the IDF developed a new definition to diagnose MS in children and adolescents aged 10-16 years old using modified adult criteria and all the variables remained with the adult cut-offs except for WC, where the 90th percentile was established as a criteria for AO, once children with a WC > 90th percentile are more likely to have multiple risk factors than those with a WC below this level (Zimmet, et al., 2007). On the other hand, hormonal, metabolic and psychological changes in adolescence raise instability on cardiovascular risk factors control due to the direct influence caused on insulin sensitivity (Tfayli & Arslanian, 2007), suggesting that the 90th percentile might not compensate for adolescents specific age and gender metabolic variations as we referred upwards in the paragraph "abdominal obesity, cardiovascular disease and the metabolic syndrome". Therefore, the IDF states in their consensus that an endeavour should be made to reassess these

WC cut-offs in order to modify the guidelines, if necessary, based on the new outcome data (Zimmet, et al., 2007).

Studying the AO in Portuguese Children and Adolescents: The "*Observatório Nacional da Actividade Física e Aptidão Física*"

The *Observatório Nacional da Actividade Física e da Aptidão Física* (ONAFAF) is a cross-sectional school-based study that evaluated PA, physical fitness, OW/obesity prevalence and related factors. All mainland Portuguese administrative regions (Alentejo, Algarve, Centro, Lisboa and Norte) were surveyed. The regions of Madeira and Açores (Portuguese Archipelagos) were not included in this work. The population was selected by means of proportionate stratified random sampling taking into account the location (region), and the number of students by age and gender in each school. Schools were randomly selected within each region until the established number of subjects by region was attained.

Figure 4 Study locations in the ONAFAF

Prior main results from the ONAFAF revealed age and sex-specific WC reference values for Portuguese children and adolescents aged 10–18 years (Sardinha, et al., 2012) allowing comparisons with results from other countries. Furthermore, it was found that the prevalence of OW and obesity among Portuguese children and adolescents ranges from 21.6% and 32.7% in girls and 23.5% and 30.7% in boys, using IOTF and WHO criteria, respectively (Sardinha, et al., 2011).

Aims

The fact that the MS is a current concern for health experts worldwide, covering also the youth population, aroused our attention.

Literature suggests the need for specific cut-off values for youth in all the variables of the MS, which should be specific to each population. Various methods are mentioned by experts to diagnose the MS in youth, however we believe as suggested by some authors, that the creation of a continuous score can do more justice to the relationship between physiological and metabolic variables that make up the constellation of risk factors for the MS, both in research and in clinical setting.

Moreover, we found the lack of agreement in terms of the criteria for diagnosis of MS in children and adolescents, especially with regard to the risk factor directly related to AO, the WC.

Thus, we propose to achieve the following objectives in this work:

General Aim:

To examine the validity of the IDF paediatric criteria to diagnose the MS in children and adolescents, with special attention to WC once the criteria is specific for youth.

Specific Aims:

1. To develop a continuous MS risk score for youth.
2. To compare the MS prevalence in youth through two different dichotomous methods: IDF paediatric criteria and age-specific growth curves linked to adult internationally recommended cut-offs.
3. To examine the accuracy of the dichotomous methods to diagnose the MS in children and adolescents, comparing them with the developed continuous score:

- IDF paediatric criteria Vs continuous MS risk score
- Age-specific growth curves Vs continuous MS risk score

- IDF paediatric criteria with age-specific growth curve only for WC Vs continuous MS risk score

4. To test the utility of IDF paediatric criteria and age-specific growth curves to diagnose AO in a different sample.

Materials and methods

Subjects

The present work relies on a sample of two different data collections, one collection made in Denmark and the other collection made in Portugal, with a total of 18,599 children and adolescents aged between 9.0 and 16.49 years old, resulting in 9,105 boys and 9,494 girls. The two collections were made independently with the following specifications:

- the Danish sample frame was a complete list of schools in the municipality of Odense. Schools were stratified according to the location (urban, suburban, and rural) and the socio-economic character (high, middle, and low). From each stratum, a proportional, two-stage cluster sample of children was selected. The primary units were the schools. Schools were selected using probability proportional to school size. Each school on the sampling list was allocated a weighting equivalent to the number of children in the schools. Equal numbers of children were sampled from each school. Children were allocated code numbers and randomly selected using random number tables. Within the framework of EYHS in Denmark, two measurements have been conducted. In 1997 a sample of 589 3^{rd} grade children (310 girls and 279 boys) and 430 9^{th} grade adolescents (224 girls and 206 boys) participated in EYHS-I. The EYHS-II cross-sectional sample was collected in 2003 with a sample of 458 children (259 girls and 199 boys) and 444 adolescents (251 girls and 193 boys). Missing data for MS risk factors and children younger than 9.0 years old and adolescents older than 16.49 years old were excluded, resulting in a total of 983 girls and 828 boys.
- the Portuguese sample frame data were collected on 22 179 children and adolescents from whom written informed consent was obtained from the parents or guardians (89% response rate). One hundred and thirty-one subjects

who failed inclusion criteria (aged between 9.50 and 18.49 and/or having a health condition that did not allow participation in physical education classes) or had missing information on the variables of interest were excluded, resulting in a total of 22 048 participants. Finally, the sample was adjusted by a weight factor in order to balance the sample in accordance to the distribution of the Portuguese population in the schools and to guarantee the real representativeness of each of the groups (age and gender). The maximum ponderal coefficient was of 1.29 (Region of Norte). The data derived from 14,189 children and adolescents aged between 9.50 and 16.49 years old, from whom written informed consent was obtained from the parents or guardians (89% response rate). Participants with a WC above ± 5 SD of the corresponding age and sex-Z score were excluded from the analysis resulting in a total of 8277 boys and 8511 girls. Data were collected by means of proportionate stratified random sampling accounting for the location (Portuguese administration regions of Alentejo, Algarve, Centro, Lisboa and Norte) and the number of students by age and gender in each school.

Design

This work comprises two different groups for which independent evaluations were made according to the proposed objectives.

The first group (Danish sample frame) derives from the Danish part of "The European Youth Heart Study" and the data supported the following specific aims of the present work:

- To develop a continuous MS risk score for youth.
- To compare the MS prevalence in youth through two different dichotomous methods: IDF paediatric criteria and age-specific growth curves linked to adult internationally recommended cut-offs.

- To examine the accuracy of the dichotomous methods to diagnose the MS in children and adolescents, comparing them with the developed continuous score.

The second group (Portuguese sample frame) derives from the "*Observatório Nacional da Actividade Física e Aptidão Física*" whose data supported the following specific aim of the present work:

- To test the utility of IDF paediatric criteria and age-specific growth curves to diagnose AO in a different sample.

Measurements

Data were collected by investigators specially trained for the data collection, participants were evaluated during school physical education classes.

Age

Age was calculated as the difference between date of birth and date of the data collection. Each age group was categorized by decimal age range. For example, the group of children with 10 years old included all the children between 9.50 and 10.49 years, and so on.

Anthropometry

In the Danish sample frame WC was measured with a metal anthropometric tape midway between the lower rib margin and the iliac crest, at the end of gentle expiration based in the WHO protocol (Alberti, et al., 2006).

In the Portuguese sample frame WC measurement was taken with the participant in a standing position, over the naked skin, to the nearest 0.1 cm. The tape was applied horizontally just above the uppermost lateral border of the right ilium at the end of normal expiration, based in the National Institutes of Health (NIH) protocol (NHANES, 2000). The mean of two measurements was considered. If the two measurements differed by more than 1 cm, a third measurement was taken, and the

two closest measurements were averaged.

Thus, in order to adequate our measurements to WHO protocol we used the modified formula proposed by Jennifer Patry-Parisien and colleagues (Patry-Parisien, Shields, & Bryan, 2012a) to convert WC measurements for Portuguese boys and girls:

- Boys WC_WHO = WC_NIH + 0.89911 – 0.05164*(AGE) / 1.01829
- Girls WC_WHO = WC_NIH + 0.70299 – 0.12297*(AGE) / 1.01891

Blood pressure

Resting systolic and diastolic blood pressure were measured in the sitting position using the individual's left arm, with a Dinamap adult/paediatric and neonatal vital signs monitor (model XL, Critikron, Inc., Tampa, FL). Measurements were taken using a standard pressure cuff of the correct size. The children were introduced to the monitor and allowed to sit quietly by themselves for at least 5 min prior to measurement. Five measurements were then taken at 2-min intervals. The mean of the last three measurements was used for analysis.

Blood sampling and analysis

Fasting (overnight) intravenous blood samples were taken at the start of the day from the antecubital vein, 1 h after application of an anesthetic cream (lidocaine/prilocaine; EMLA cream, AstraZeneca). Breakfast was provided immediately after blood sampling. Blood samples were aliquoted and separated within 30 min of venipuncture and stored at –80°C until transported to a WHO-certified laboratory for analysis.

Total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were measured by enzymatic methods. Glucose was analysed by the hexokinase method. Each of these was measured on an Olympus auto-analyser (model AU600, Olympus Diagnostica GmbH, Hamburg, Germany). Insulin was measured by enzyme immunoassay (microtitre plate format; Dako Diagnostics Ltd., Ely, England). The HDL-C:TC ratio was subsequently calculated, and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedwald equation (Wedderkopp, et

al., 2004).

Continuous metabolic syndrome risk score

The cMSr score was calculated based on the current IDF definition for children and adolescents (Zimmet, et al., 2007) encompassing WC, TG, HDL-C, SBP and DBP, and fasting plasma glucose.

Continuous metabolic syndrome score calculation involved three successive steps:

a) all variables were normalized (log10) because of their non-normal distribution confirmed through the Shapiro-Wilk test for normality;

b) Principal Component Analysis (PCA) with orthogonal (varimax) rotation was applied, and variables with a factor loading ≥ 0.4 were used in the interpretation. Variables with factor loadings of at least 0.3 are usually included, although it has been suggested that only higher loadings ≥ 0.4, which share at least 15% of variance with the factor, should be used (Stevens, 1986). This analysis revealed two principal components with eigenvalue ≥ 1.0 for boys and three principal components with eigenvalue ≥ 1.0 for girls (Table 4);

c) cMSr score was computed by summing the individual principal component scores, each weighted for the relative contribution of the principal components to the explained variance.

Dichotomous diagnostic methods

Metabolic syndrome prevalence was determined based on three different methods: a) the current IDF criteria for children and adolescents (WC $\geq 90^{th}$ percentile or adult cut-off if lower, TG ≥ 1.7 mmol/l, HDL-C < 1.03 mmol/l, SBP ≥ 130 mmHg, DBP $\geq$ 85 mmHg, and GLU ≥ 5.6 mmol/l or known type 2 diabetes mellitus) (Zimmet, et al., 2007), b) age and gender adjusted cut-offs for all variables of the MS based on *LMS* growth curves, and c) the current paediatric IDF criteria, except for WC where age and gender specific cut-offs were established based on *LMS* growth curves method.

The *LMS* Growth Curves

Age and gender specific growth curves were estimated with the Cole's Lambda Mu Sigma method (Cole & Green, 1992). The distribution of the MS variables was summarized by Lambda (L), Mu (M), and Sigma (S) curves representing, respectively, the skewness, the median, and the coefficient of variance of the distribution at each age.

The growth curve was linked to the respective IDF cut-off established for adolescents at 16 years old. The first step in creating a growth curve involved defining the z-score (or percentile) that corresponded to the IDF adult cut-off at 16 years of age with the following equation:

$$Z\ score = [(Y/M)^{L} - 1] / (LS)$$

where Y was the cut-off for 16 years old and L, M, and S were the respective values at the age of sixteen years (Cole & Green, 1992). The second step involved calculating points on the growth curve at each age by regressing the previously defined z-score through the children and adolescent distribution as follows:

$$point\ on\ curve = M\ (1+ LSz)^{1/L}$$

where L, M, and S are the respective age-specific values and z is the z-score that corresponded to the cut-off at sixteen (Cole & Green, 1992). Thus, by defining the percentile that corresponded to the IDF cut-off for adults at the age of 16 years and regressing it backward until 10 years old we managed to link children and adolescent cut-offs to adult cut-offs for all variables.

Statistical Analysis

Statistical analysis was performed in accordance to the aims proposed based in the two sample frames.

Based in the Danish sample frame:

- the percentage of subjects with varying number of adverse risk factors was

calculated by sex and for the sample frame. Descriptive data are presented as mean ± SD for physical and metabolic characteristics. Individual risk factors were calculated by the number of adverse risk factors.

- the primary specific aim of our work was examined using analysis of variance (ANOVA) with *Tukey's* honestly significance test to test for differences in the cMSr score across the number of adverse risk factors. Previously, a normality test of the MS variables was performed through the *Shapiro-Wilk* test, and because of their positively skewed distribution, variables were logarithmically transformed (log10). To study the correlation between variables of the MS a coefficients matrix Pearson's correlation was applied. Posterior Bartlett's test (*test of sphericity*) and KMO measure of sampling adequacy (*Kaiser-Meyer-Olkin*) concluded about the significance level between variables. A PCA with varimax rotation was applied to the risk factors to derive components that represented large fractions of the MS variance and, consequently, to give each risk factor the most appropriate weight in calculating the cMSr score.

- for the second specific aim of the work *LMS* growth curves were performed for all the MS variables and posterior Pearson's χ^2 test was made to compare the MS prevalence through the different dichotomous methods.

- the third specific aim of the work was performed through the Receiving Operating Characteristic (ROC) analysis, which is commonly used to evaluate the performance of any continuous variable to discriminate between two mutually exclusive states of disease (Altman, 1991; Greiner, Pfeiffer, & Smith, 2000; Zweig & Campbell, 1993). Our work, it was primarily performed to determine, based on the measures of sensitivity (Se) and specificity (Sp), the cMSr score cut-off value to discriminate between those with or without the MS. Furthermore, based on the area under the curve (AUC), the ROC analysis measured the global accuracy of the cMSr score as a diagnostic test (Greiner, et al., 2000; Swets, 1988). The AUC can be considered equivalent to the

probability that a randomly drawn individual identified with MS by the proposed cMSr score cut-off, being also identified according to the criteria proposed by the paediatric IDF criteria (Paul Zimmet, et al., 2007). It has been suggested that the AUC should be interpreted according to the following guidelines: non-informative/test equal to chance (AUC = 0.5), less accurate ($0.5 < AUC \leq 0.7$), moderately accurate ($0.7 < AUC \leq 0.9$), highly accurate ($0.9 < AUC \leq 1.0$), and perfect discriminatory tests (AUC = 1.0) (Swets, 1988). The AUC measured the accuracy of each dichotomous method to diagnose the MS.

Based in the Portuguese sample frame:

- differences between NIH and WHO protocol were tested by means of one sample *t*-test.
- descriptive data are presented as mean ± standard deviation (SD) and for the fourth specific aim of the work, differences between sexes were tested by means of independent-samples *t*-test and incidence differences were analysed by Pearson's χ^2 test. All further analyses were carried out in both genders separately.

Data management, descriptive and analysis were performed with SPSS for Windows (version 18.0), whereas the *LMS* regressions were performed using *LMS* Pro software (The Institute of Child Health, London). The *LMS* software took into consideration the weighting for the representativeness of each sample frame.

Ethics

All procedures and methods in this work are conformed to the ethical guidelines laid down in the World Medical Association's Declaration of Helsinki and its subsequent revisions (Principles, 2013). The ethics committee of Vejle and Funen approved the EYHS.

The ONAFAF study was approved by the Portuguese Institute of Sport Ethics

Committee and conducted in accordance with the Declaration of Helsinki for human studies of the World Medical Association (Principles, 2013).

Results

The paragraph "*Results*" is described in four parts: 1) Development of the cMSr score, 2) MS prevalence: IDF paediatric criteria Vs age-specific growth curves 3) Accuracy of dichotomous methods to diagnose the MS in children and adolescents, 4) Abdominal obesity diagnose in a different sample: IDF paediatric criteria Vs age-specific growth curves.

Development of the cMSr score

Table 1 presents the number and percentage of subjects by the number of MS risk factors and it is based on the data collected in Danish children and adolescents. About 26% of the subjects have one or more adverse risk factors. No one possessed all five risk factors, however 12 subjects possessed the MS according actual paediatric IDF criteria (AO + 2 risk factors). No significant sex differences ($p < 0.05$) were found in the occurrence of any given risk factor (Table 1).

Table 1 Sample distribution by number of adverse risk factors in boys and girls

N° of risk factors	Boys (n/%) N=828	Girls (n/%) N=983	Total (n/%) N=1811	p*
0	571 (69%)	762 (77.5%)	1333 (73.6%)	N.S.
1	210 (25.4%)	195 (19.8%)	405 (22.4%)	N.S.
2	38 (4.6%)	23 (2.3%)	61 (3.4%)	N.S.
3	6 (0.7%)	3 (0.3)	9 (0.5%)	N.S.
4	3 (0.4%)	0 (0%)	3 (0.2%)	N.S.
5	0 (0%)	0 (0%)	0 (0%)	N.S.

* Proportions did not differ significantly between genders at a 95% confidence interval, data analysed by chi-square test. "N.S.": Non-significant.

Table 2 shows the descriptive characteristics of each variable according to the number of risk factors based on the paediatric IDF criteria. Elevated WC was the most common risk factor (10%) and abnormal SBP and DBP were the least common (3% and 0% respectively) (Table 2).

Table 2 Variable characteristics of the entire sample by number of adverse risk factors

	Number of risk factors				
	0	1	2	3+	Total
N	1333	405	61	12	1811
Age (yrs)	12.3 ± 3.0	12.9 ± 2.9	14.1 ± 2.6	14.0 ± 2.5	12.5 ± 3.0
WC (cm)	63.4 ± 7.4	70.7 ± 10.0	77.1 ± 9.7	81.0 ± 9.6	65.6 ± 9.0
% elevated WC	-	-	-	-	10%
SBP (mm Hg)	104.5 ± 8.9	108.7 ± 10.9	118.9 ± 14.2	122.2 ± 13.3	106.0 ± 10.2
% elevated SBP	-	-	-	-	3%
DBP (mm Hg)	60.9 ± 6.0	62.2 ± 6.6	64.0 ± 6.7	65.3 ± 7.2	61.3 ± 6.2
% elevated DBP	-	-	-	-	0%
GLU (mmol/L)	5.0 ± 0.3	5.3 ± 0.5	5.4 ± 0.5	5.8 ± 0.4	5.1 ± 0.4
% elevated GLU	-	-	-	-	8%
HDL-C (mmol/L)	1.5 ± 0.3	1.4 ± 0.4	1.2 ± 0.3	1.0 ± 0.2	1.5 ± 0.3
% elevated HDL-C	-	-	-	-	7%
TG (mmol/L)	0.8 ± 0.3	1.0 ± 0.5	1.4 ± 0.7	2.2 ± 0.8	0.8 ± 0.4
% elevated TG	-	-	-	-	4%

Data are mean ± SD and percentage (%) were indicated.

The correlation between variables of the MS was analysed trough a coefficients matrix Pearson's correlation that showed a mid-correlation between risk factors. Posterior Bartlett's (*test of sphericity*) and KMO measure of sampling adequacy (*Kaiser-Meyer-Olkin*) concluded that the variables were significantly correlated ($p < 0.001$) for boys (KMO = 0.58) and girls (KMO = 0.53), showing that the factor analysis were executable. Posterior factor analysis of the MS variables reduced six inter-correlated variables into two principal components (PC) in boys and three PC in girls (Table 3).

In boys, all the variables constituted the principal component (PC) 1 explaining 37.5% of the variance while WC, DBP and HDL-C have performed PC 2 and explained 19.8% of the variance. In girls, WC, SBP, DBP and TG constituted PC 1 explaining together 31.1% of the variance; WC, HDL-C and GLU have formed PC 2 and explained 18.9% of the variance and finally WC, TG and GLU constituted PC 3 explaining 17.6% of the variance, as shown in table 3.

Table 3 Factor analysis after orthogonal rotation of principal components (PC)

	Boys		Girls		
	PC 1	PC 2	PC 1	PC 2	PC 3
WC (cm)	0.63	-0.45	0.47	-0.40	-0.41
SBP (mm Hg)	0.81	0.23	0.84	0.24	-0.22
DBP (mm Hg)	0.54	0.68	0.77	0.36	-0.07
TG (mmol/L)	0.63	-0.14	0.51	-0.34	0.44
HDL-C (mmol/L)	-0.57	0.58	-0.26	0.71	-0.34
GLU (mmol/L)	0.43	0.34	0.17	0.41	0.73
Percentage of explained variance	37.5%	19.8%	31.1%	18.9%	17.6%
Cumulative percentage of total variance	37.5%	57.3%	31.1%	50.0%%	67.6%

Factor loadings ≥ 0.4 were consider having an important association between the measured variable and the principal component

There was a graded and proportional relationship between the number of adverse risk factors and the cMSr score (Figure 5). The cMSr score increased progressively (*Tukey's* honestly significance difference comparison $p < 0.001$) with the number of adverse risk factors, being lowest in the group without risk factors (-0.35 ± 1.4), higher ($p < 0.001$) in the group with one risk factor (0.78 ± 1.6), even higher ($p < 0.001$) in the group with two risk factors (1.98 ± 1.2) and highest in those possessing the MS according to IDF criteria for youth (3.17 ± 1.5). The mean of cMSr score for the total sample was 0.00 ± 1.59.

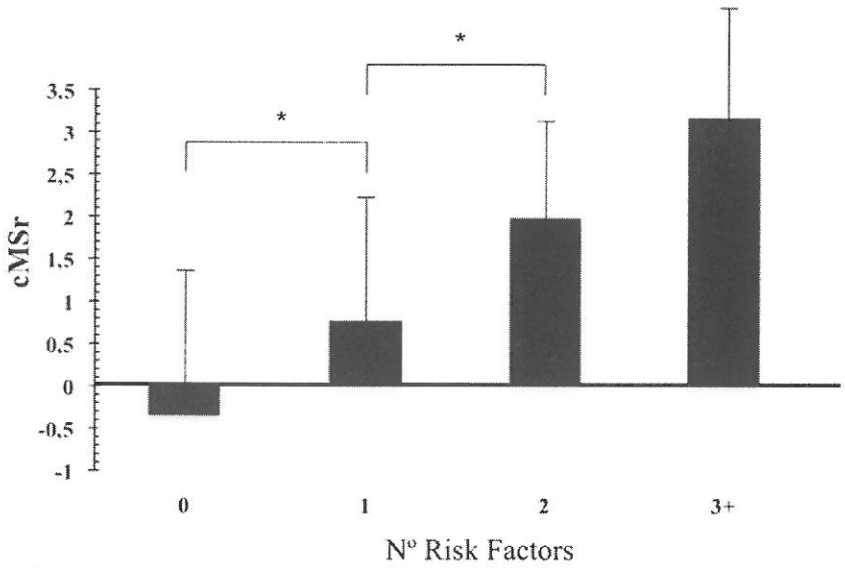

Figure 5 Continuous metabolic syndrome score by the number of adverse risk factors
* ($p < 0.05$) ANOVA.

MS prevalence: IDF paediatric criteria Vs age-specific growth curves

Table 4 reports the age-specific WC percentiles for boys from 10 to 16 years of age. The adult cut-off of 94 cm for abnormally high WC was assigned at 16 years of age by the 98th percentile.

Table 4 Percentile curves for WC in 10 to 16-year-old boys

Age (years)	IDF (94 cm)	Percentiles									
		90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th
10	94	67.8	68.3	68.9	69.5	70.2	71.1	72.2	73.6	75.6	79.1
11	94	70.5	71.0	71.6	72.3	73.1	74.1	75.3	76.8	79.0	83.0
12	94	74.3	74.9	75.6	76.4	77.3	78.3	79.6	81.3	83.7	88.0
13	94	78.1	78.7	79.4	80.1	81.0	82.1	83.4	85.1	87.5	91.7
14	94	81.0	81.6	82.2	83.0	83.9	84.9	86.2	87.8	90.2	94.3
15	94	82.4	83.0	83.6	84.4	85.3	86.3	87.5	89.2	91.5	95.7
16	94	83.3	83.9	84.6	85.4	86.3	87.4	88.8	90.5	94.0	97.7

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in cm.

Figure 6 shows a similar pattern between percentile curves, except when considering

the 90th percentile where a slightly inverted curve was observed from ages of 13 and 14 years.

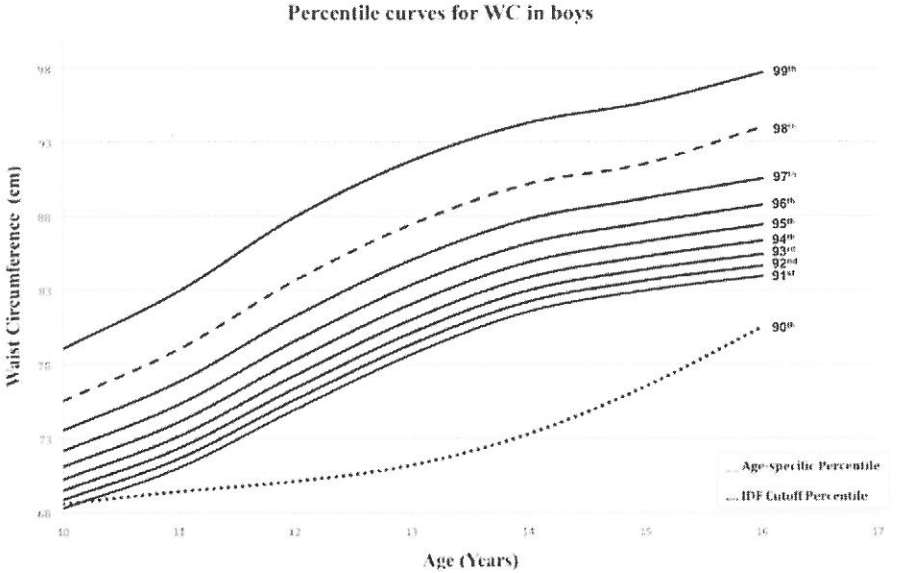

Figure 6 Percentile curves for waist circumference in boys from 10 to 16 years old
98th percentile curve passes through 94 cm at 16 years. 90th percentile is the cut-off actually recommended by the International Diabetes Federation.

Table 5 reports the age-specific WC percentiles for girls from 10 to 16 years of age. The adult cut-off of 80 cm for abnormally high WC was assigned at 16 years of age by the 89th percentile.

Table 5 Percentile curves for WC in 10 to 16-year-old girls

Age (years)	IDF (80 cm)	Percentiles									
		85th	86th	87th	88th	89th	90th	91st	92nd	93rd	94th
10	80	66.3	66.7	67.1	67.6	68.0	68.6	69.2	69.9	70.6	71.5
11	80	66.8	67.2	67.7	68.2	68.8	69.4	70.1	70.9	71.8	72.9
12	80	67.5	68.0	68.4	68.9	69.5	70.1	70.8	71.6	72.5	73.5
13	80	68.9	69.3	69.7	70.2	70.7	71.2	71.8	72.5	73.3	74.3
14	80	71.1	71.5	71.9	72.3	72.8	73.3	73.8	74.4	75.1	75.9
15	80	74.5	74.8	75.2	75.6	76.0	76.5	77.0	77.6	78.3	79.0
16	80	78.4	78.8	79.1	79.6	80.0	80.5	81.0	81.6	82.3	83.0

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in cm.

Figure 7 shows a similar pattern between percentile curves with a continuous increase of WC from 10 to 16 years of age.

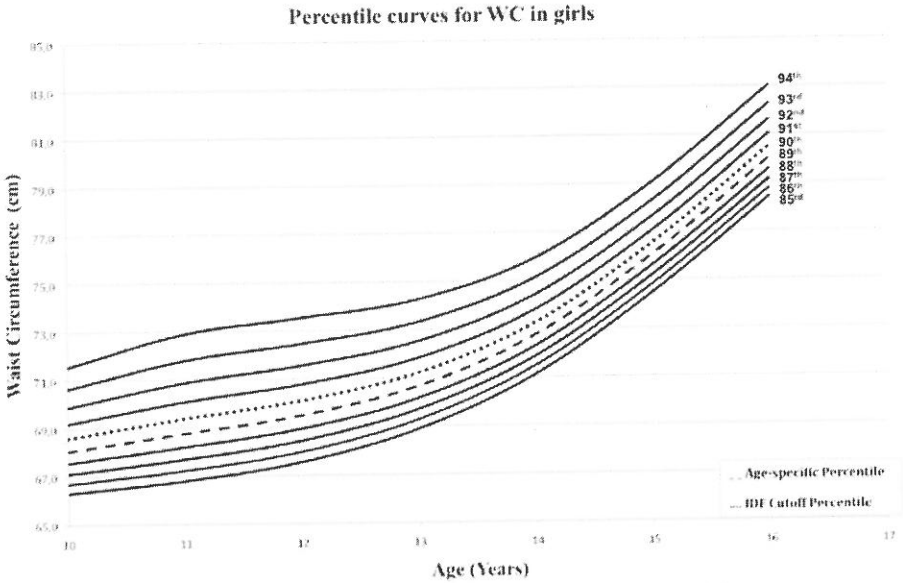

Figure 7 Percentile curves for waist circumference in girls from 10 to 16 years old
89th percentile curve passes through 80 cm at 16 years. 90th percentile is the cut-off actually recommended by the International Diabetes Federation.

Table 6 reports the age-specific SBP percentiles for boys from 10 to 16 years of age. The adult cut-off of 130 mmHg for abnormally high SBP was assigned at 16 years of age by the 92nd percentile.

Table 6 Percentile curves for SBP in 10 to 16-year-old boys

		Percentiles									
Age (years)	IDF (130 mmHg)	87th	88th	89th	90th	91st	92nd	93rd	94th	95th	96th
10	130	111.5	111.9	112.4	112.8	113.3	113.9	114.5	115.1	115.9	116.8
11	130	111.8	112.2	112.6	113.1	113.6	114.1	114.7	115.4	116.2	117.1
12	130	115.5	115.9	116.4	116.9	117.4	118.0	118.6	119.4	120.2	121.2
13	130	121.4	121.8	122.4	122.9	123.5	124.1	124.9	125.7	126.6	127.7
14	130	126.6	127.1	127.7	128.3	129.0	129.8	130.6	131.5	132.5	133.8
15	130	128.4	129.0	129.6	130.3	131.0	131.9	132.8	133.8	135.0	136.4

16	130	125.8	126.5	127.1	127.9	128.6	130.0	130.5	131.5	132.8	134.3

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmHg.

Figure 8 shows a similar pattern between percentile curves with a pronounced upward curve at age of 11 years, reaching the peak at 15 years of age.

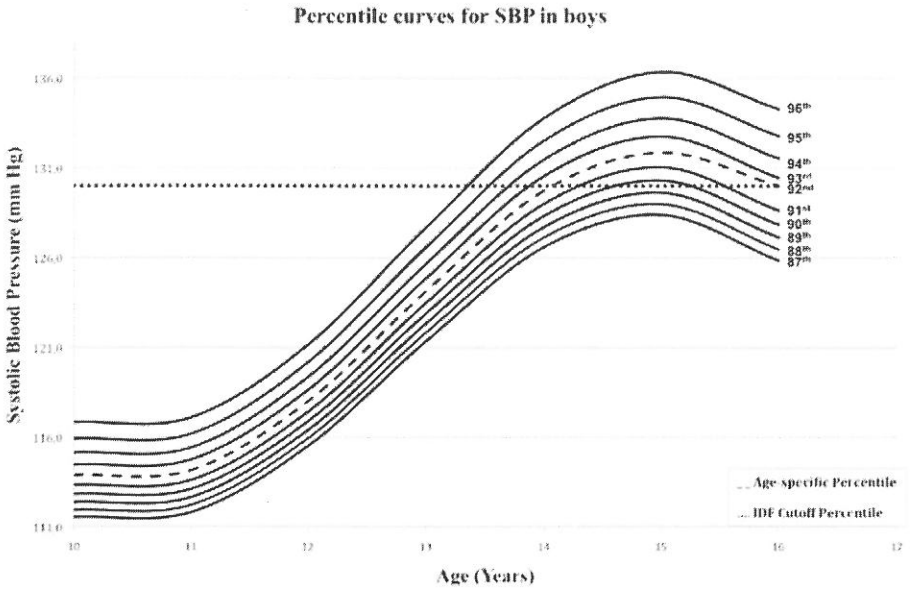

Figure 8 Percentile curves for systolic blood pressure in boys from 10 to 16 years old
92nd percentile curve passes through 130 mmHg at 16 years. 130 mmHg is the cut-off actually recommended by the International Diabetes Federation.

Table 7 reports the age-specific SBP percentiles for girls from 10 to 16 years of age. The adult cut-off of 130 mmHg for abnormally high SBP was not reached by any girl.

Table 7 Percentile curves for SBP in 10 to 16-year-old girls

Age (years)	IDF (130 mmHg)	Percentiles									
		90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th
10	130	111.2	111.7	112.2	112.8	113.5	114.2	115.1	116.2	117.7	120.0
11	130	110.8	111.2	111.8	112.3	113.0	113.7	114.5	115.5	116.9	119.0
12	130	112.0	112.4	112.9	113.5	114.1	114.8	115.6	116.6	117.9	119.9
13	130	114.0	114.4	114.9	115.5	116.1	116.8	117.6	118.6	119.9	121.9

14	130	116.0	116.5	117.0	117.5	118.2	118.9	119.7	120.7	122.1	124.2
15	130	117.3	117.8	118.4	119.0	119.6	120.4	121.3	122.4	123.8	126.1
16	130	119.0	119.5	120.1	120.8	121.5	122.4	123.4	124.7	126.4	129.1

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmHg.

Figure 9 shows a similar pattern between percentile curves with a gradual upward curve from age of 11 years.

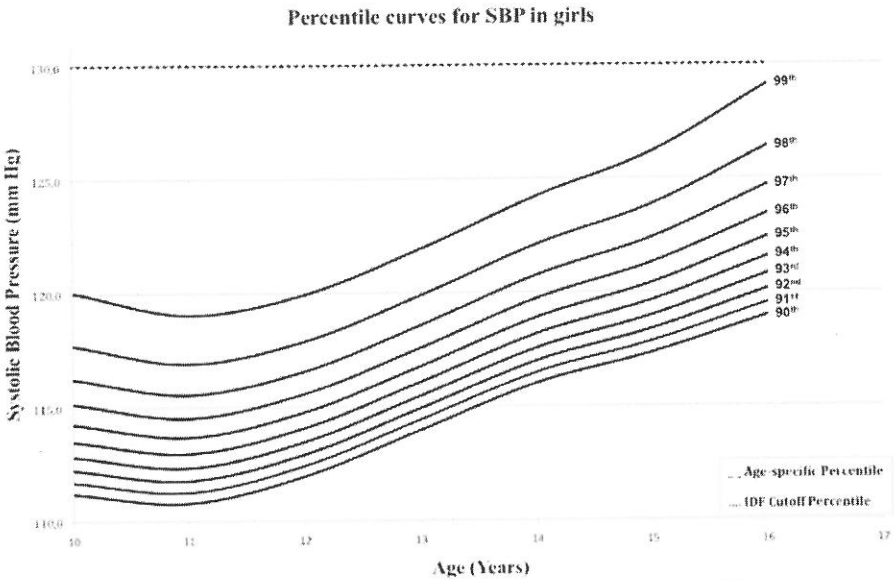

Figure 9 Percentile curves for systolic blood pressure in girls from 10 to 16 years old
Any girl reached the 130 mmHg. 130 mmHg is the cut-off actually recommended by the International Diabetes Federation.

Table 8 reports the age-specific DBP percentiles for boys from 10 to 16 years of age. Any subject reached the adult cut-off of 85 mmHg for abnormally high DBP.

Table 8 Percentile curves for DBP in 10 to 16-year-old boys

Age (years)	IDF (85 mmHg)	Percentiles									
		90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th
10	85	69.0	69.4	69.9	70.4	70.9	71.6	72.3	73.2	74.5	76.5
11	85	68.9	69.4	69.8	70.3	70.9	71.5	72.2	73.2	74.4	76.4

12	85	69.8	70.2	70.6	71.2	71.7	72.4	73.2	74.1	75.4	77.4
13	85	71.1	71.5	72.0	72.5	73.1	73.8	74.6	75.6	77.0	79.2
14	85	72.0	72.4	72.9	73.5	74.1	74.8	75.6	76.7	78.1	80.3
15	85	71.5	72.0	72.4	73.0	73.6	74.3	75.1	76.1	77.5	79.7
16	85	68.9	69.3	69.7	70.2	70.8	71.4	72.2	73.1	74.4	76.4

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmHg.

Figure 10 shows a similar pattern between percentile curves with a pronounced drop curve from 14 to 16 years, being the value at age of 16 lower than the value at 10 years of age.

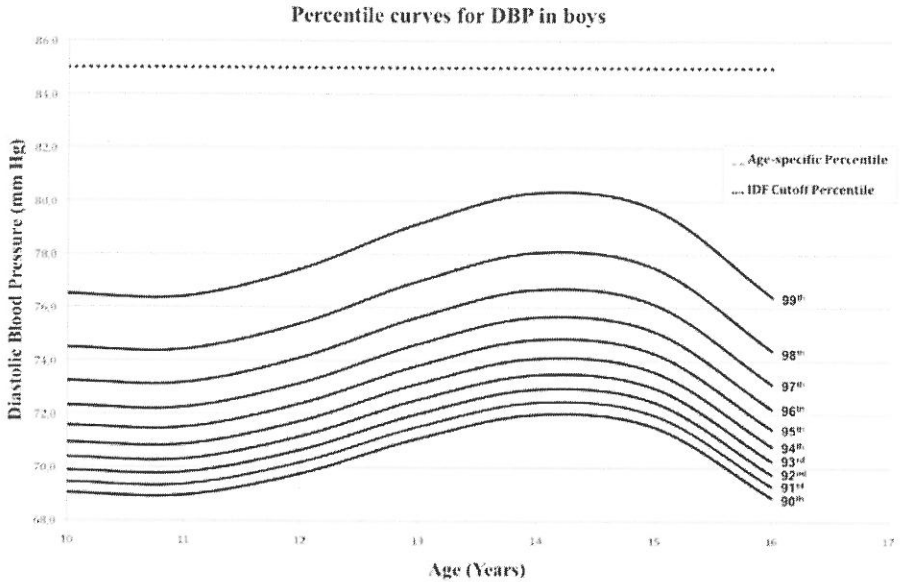

Figure 10 Percentile curves for diastolic blood pressure in boys from 10 to 16 years old
Any boy reached the 85 mmHg. 85 mmHg is the cut-off actually recommended by the International Diabetes Federation.

Table 9 reports the age-specific DBP percentiles for girls from 10 to 16 years of age. The adult cut-off of 85 mmHg for abnormally high DBP was not reached by any subject.

Table 9 Percentile curves for DBP in 10 to 16-year-old girls

Age (years)	IDF (85 mmHg)	Percentiles									
		90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th
10	85	67.9	68.2	68.6	69.1	69.6	70.2	70.9	71.8	72.9	74.8
11	85	67.9	68.3	68.8	69.3	69.9	70.5	71.3	72.2	73.5	75.5
12	85	68.2	68.6	69.1	69.6	70.1	70.8	71.6	72.6	73.9	76.0
13	85	68.6	69.0	69.5	70.0	70.5	71.2	72.0	73.0	74.3	76.4
14	85	69.1	69.5	69.9	70.4	71.0	71.6	72.4	73.3	74.6	76.6
15	85	69.6	70.0	70.5	70.9	71.5	72.1	72.8	73.7	74.9	76.8
16	85	71.2	71.6	72.0	72.5	73.0	73.6	74.3	75.1	76.3	78.1

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmHg.

Figure 11 shows a similar pattern between percentile curves with a progressive increase from 10 to 16 years of age, yet any subject reached the adult cut-off for DBP.

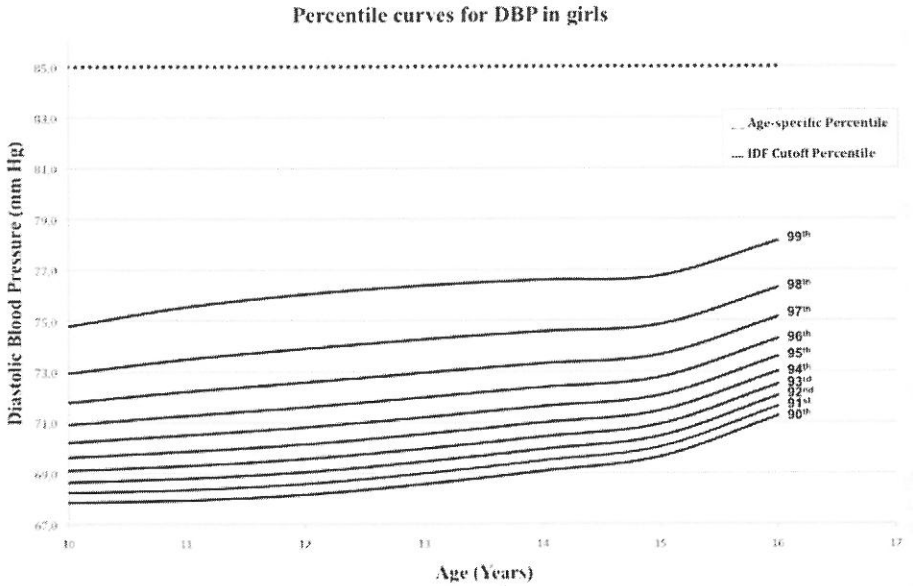

Figure 11 Percentile curves for diastolic blood pressure in girls from 10 to 16 years old
Any girl reached the 85 mmHg. 85 mmHg is the cut-off actually recommended by the International Diabetes Federation.

Table 10 reports the age-specific TG percentiles for boys from 10 to 16 years of age. The adult cut-off of 1.7 mmHg for abnormally high TG was assigned at 16 years of

age by the 96th percentile.

Table 10 Percentile curves for TG in 10 to 16-year-old boys

Age (years)	IDF (1.7 mmol/l)	Percentiles									
		90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th
10	1.7	1.1	1.2	1.2	1.3	1.3	1.4	1.4	1.5	1.7	2.0
11	1.7	1.1	1.1	1.1	1.2	1.2	1.3	1.4	1.5	1.6	1.9
12	1.7	1.2	1.2	1.3	1.3	1.4	1.4	1.5	1.6	1.8	2.1
13	1.7	1.4	1.4	1.5	1.6	1.6	1.7	1.8	1.9	2.1	2.5
14	1.7	1.6	1.6	1.7	1.7	1.8	1.9	2.0	2.2	2.4	2.7
15	1.7	1.6	1.6	1.7	1.7	1.8	1.9	2.0	2.1	2.3	2.7
16	1.7	1.4	1.4	1.5	1.5	1.6	1.6	1.7	1.9	2.0	2.3

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmol/l.

Figure 12 shows a similar pattern between percentile curves with a pronounced upward curve at age of 11 years and a pronounced drop after the age of 15 years.

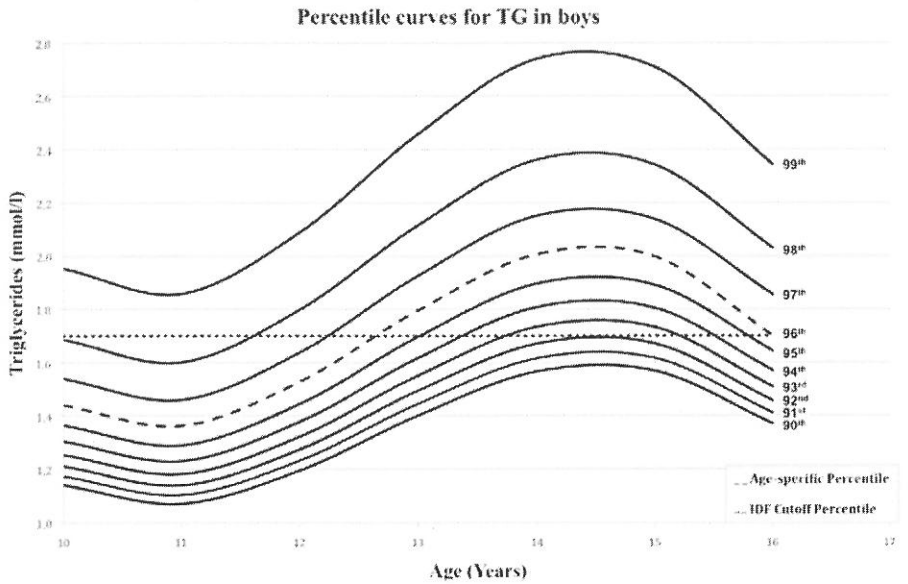

Figure 12 Percentile curves for triglycerides in boys from 10 to 16 years old
96th percentile curve passes through 1.7 mmol/l at 16 years. 1.7 mmol/l is the cut-off actually recommended by the International Diabetes Federation.

Table 11 reports the age-specific TG percentiles for girls from 10 to 16 years of age. The adult cut-off of 1.7 mmHg for abnormally high TG was assigned at 16 years of age by the 94th percentile.

Table 11 Percentile curves for TG in 10 to 16-year-old girls

Age (years)	IDF (1.7 mmol/l)	Percentiles									
		90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th
10	1.7	1.3	1.3	1.4	1.4	1.4	1.5	1.6	1.7	1.8	2.1
11	1.7	1.4	1.5	1.5	1.6	1.6	1.7	1.8	1.9	2.1	2.4
12	1.7	1.5	1.6	1.6	1.7	1.7	1.8	1.9	2.0	2.2	2.5
13	1.7	1.6	1.6	1.7	1.7	1.8	1.9	1.9	2.1	2.2	2.5
14	1.7	1.6	1.6	1.7	1.7	1.8	1.9	1.9	2.0	2.2	2.5
15	1.7	1.5	1.6	1.6	1.7	1.7	1.8	1.9	2.0	2.1	2.4
16	1.7	1.5	1.5	1.6	1.6	1.7	1.8	1.8	1.9	2.1	2.3

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmol/l.

Figure 13 shows a similar pattern between percentile curves reaching the peak at age of 12 years, decreasing afterwards until the age of 16 years.

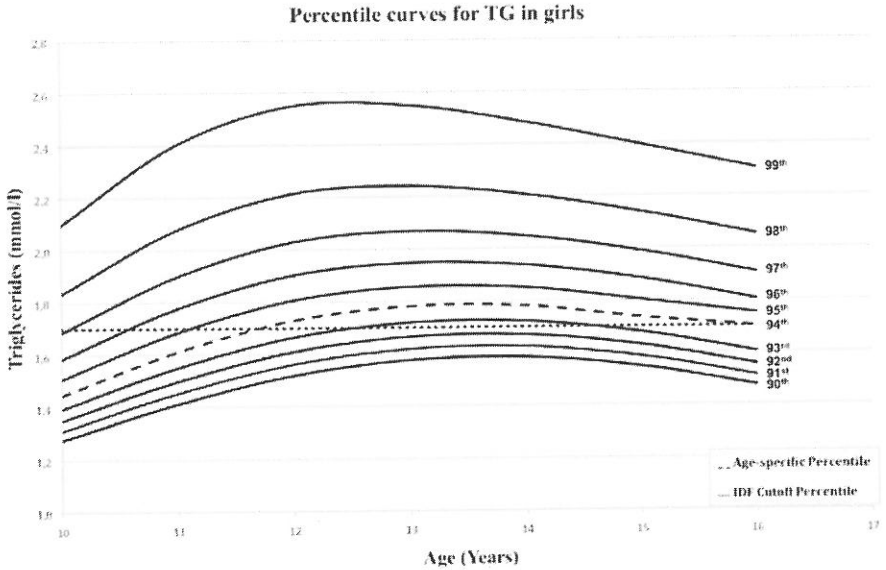

Figure 13 Percentile curves for triglycerides in girls from 10 to 16 years old
94th percentile curve passes through 1.7 mmol/l at 16 years. 1.7 mmol/l is the cut-off actually recommended

by the International Diabetes Federation.

Table 12 reports the age-specific HDL-C percentiles for boys from 10 to 16 years of age. The adult cut-off of 1.03 mmHg for abnormally low HDL-C was assigned at 16 years of age by the 16th percentile.

Table 12 Percentile curves for HDL-C in 10 to 16-year-old boys

Age (years)	IDF (1.03mmol/l)	Percentiles									
		10th	11th	12th	13th	14th	15th	16th	17th	18th	19th
10	1.03	1.17	1.19	1.20	1.21	1.23	1.24	1.25	1.27	1.28	1.29
11	1.03	1.19	1.21	1.22	1.23	1.25	1.26	1.27	1.28	1.29	1.30
12	1.03	1.16	1.18	1.19	1.20	1.22	1.23	1.24	1.25	1.26	1.27
13	1.03	1.11	1.13	1.14	1.15	1.16	1.17	1.18	1.19	1.20	1.21
14	1.03	1.05	1.06	1.07	1.09	1.10	1.11	1.12	1.13	1.14	1.14
15	1.03	0.99	1.00	1.01	1.02	1.04	1.05	1.06	1.06	1.07	1.08
16	1.03	0.96	0.98	0.99	1.00	1.01	1.02	1.03	1.04	1.05	1.06

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmol/l.

Figure 14 shows a similar pattern between percentile curves with a pronounced decline after the age of 11 years until the age of 16 years. Values considerably lower of HDL-C were found only in 16 years old subjects.

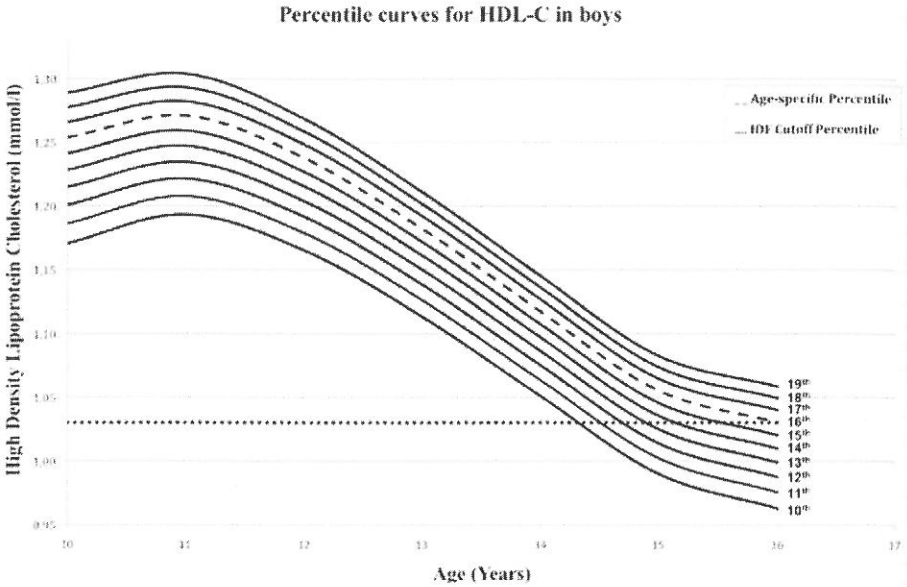

Figure 14 Percentile curves for high density lipoprotein cholesterol in boys from 10 to 16 years old
16th percentile curve passes through 1.03 mmol/l at 16 years. 1.03 mmol/l is the cut-off actually recommended by the International Diabetes Federation.

Table 13 reports the age-specific HDL-C percentiles for girls from 10 to 16 years of age. The adult cut-off of 1.03 mmHg for abnormally low HDL-C was assigned at 16 years of age by the 6th percentile.

Table 13 Percentile curves for HDL-C in 10 to 16-year-old girls

Age (years)	IDF (1.03mmol/l)	Percentiles									
		5th	6th	7th	8th	9th	10th	11th	12th	13th	14th
10	1.03	1.06	1.08	1.10	1.12	1.13	1.15	1.16	1.17	1.18	1.19
11	1.03	1.05	1.07	1.09	1.11	1.12	1.13	1.15	1.16	1.17	1.18
12	1.03	1.02	1.04	1.06	1.07	1.09	1.10	1.11	1.12	1.14	1.15
13	1.03	0.98	1.00	1.02	1.03	1.05	1.06	1.07	1.08	1.10	1.11
14	1.03	0.96	0.98	1.00	1.01	1.03	1.04	1.05	1.06	1.07	1.08
15	1.03	0.98	1.00	1.01	1.03	1.04	1.06	1.07	1.08	1.09	1.10
16	1.03	1.01	1.03	1.04	1.06	1.08	1.09	1.10	1.12	1.13	1.14

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmol/l.

Figure 15 shows a similar pattern between percentile curves with a pronounced

decline from 10 to 14 years of age. The bottom was reached at age of 14 years. Considerably lower of HDL-C values were found in girls with 14, 15 and 16 years old.

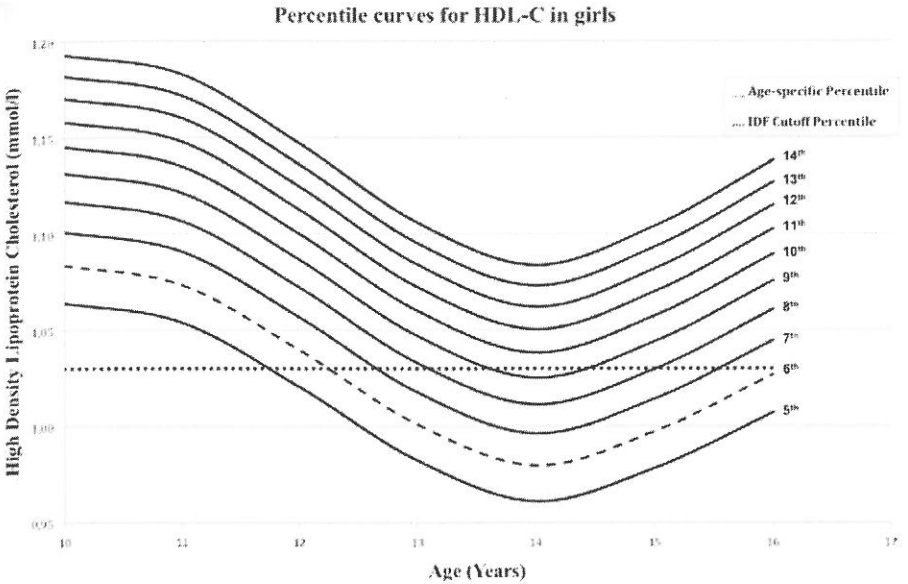

Figure 15 Percentile curves for high density lipoprotein cholesterol in girls from 10 to 16 years old
6th percentile curve passes through 1.03 mmol/l at 16 years. 1.03 mmol/l is the cut-off actually recommended by the International Diabetes Federation.

Table 14 reports the age-specific GLU percentiles for boys from 10 to 16 years of age. The adult cut-off of 5.6 mmHg for abnormally high GLU was assigned at 16 years of age by the 84th percentile.

Table 14 Percentile curves for Glucose in 10 to 16-year-old boys

Age (years)	IDF (5.6 mmol/l)	Percentiles									
		80th	81st	82nd	83rd	84th	85th	86th	87th	88th	89th
10	5.6	5.4	5.4	5.4	5.4	5.4	5.5	5.5	5.5	5.5	5.5
11	5.6	5.5	5.5	5.5	5.5	5.5	5.5	5.6	5.6	5.6	5.6
12	5.6	5.6	5.6	5.6	5.7	5.7	5.7	5.7	5.7	5.7	5.8
13	5.6	5.7	5.7	5.7	5.8	5.8	5.8	5.8	5.8	5.9	5.9
14	5.6	5.7	5.8	5.8	5.8	5.8	5.8	5.9	5.9	5.9	5.9
15	5.6	5.7	5.7	5.7	5.7	5.8	5.8	5.8	5.8	5.9	5.9
16	5.6	5.5	5.5	5.6	5.6	5.6	5.6	5.6	5.7	5.7	5.7

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmol/l.

Figure 16 shows a similar pattern between percentile curves with an increase from 10 to 14 years of age, where the peak was reached. At age of 10 years any subject reached the abnormal values for GLU.

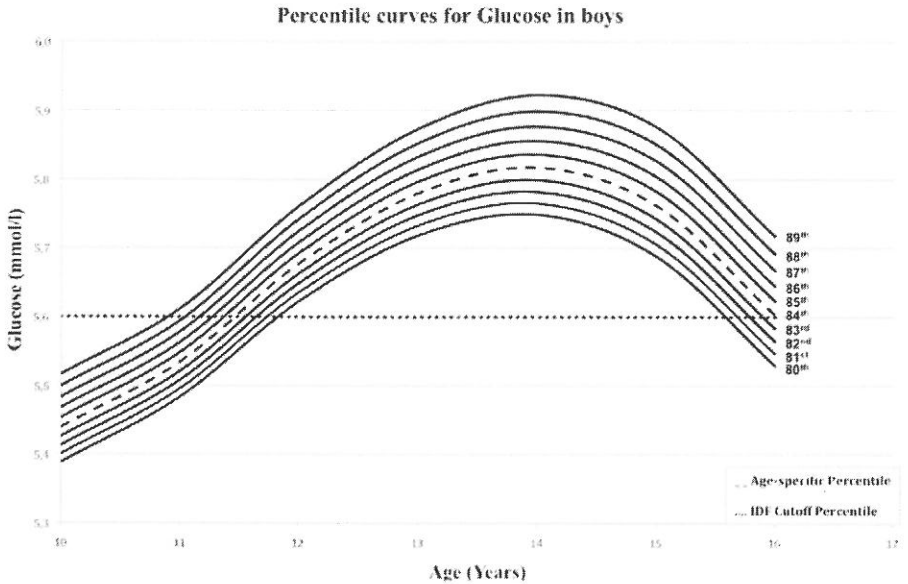

Figure 16 Percentile curves for glucose in boys from 10 to 16 years old
84th percentile curve passes through 5.6 mmol/l at 16 years. 5.6 mmol/l is the cut-off actually recommended by the International Diabetes Federation.

Table 15 reports the age-specific GLU percentiles for girls from 10 to 16 years of age. The adult cut-off of 5.6 mmHg for abnormally high GLU was assigned at 16 years of age by the 95th percentile.

Table 15 Percentile curves for Glucose in 10 to 16-year-old girls

Age (years)	IDF (5.6 mmol/l)	Percentiles									
		90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th
10	5.6	5.5	5.5	5.5	5.6	5.6	5.6	5.7	5.7	5.8	5.9
11	5.6	5.6	5.7	5.7	5.7	5.8	5.8	5.8	5.9	6.0	6.1

12	5.6	5.8	5.8	5.9	5.9	5.9	6.0	6.0	6.1	6.2	6.3
13	5.6	5.9	5.9	6.0	6.0	6.0	6.1	6.1	6.2	6.3	6.5
14	5.6	5.9	5.9	5.9	6.0	6.0	6.1	6.1	6.2	6.3	6.5
15	5.6	5.7	5.7	5.8	5.8	5.8	5.9	5.9	6.0	6.1	6.3
16	5.6	5.4	5.4	5.5	5.5	5.5	5.6	5.6	5.7	5.8	5.9

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in mmol/l.

Figure 17 shows a similar pattern between percentile curves with *Gaussian* shape, having the peak between ages of 13 and 14 years.

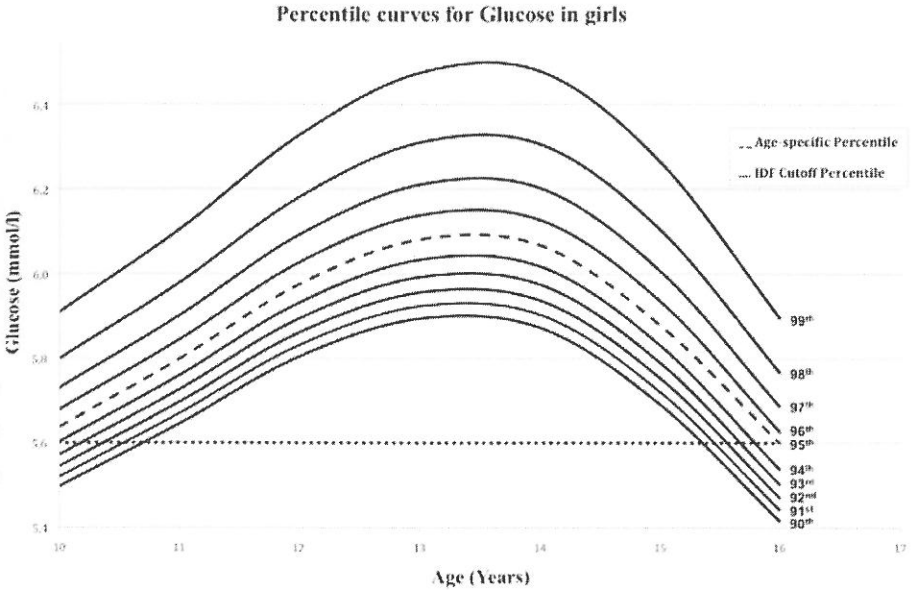

Figure 17 Percentile curves for glucose in girls from 10 to 16 years old
95th percentile curve passes through 5.6 mmol/l at 16 years. 5.6 mmol/l is the cut-off actually recommended by the International Diabetes Federation.

Tables 16 and 17 values derive from the curves developed to identify age- and sex-specific cut-offs according to the IDF criteria for youth and the age-specific growth curves method.

The WC cut-offs at 16 years of age, corresponded to the 98th and 89th percentiles for boys and girls respectively according to the performed age-specific growth curves,

indicating that the paediatric IDF criteria overestimates the presence of the risk factor in boys and slightly underestimates the presence of the risk factor in girls as confirmed in Tables 18 and 19 respectively.

Table 16 Age-specific MS cut-offs and corresponding percentiles for boys

	WC (cm)		SBP (mmHg)	TG (mmol/l)	HDL-C (mmol/l)	GLU (mmol/l)
Age (years)	IDF youth (90^{th})	Age-Specific (98^{th})	Age-Specific (92^{nd})	Age-Specific (96^{th})	Age-Specific (16^{th})	Age-Specific (84^{th})
10	67.8	75.6	113.9	1.4	1.30	5.4
11	70.5	79.0	114.1	1.4	1.30	5.5
12	74.3	83.7	118.0	1.5	1.20	5.7
13	78.1	87.5	124.1	1.8	1.20	5.8
14	81.0	90.2	129.8	2.0	1.10	5.8
15	82.4	91.5	131.9	2.0	1.10	5.7
Adult	-	94.0	130.0	1.7	1.03	5.6

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 15.9 years old.

DBP was suppressed in both genders because there were no subjects reaching the adult cut-off level of 83 mmHg. For the same reason SBP was suppressed in girls. Abdominal obesity prevalence was 10.2% and 10.1% in boys and girls respectively (Figures 18 and 19) with the IDF criteria and 2.7% and 11.4% in boys and girls (Figures 18 and 19) respectively with the age-specific cut-offs, confirming the differences in the risk factor prevalence ($p < 0.05$).

Table 17 Age-specific MS cut-offs and corresponding percentiles for girls

	WC (cm)		TG (mmol/l)	HDL-C (mmol/l)	GLU (mmol/l)
Age (years)	IDF youth (90^{th})	Age-Specific (89^{th})	Age-Specific (94^{th})	Age-Specific (6^{th})	Age-Specific (95^{th})
10	68.6	68.0	1.4	1.08	5.6
11	69.4	68.8	1.6	1.07	5.8
12	70.1	69.5	1.7	1.04	6.0
13	71.2	70.7	1.8	1.00	6.1
14	73.3	72.8	1.8	1.00	6.1
15	76.5	76.0	2.0	1.00	5.9

Adult	-	80.0	1.7	1.03	5.6

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 15.9 years old.

The SBP curve indicates that actual IDF criteria for youth generally underestimates the presence of the risk factor in boys younger than 16 years old ($p < 0.05$) compared to the growth curves method (5.3% and 8.3% respectively) (Figure 18). The same effect was observed in boys and girls on TG, with a total prevalence of 3.6% and 5% respectively for IDF and age-specific cut-offs in boys (Figure 18) and 4.2% and 6.3% in girls ($p < 0.05$) (Figure 19). Similar effect was found on HDL-C ($p < 0.05$) where the risk factor presence found in boys through the IDF criteria was 8.3% and 17.0% through age-specific cut-offs (Figure 18). In girls (5.4% and 5.7%) the risk factor presence found in through the IDF criteria was 5.4%, being 5.7% through age-specific cut-offs (Figure 19). Still, compared to the growth curves method, actual IDF criteria for youth generally underestimate high GLU levels in boys (10.6% and 16.8%) (Figure 18), and overestimate in girls (5.2% and 4.4%) ($p < 0.05$) as shown in Figure 19.

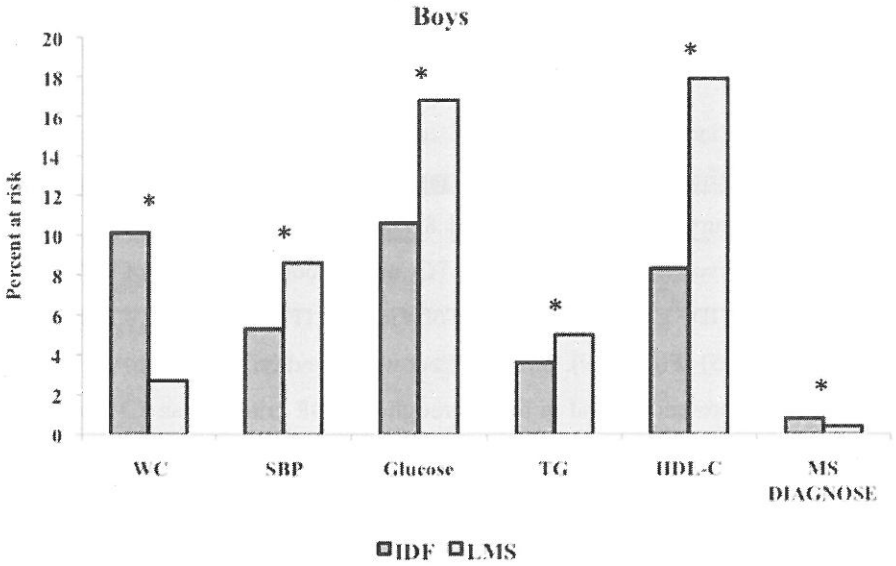

Figure 18 Presence of each risk factor and the metabolic syndrome diagnose in boys, according to both methods: IDF (international diabetes federation criteria for youth) and *LMS* (age-specific growth curves). WC, waist circumference; SBP, systolic blood pressure; TG, triglycerides; HDL-C, high density low cholesterol; MS, metabolic syndrome.
* ($p < 0.05$) χ^2test.

Furthermore, the paediatric IDF criteria overestimates the presence of the MS in boys, being identified 0.8% of boys compared to 0.4% through the growth curves method (Figure 18). On the other hand, the IDF paediatric criteria underestimates the presence of the MS in girls (0.2%) when compared to the growth curves method (0.6%) ($p < 0.05$) as shown in Figure 19.

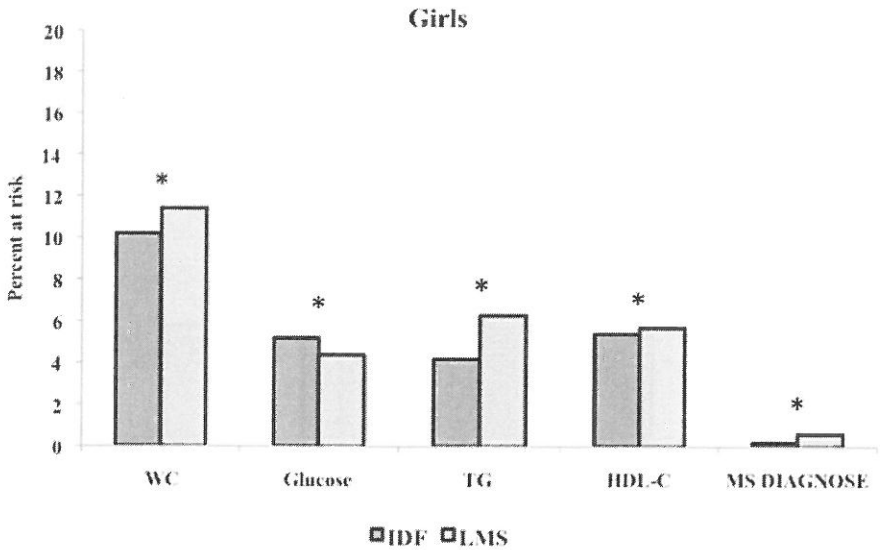

Figure 19 Presence of each risk factor and the metabolic syndrome diagnose in girls, according to both methods: IDF (international diabetes federation criteria for youth) and *LMS* (age-specific growth curves). WC, waist circumference; SBP, systolic blood pressure; TG, triglycerides; HDL-C, high density low cholesterol; MS, metabolic syndrome.
* ($p < 0.05$) χ^2 test.

Significant differences for independent risk factors presence remain ($p < 0.05$) when comparing both methods for the total sample (Figure 21), however MS diagnose was the same independently of the method used (0.5%).

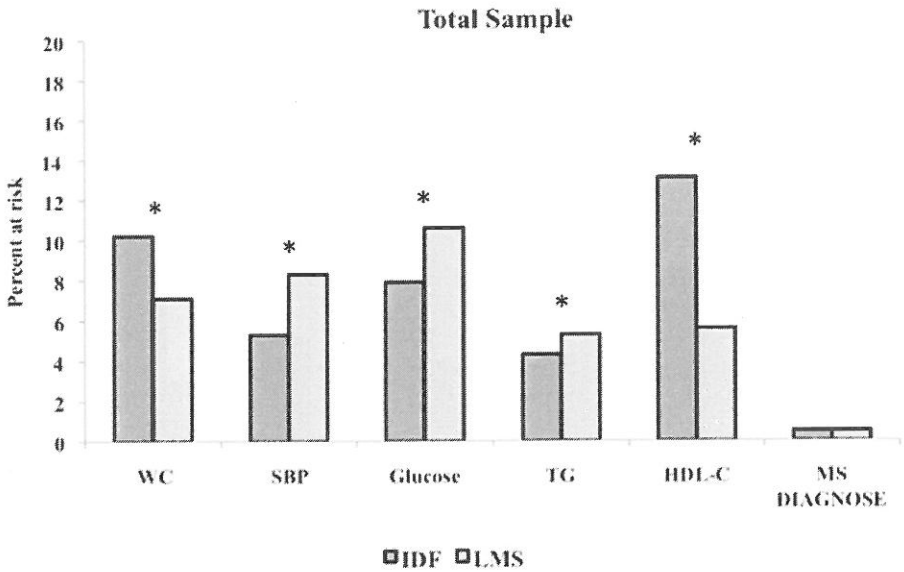

Figure 20 Presence of each risk factor and the metabolic syndrome diagnose for the entire sample, according to both methods: IDF (international diabetes federation criteria for youth) and *LMS* (age-specific growth curves).
WC, waist circumference; SBP, systolic blood pressure; TG, triglycerides; HDL-C, high density low cholesterol; MS, metabolic syndrome.
* ($p < 0.05$) χ^2test.

Accuracy of dichotomous methods to diagnose the MS in children and adolescents

Paediatric IDF criteria Vs cMSr score

Accuracy comparison between the cMSr score and the paediatric IDF criteria is provided in Figure 21.

The ROC curve analysis revealed a cut-off level for the cMSr score of 1.98 as yielding the maximal sensitivity (100%) and specificity (99%) for predicting the presence of the MS and the AUC was 0.977 (0.957 - 0.997, 95% confidence intervals) ($p < 0.001$) (Figure 21). The AUC shows this method to be a highly accurate test to diagnose the MS in children and adolescents.

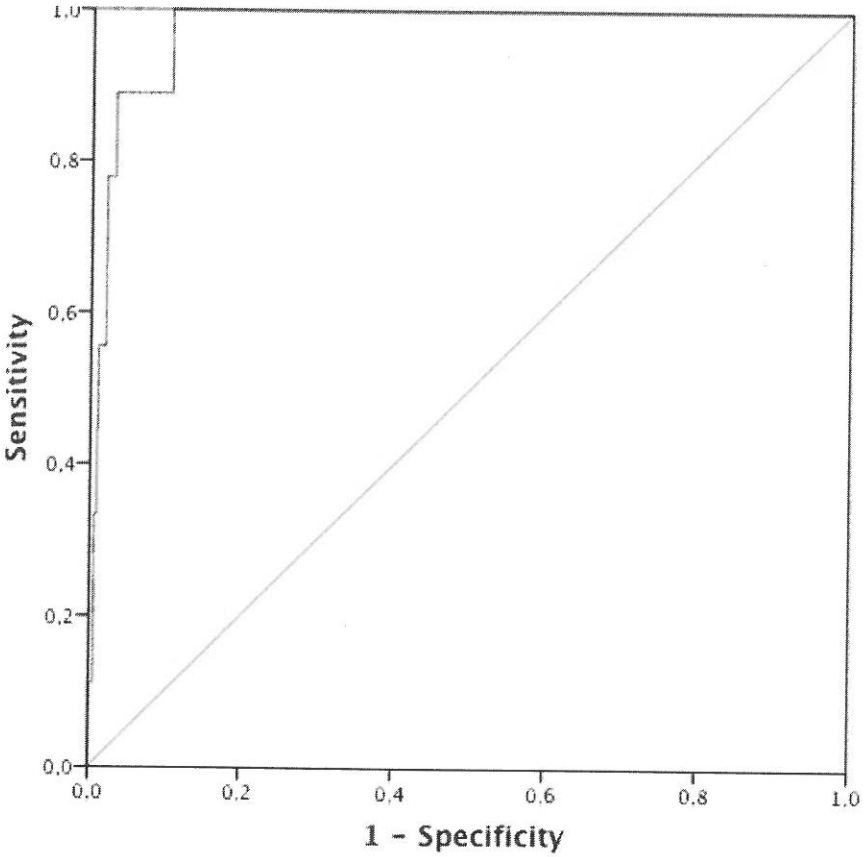

Figure 21 Receiver operating characteristic curve for the continuous metabolic syndrome risk score as a predictor of metabolic syndrome among children and adolescents according to International Diabetes Federation paediatric criteria
AUC = 0.977 (0.957 - 0.997, 95% confidence intervals).

Age-specific growth curves Vs cMSr score

Accuracy comparison between the cMSr score and the age-specific growth curves is provided in Figure 22.

The ROC curve analysis revealed a cut-off level for the cMSr score of 1.98 as yielding the maximal sensitivity (71%) and specificity (99%) for predicting the presence of the MS and the AUC was 0.890 (0.816 - 0.964, 95% confidence

intervals) ($p < 0.001$) (Figure 22). The AUC shows this method to be a moderately accurate test to diagnose the MS in children and adolescents.

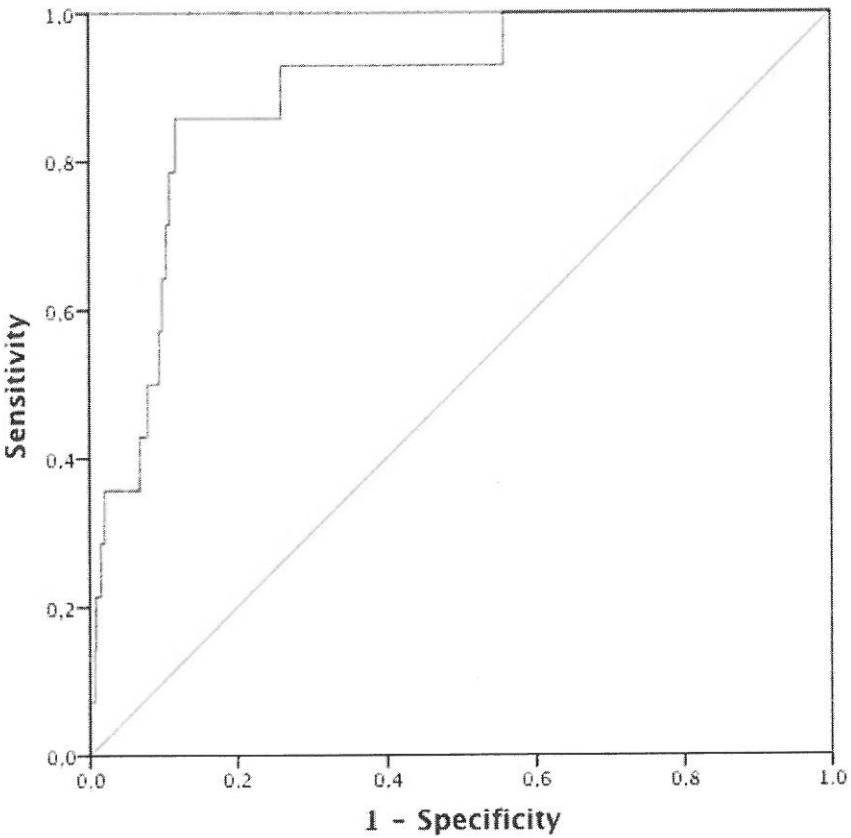

Figure 22 Receiver operating characteristic curve for the continuous metabolic syndrome risk score as a predictor of metabolic syndrome among children and adolescents according to age-specific growth curves
AUC = 0.890 (0.816 - 0.964, 95% confidence intervals).

IDF paediatric criteria with age-specific growth curve for WC only Vs cMSr score

Accuracy comparison between the cMSr score and the IDF paediatric criteria with age-specific growth curve only for the WC is provided in Figure 23.

The ROC curve analysis revealed a cut-off level for the cMSr score of 1.98 as

yielding the maximal sensitivity (100%) and specificity (99%) for predicting the presence of the MS and the AUC was 0.978 (0.952 - 1.0, 95% confidence intervals) ($p < 0.001$) (Figure 23). The AUC shows this method to be a highly accurate test to diagnose the MS in children and adolescents. Furthermore, despite the actual IDF criteria for youth high accuracy, adjusting the age-specific WC growth curves instead the 90th percentile allowed the highest accuracy to predict children and adolescents with increased risk for MS.

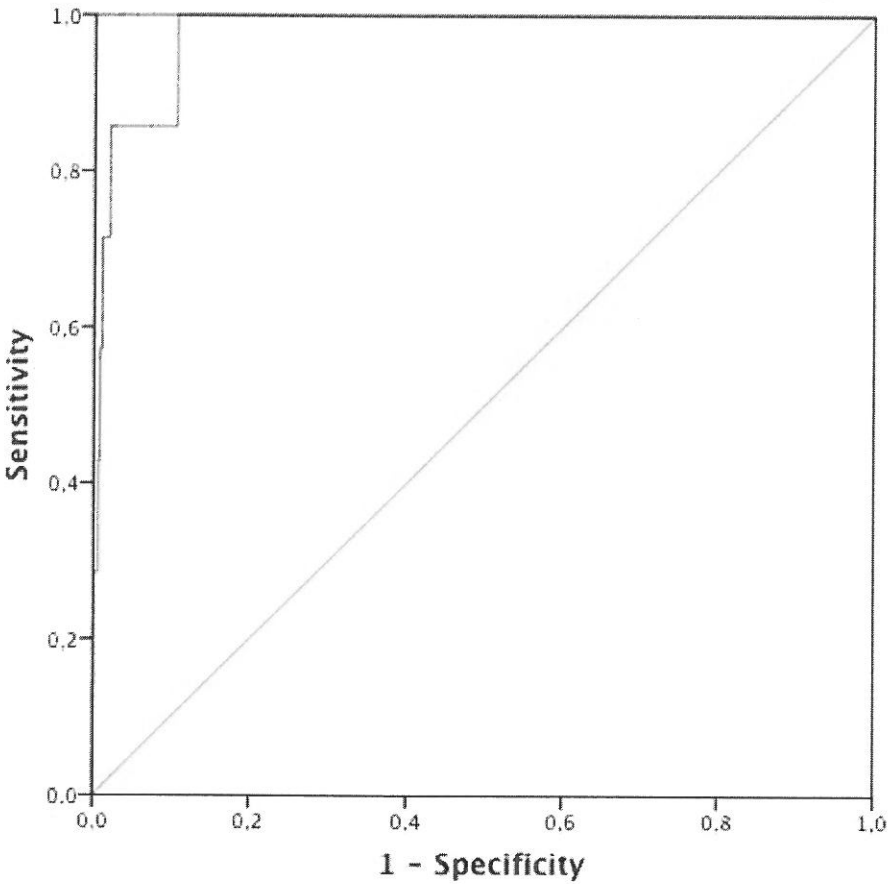

Figure 23 Receiver operating characteristic curve for the continuous metabolic syndrome risk score as a predictor of metabolic syndrome among children and adolescents according to age-specific growth curves

AUC = 0.978 (0.952 – 1.0, 95% confidence intervals).

Abdominal obesity diagnose in a different sample: IDF paediatric criteria Vs age-specific growth curves

Waist circumference measurement conversion, from NIH to WHO protocol

The following analysis is based on data collected in Portuguese children and adolescents.

Regardless of age and sex, mean values of WC based on NIH protocol significantly exceeded those of WHO protocol: 1.1 cm for boys and 2.3 cm for girls (Table 18). The differences increased progressively with the age in both genders, being higher in the older groups. Furthermore, the differences were greatest for girls aged 16 (2.6 cm).

Table 18 Mean WC (cm) based on NIH and WHO protocols, by age and gender

Sex/Age (years)	N	NIH	WHO	Difference in cm (NIH minus WHO)
Boys	**8277**	**72,1**	**71.0**	**1.1***
10	476	66.9	66.1	0.8*
11	1141	67.5	66.6	0.9*
12	1237	69.6	68.7	0.9*
13	1352	71.3	70.3	1.0*
14	1154	72.9	71.8	1.1*
15	1384	74.8	73.6	1.2*
16	1533	76.7	75.4	1.3*
Girls	**8511**	**70.8**	**68.5**	**2.3***
10	507	65.1	63.4	1.7*
11	1161	66.8	65.0	1.8*
12	1189	69.2	67.1	2.1*
13	1361	70.8	68.6	2.2*
14	1185	71.5	69.2	2.3*
15	1414	72.7	70.3	2.4*
16	1694	74.0	71.4	2.6*

* significantly different from zero ($p < 0.05$)

IDF paediatric criteria Vs age-specific growth curves

Descriptive statistics of WC are shown in table 19, as well as the number of subjects used to develop the growth curves.

Table 19 Sample's mean and SD

Age (years)	Boys WC (cm)		Girls WC (cm)		
	N	Mean (±SD)	N	Mean (±SD)	p*
10	476	66.1 (±7.7)	507	63.4 (±7.0)	< 0.001
11	1141	66.6 (±8.3)	1161	65.0 (±8.1)	< 0.001
12	1237	68.7 (±9.1)	1189	67.1 (±8.5)	< 0.001
13	1352	70.3 (±8.9)	1361	68.6 (±8.2)	< 0.001
14	1154	71.8 (±8.3)	1185	69.2 (±8.0)	< 0.001
15	1384	73.6 (±8.0)	1414	70.3 (±7.9)	< 0.001
16	1533	75.4 (±8.1)	1694	71.4 (±8.1)	< 0.001
Total	8277	71.0 (±9.0)	8511	68.5 (±8.4)	< 0.001

WC: Waist circumference; SD: Standard deviation. "NS": Non-Significant.
*Compares mean values between genders with T-Test (Bonferroni adjustments).

Boys showed generally higher WC in comparison to girls ($P < 0.001$) at all ages in the. Furthermore, WC mean rises in both genders from 10 to 16 years (Table 19). Table 20 lists the cut-offs for each age group according to the criteria used, more precisely, actual paediatric IDF criteria and age-specific growth curves linked to adult cut-offs. As an alternative, Figures 24 and 25 show the growth curves for both criteria in boys and girls respectively as well as the 90th percentile curve for age and gender.

Table 20 Age-specific WC cut-offs and corresponding percentiles for boys and girls. AO prevalence in boys and girls

Age (years)	Boys WC (cm)					Girls WC (cm)				
	Portugal									
	IDF youth		Age-specific			IDF youth		Age-specific		
	(90th)	N$^+$	(98th)	N$^+$	p^a	(90th)	N$^+$	(87th)	N$^+$	p^a
10	75.4	47	86,9	20	*	73.1	48	71.5	59	*
11	77.9	117	87,8	38	*	75.9	116	73.6	159	*
12	81.8	122	89,5	63	*	78.5	118	75.8	170	*
13	82.4	135	91,0	77	*	79.6	132	77.3	182	*
14	83.8	115	92,2	45	*	79.6	117	78.0	152	*
15	83.6	138	93,6	63	*	80.8	140	78.8	179	*
16	94.0	61	94,0	61	-	80.0	235	80.0	235	-
Total		735		368	*		907		1138	*

IDF youth: International diabetes federation paediatric criteria; Age-specific: Growth curve with the *LMS* method; N$^+$: Number of subjects identified with abdominal obesity.
[a]Compares the prevalence of abdominal obesity between the paediatric IDF criteria and the *LMS* growth curves method.
*($p < 0.05$) χ^2 test.

Table 21 reports the age-specific WC percentiles for boys from 10 to 16 years of age.

The adult cut-off of 94 cm for abnormally high WC was assigned at 16 years of age by the 98th percentile.

Table 21 Percentile curves for WC in 10 to 16-year-old boys

Age (years)	Percentiles									
	90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th
10	75.4	77,2	78,0	78,8	79,8	81,0	82,4	84,3	86,9	91,6
11	77.9	78,2	78,9	79,8	80,8	81,9	83,4	85,2	87,8	92,3
12	81.8	80,0	80,7	81,6	82,6	83,7	85,1	86,9	89,5	93,8
13	82.4	81,7	82,5	83,3	84,3	85,4	86,8	88,5	91,0	95,1
14	83.8	83,2	83,9	84,7	85,7	86,7	88,1	89,8	92,2	96,2
15	83.6	84,5	85,3	86,1	87,0	88,1	89,4	91,2	93,6	97,8
16	85.2	85,8	86,5	87,3	88,2	89,3	90,6	92,4	94,0	99,1

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in cm.

Figure 24 shows a similar pattern between percentile curves, except when considering the 90th percentile where three peaks are highlighted at the age of 12, 14 and 16 years of age, resulting in an irregular curve pattern.

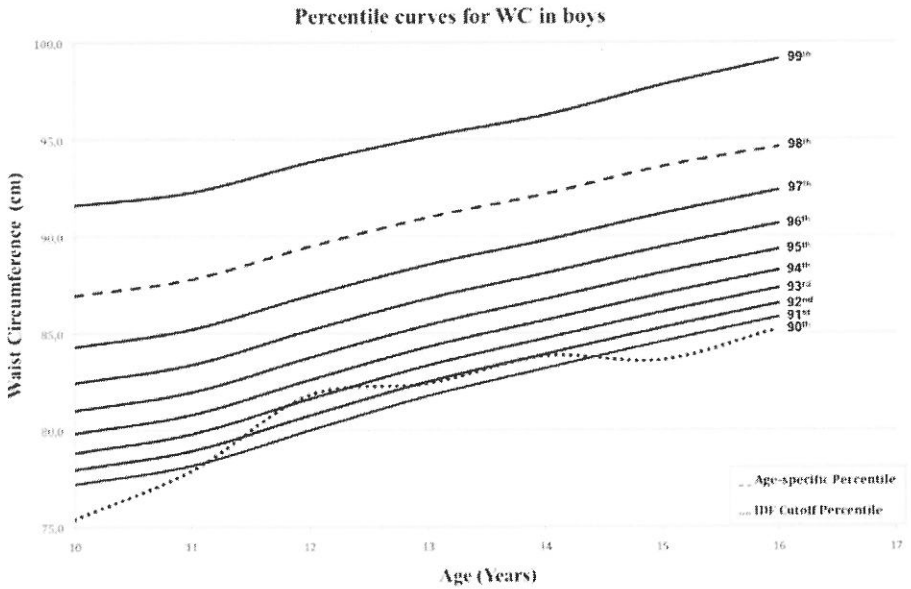

Figure 24 Percentile curves for waist circumference in boys from 10 to 16 years old

98th percentile curve passes through 94 cm at 16 years. 90th percentile is the cut-off actually recommended by the International Diabetes Federation.

Table 22 reports the age-specific WC percentiles for girls from 10 to 16 years of age. The adult cut-off of 80 cm for abnormally high WC was assigned at 16 years of age by the 87th percentile.

Table 22 Percentile curves for WC in 10 to 16-year-old girls

	Percentiles									
Age (years)	85th	86th	87th	88th	89th	90th	91st	92nd	93rd	94th
10	70,7	71,1	71,5	72,0	72,5	73,1	73,5	74,2	74,8	75,6
11	72,8	73,2	73,6	74,0	74,5	75,9	75,7	76,3	77,0	77,8
12	75,0	75,4	75,8	76,3	76,8	78,5	78,0	78,6	79,4	80,2
13	76,5	76,9	77,3	77,8	78,3	79,6	79,5	80,2	80,9	81,8
14	77,2	77,6	78,0	78,5	79,0	79,6	80,2	80,8	81,6	82,4
15	77,9	78,4	78,8	79,3	79,8	80,8	81,0	81,6	82,4	83,2
16	79,0	79,5	80,0	80,4	80,9	81,5	82,1	82,8	83,6	84,5

Age groups were calculated based on the decimal year distribution (i.e., from 11.0 to 11.9 represent the 11 years old group). The maximal age included was 16.9 years old. Values are in cm.

Figure 25 shows a similar pattern between percentile curves, except when considering the 90th percentile where a bigger peak was reached at the age of 13 years, followed by a drop at the age of 14 years, increasing afterwards until the age of 16 years, resulting in an irregular curve pattern.

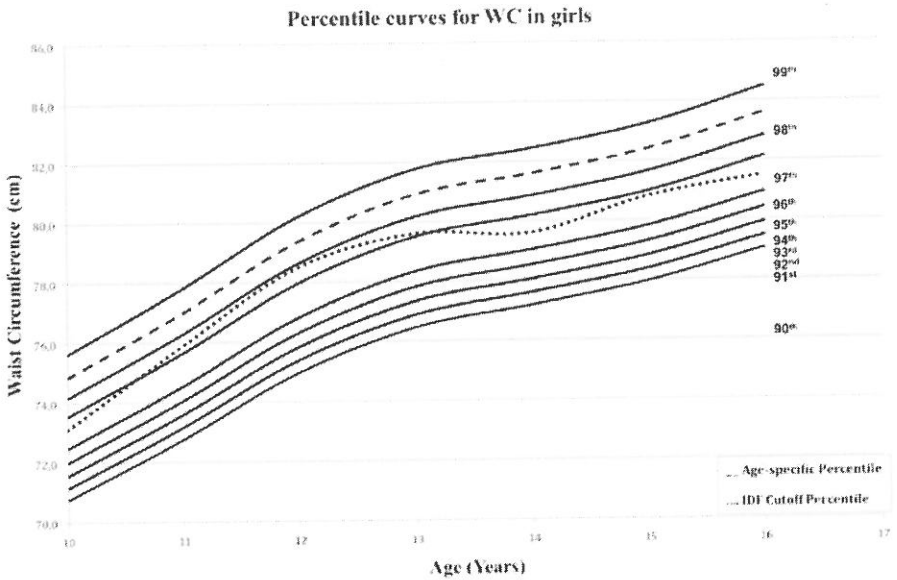

Figure 25 Percentile curves for waist circumference in girls from 10 to 16 years old
87th percentile curve passes through 80 cm at 16 years. 90th percentile is the cut-off actually recommended by the International Diabetes Federation.

Based on the *LMS* growth curves method, the percentiles that corresponded to adult IDF recommendations were the 98th and the 87th percentiles respectively for boys and girls (Table 20). Compared to the IDF paediatric criteria (90th percentile), the age-specific cut-offs were generally higher in boys (Figure 26) and lower in girls (Figure 27), as visible in Figures 24 and 25 respectively for boys and girls and highlighted as well in Figures 26 and 27. When compared the number of children and adolescents identified as possessing the risk factor related to AO, the actual IDF criteria overestimates the number of boys with high WC in all age groups ($P < 0.001$), underestimating the number of girls with high WC in all age groups ($P < 0.001$) as shown in table 20.

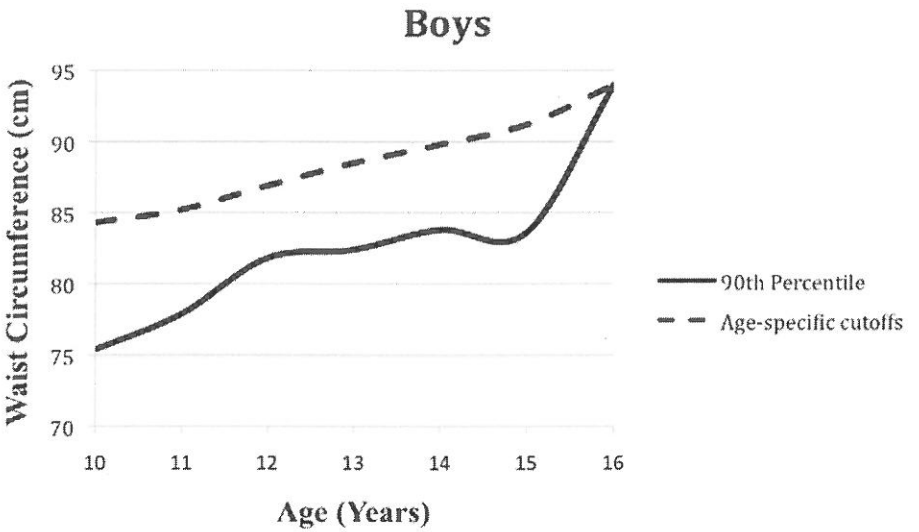

Figure 26 Waist circumference growth curves for boys according to both methods: 90th Percentile (recommended by the International Diabetes Federation for children and adolescents) and Age-specific (*LMS* growth curves) cut-offs.

Furthermore, table 20 shows 735 boys identified as possessing AO by the IDF paediatric criteria, being only 368 boys diagnosed by linking the adult cut-offs through the *LMS* growth curve.

In girls, 907 subjects were diagnosed with AO by the actual IDF paediatric criteria, being 1138 girls diagnosed by the *LMS* growth curves method (Table 20).

Figure 27 Waist circumference growth curves for girls according to both methods: 90th Percentile (recommended by the International Diabetes Federation for children and adolescents) and Age-specific (*LMS* growth curves) cut-offs.

Results show that current IDF paediatric criteria for diagnose AO in children and adolescents overestimates the number of boys with AO and underestimates the number of girls with AO (Figures 26 and 27, respectively).

Discussion

The paragraph "*Discussion*" is described in four parts: 1) Development of the cMSr score, 2) MS prevalence: IDF paediatric criteria Vs age-specific growth curves 3) Accuracy of dichotomous methods to diagnose the MS in children and adolescents, 4) Abdominal obesity diagnose in a different sample: IDF paediatric criteria Vs age-specific growth curves.

Development of the cMSr score

The literature lacks a universal definition of the MS definition in children and adolescents, and the prevalence is relatively low using the current suggestions of definitions in children, especially given the obesity rates among children and adolescents. Metabolic syndrome prevalence rates in children and adolescents was reported to be 2% in Turkey (Agirbasli, et al., 2006), 9% in Korea (Kim, et al., 2007), 10% in Canadian Quebec (Lambert, et al., 2004), 6.5% in northern Mexico (Rodríguez-Morán, et al., 2004), whereas the obesity prevalence was approximated 30-50% (Cook, et al., 2003; Dhuper, et al., 2007; Sen, et al., 2008). A recent study of the worldwide prevalence of the MS in children and adolescents showed that the prevalence ranged from 1.2-22.6%, being observed rates of up to 60% in the OW and obese youth (Tailor, et al., 2010). This discrepancy between the obesity rates and the reported MS prevalence made us think about the accuracy of the actually recommended MS criteria for youth.

The paediatric IDF criteria (Zimmet, et al., 2007) provided a helpful consensus especially for the clinical use in children and adolescents. However, as showed in our work, the DBP cut-off was not reached from any subject in our sample, indicating that a PCA might better compensate for the independent contribution of each variable in the overall MS diagnose. Moreover, we used the fasting plasma glucose in our analysis to follow the paediatric IDF criteria in order to validate the cMSr score with international guidelines. Nevertheless, we would have preferred to use the

homeostasis model assessment insulin resistance score (HOMA), as a better predictor of clustering coronary heart disease risk factors among young healthy subjects than fasting GLU, once insulin resistance may be compensated by increased insulin secretion (Andersen, et al., 2006).

Literature indicates that continuous scores, such as z-scores or PCA, are statistically more sensitive and less error prone when compared to the dichotomous approach (Brage, et al., 2004; Ragland, 1992) allowing each child to have a continuous value, where the lower values indicate a better metabolic profile and higher values indicate a poorer metabolic profile.

We found in our work through the PCA analysis principal components in boys and girls that explained a relatively high percentage of the total variance. In boys, the variables that repeatedly explained the variance, either in the PC 1 or in the PC 2, were WC, DBP and HDL-C and in girls the variables highlighted were WC, TG, SBP and DBP. Such findings stress especially the importance of WC in the MS diagnose not taking yet the importance of the other variables, meaning that more than the contribution of each variable independently, it is the way they relate that confers higher metabolic/physiological risk.

A study performed in Cuenca (Spain) used the confirmatory analysis to test whether a single factor might explain the clustering of the MS components in children, although they have done with a different statistical method (Martínez-Vizcaino, et al., 2010). They performed the study with 1,020 children between 10 and 13 years of age and the single-factor model included WC, fasting insulin, TG to HDL-C ratio and mean arterial pressure. Factor loadings of 0.67 for WC, 0.68 for fasting insulin, 0.57 for TG to HDL-C ratio and 0.37 for mean arterial pressure were obtained. Moreover, when compared to ATP III criteria, their MS index showed to be highly accurate in the diagnosis of MS with an AUC of 0.98 (95% CI 0.96-0.99) (Martínez-Vizcaino, et al., 2010). Our findings are in accordance once the WC, TG, HDL-C and blood pressure also had strong factor loadings after a MS score creation, rather than a dichotomous

isolated classification.

Several researchers (Andersen, et al., 2006; Brage, et al., 2004; DuBose, et al., 2007; Eisenmann, et al., 2005; Eisenmann, et al., 2007) have constructed a cMSr score for paediatric epidemiology and medicine showing also that cMSr score tracks from childhood/adolescence into young adulthood (Bao, et al., 1994; Eisenmann, et al., 2005; Katzmarzyk, et al., 2001; Raitakari, et al., 1994). However, only one study seemed to validate the cMSr score in children through a PCA (Eisenmann, et al., 2010), and despite being a sample specific method, our findings were in accordance with Eisenman and colleagues. Eisenman and colleagues also found a graded relationship between the cMSr score and the number of adverse risk factors, with higher cMSr score in subjects with more risk factors. Similar validation findings were also provided in a randomly selected sample of 18- to 75-year-old Flemish Adults (Wijndaele, et al., 2006) where a continuous metabolic syndrome score derived from a PCA was higher in adult subjects with the MS and that the score increased progressively with increasing number of adverse risk factors.

Recently, another study validated a continuous MS score in children and adolescents yet with a different method (Shafiee, et al., 2013). As in our work, they tried to validate a continuous MS score and identify sex- and age-specific optimal cut points of the continuous MS score associated to the MS. The study was performed with 3.254 school children from 10-18 years old and the continuous MS score was derived by aggregating age- and sex-standardized residuals of WC, mean arterial pressure, GLU, HDL-C and TG. As well as we found in our work, they founded a graded relationship between the continuous MS score and the number of risk factors.

The similar findings between our work and previously mentioned studies (Eisenmann, et al., 2010; Shafiee, et al., 2013; Wijndaele, et al., 2006) support the use of the cMSr score in epidemiological analyses, more as a preventative measure rather than a diagnostic tool. Moreover, in their investigation, Eisenmann and collegues (Eisenmann, et al., 2010; Wijndaele, et al., 2006) recommend that five key

components of the MS should be used in claculation of the score in future research: 1) central obesity (as measured by WC – or BMI and/or skin fold thickness if WC is not available), 2) low HDL-C, 3) elevated TG, 4) elevated BP (systolic and/or diastolic and/or MAP), and 5) abnormal GLU metabolism (impaired fasting glucose, impaired glucose tolerance, and/or HOMA). Furthermore, they suggest that the individual components should be age standardized (and maturity-standardized, if available) given the influence of growth and maturation on the development of the metabolic risk factors. Steel, it was also suggested (Eisenmann, et al., 2010) that association studies using established cohorts that link the MS score during childhood and adolescence with adult-diagnosed MS, type 2 diabetes, atherosclerosis and CVD mortality should be provided to create, and we agree entirely with this suggestion, a simple and practical yet valid tool to be used conventionally in paediatric epidemiological research, clinical medicine, and public health to better understand the prevention, diagnosis, and treatment of this emerging paediatric condition.

MS prevalence: IDF paediatric criteria Vs age-specific growth curves

Age and sex-specific cut-offs for abnormal WC and lipids were created in our work in the form of growth curves. We applied the *LMS* method to create specific percentile lines in childhood and adolescence that corresponded to currently accept abnormal cut-off values for each variable in adults older than 16 years old, including those with 16 years old. The growth curves provide one approach to the measurement and longitudinal tracking of risk factors for CVD in children and adolescents. However, the significance of these percentile curves as potential predictors of future disease warrants further research. Longitudinal studies have shown that CVD risk factors related to obesity and insulin resistance cluster together to a greater degree than expected by chance in adults, and possibly also in children (Chen, Srinivasan, Elkasabany, & Berenson, 1999; Morrison, Friedman, Wang, & Glueck, 2008; Reaven, Traustadottir, Brennan, & Nader, 2005; Srinivasan, Myers, & Berenson, 2002, 2006; Sun, et al., 2008; Webber, Srinivasan, Wattigney, & Berenson, 1991).

These clustering patterns also have been shown to track together over time (Huang, Nansel, Belsheim, & Morrison, 2008; Sun, et al., 2008). However, studies have shown that risk status is not entirely stable over time (Goodman, Daniels, Meigs, & Dolan, 2007). Some of the instability described may be the result of analyzing MS risk factors without accounting for naturally occurring age-related or pubertal fluctuation in some components of the lipid profile (Cook, Auinger, & Huang, 2009).

The smoothed growth curves based in the *LMS* method have been used in children and adolescents by several researchers to study the CVD risk factors distribution (Cook, et al., 2009; Jolliffe & Janssen, 2007). Despite being sample-specific, a study with U.S. children and adolescents (Jolliffe & Janssen, 2007) found that the WC percentile that corresponded to the adult cut-off at 20 years of age, based on the IDF definition (94 cm in men and 80 cm in women), was the 83rd percentile in boys and the 50th percentile in girls. Once they had used different criteria and a different age range, comparisons with our work become difficult. However, we observed that their curves behave similarly to ours, increasing progressively from the youngest to the oldest age groups both in boys and girls, a natural and predictable finding. Analysing the blood pressure profile, Jolliffe and Janssen (2007) found that for SBP the 92nd percentile in boys and the 93rd percentile in girls identified the individuals at higher risk when linking the growth curve to adult criteria at 20 years of age, being the 97th and 99th percentiles for boys and girls respectively found for DBP. In our work the findings where similar for SBP being the 92nd percentile that identified the boys at higher risk when linking the growth curve to adult criteria at 16 years of age. The cut-off was never achieved in girls, nor for systolic nor for diastolic blood pressure. Diastolic blood pressure cut-off was never achieved also in boys.

Inconsistencies were found in HDL-C and TG curves, once the HDL-C curve profile in U.S. boys and girls increased progressively from 12-years to 20-years of age and in our sample the curve pattern was extremely irregular in both genders. The highest inconsistency was found in TG where the U.S. sample showed different patterns between genders, increasing progressively in boys, and with an inverted curve in girls

reaching the bottom at the age of 15 years, increasing afterwards until the age of 20 years. In our sample, we found a similar effect in boys and girls, being the TG curves irregular during growth.

In another study with U.S. children and adolescents (Cook, et al., 2009) the WC growth curves behave similar to our work, increasing progressively from youngest to oldest age groups, however in their study the criteria adopted was the ATP III criteria (102 cm for men and 88 cm for women). The TG curves pattern found by Cook et al. (2009) was similar to our findings, having a bimodal pattern in the girls curve and a decline in the boys curve. In our work, the findings were similar but opposite with a bimodal pattern in boys and a continuous decline in girls' curve. As well as in our work, Cook et al. (2009) found an irregular pattern in the curves of HDL-C, low-density cholesterol and total cholesterol, a fact that has been noted in previous cross-sectional studies of lipid profiles among children and adolescents (Hickman, et al., 1998; Tamir, et al., 1981; Ventura, Loken, & Birch, 2006). In their study, Cook et al. (2009) reported age-related or pubertal fluctuations in some components of the lipid profile, in accordance to our findings.

Despite GLU being considered relatively stable in the adolescent age group when the *LMS* method was applied (Jolliffe & Janssen, 2007), in our work we found that either in boys or girls the values were lower than the cut-off at initial ages of 10 and 11 years old and higher during adolescence.

Our growth curves with Danish youth showed that the variables behave inconsistently during growth, especially at the pubertal stage for lipid and blood pressure profiles. Whereas for WC an expected progressive growth pattern until the age of 16 years was found with the *LMS* method, our results showed that when considered the 90^{th} percentile adjusted to age and gender as proposed by the IDF for youth, the curve pattern becomes irregular, ending at 15 years of age lower and far from the proposed value for adults at 16 years of age in boys, and higher but not so far from the proposed value in girls. Such findings supported our search for the most

accurate method to diagnose the MS in youth considering the *LMS* growth curves method and the IDF proposed criteria for children and adolescents. However, it is important consider that our sample age-range was not complete from 10-years to 16-years old. Growth curves are possible to build based in two age groups at least, yet a complete age-range would be preferable. This limitation was the main reason to apply the previous methods in a complete age-range sample as we did with the Portuguese cohort, discussed afterwards.

A recent update showed that the MS remains a major worldwide health concern in children and adolescents, particularly amongst the obese (Tailor, et al., 2010) independently of the used criteria.

Our prevalence estimates in children and adolescents might be compared with recent studies that used the same criteria, both in Europe (Ekelund, et al., 2009) and in U.S. (Ford, Li, Zhao, Pearson, & Mokdad, 2008). In the work by Ekelund et al (Ekelund, et al., 2009), using data from the European Youth Heart Study collected in Denmark and in addition data from Estonia and Portugal, the MS was diagnosed in 0.2% of 10-year-old children and in 1.4% of 15-year-old adolescents. These findings are in accordance with our work where a prevalence of 1.0% was found for the entire sample.

Still, in data from U.S. adolescents (Ford, et al., 2008) approximately 4.5% possessed the MS according to the IDF paediatric criteria, being a relatively low prevalence for U.S. adolescents from 12-year-old to 17-year-old, considering the AO rates (Ford, et al., 2008), but higher than our findings. The higher MS prevalence rates in the U.S. adolescents may be explained by a higher prevalence of AO in U.S. adolescents (25.6% compared with 10.2% in our work), despite the remarkably higher cut-offs for AO used by Ford et al (Ford, et al., 2008).

A recent study compared the MS prevalence in 16-year-old adolescents using both IDF paediatric and adult definitions and the results revealed that the paediatric definition rendered a higher prevalence estimate (2.4%), either for European cut-offs

(1.7%), or for North American cut-offs (1.0%) (Pirkola, et al., 2008). The new IDF criteria to diagnose MS in youth adheres to the same criteria as the adult definition (Alberti, et al., 2006), except for WC where the 90th percentile is recommended, indicating that the main difference in MS prevalence should be related to the WC criteria.

Another study (Schwandt, Bertsch, Liepold, & Haas, 2013) developed with 2228 German first graders who participated in the Prevention Education Program (PEP) Family Heart Study compared the prevalence of each risk factor in four MS components, as defined by the IDF, with age- and gender-specific growth curves. Applying the IDF recommendations they found a prevalence of hypertension of 2.0% in boys and 2.9% in girls compared with 12.7% for boys and 12.8% for girls based on age- and gender specific values. Prevalence rates for hypertension were higher in the growth curves than in the IDF criteria, similar to our findings where the prevalence of high SBP according to IDF criteria was 5.3% against 8.3% with age-specific growth curves ($p < 0.05$).

A Turkish study with obese children (Sangun, Dundar, Kosker, Pirgon, & Dundar, 2011) aged 11.3±2.5 years compared the MS prevalence according three different methods, the modified WHO (Consultation, 1999), Cook (Stephen Cook, et al., 2003) and the IDF paediatric criteria (Zimmet, et al., 2007). The MS prevalence was found to be 39% with the WHO criteria, 34% with the Cook criteria and 33% with the IDF paediatric criteria. Such prevalence rates are substantially higher than those founded in our work, 0.8% with the IDF paediatric criteria and 0.4% with the age-specific growth curves, due to the presence of obesity in their patients.

A recent systematic review of 85 papers from recognized databases reported a median prevalence of MS in children of 3.3% (range 0%-19.2%), being 11.9% (range 2.8%-29.3%) reported in OW and 29.2% (range 10%-66%) in obese children (Friend, Craig, & Turner, 2013). Moreover, they've reported higher prevalence in boys (5.1%) than girls (3.0%) (p <0.001). In our work the prevalence rates, according to the IDF

paediatric criteria were similar, being the prevalence higher in boys than girls, however based in the age-specific growth curves the prevalence was slightly higher in girls. Furthermore, another systematic review (Friend, Craig, & Turner, 2012) found prevalence rates between 3-10% in children and adolescents using ATP III criteria and between 1-7% using IDF criteria, with no differences between genders, being the prevalence lowest for studies of European and Asian populations (3.3%-4.2%) and highest for the Middle East and North American populations (4.2%-10%).

The cut-offs developed in our work, linking the children and adolescent cut-offs to IDF adult cut-offs reflected the fluctuations in WC, blood pressure and plasma lipid profile that occur naturally with age (Hickman, et al., 1998; Katzmarzyk, 2004; Muntner, He, Cutler, Wildman, & Whelton, 2004), producing similar findings to those pointed out by Jolliffe and Janssen (Jolliffe & Janssen, 2007), showing the need for age-specific cut-offs adjustment during childhood and adolescence. In their study, the WC percentiles that linked the adult cut-offs according to adult IDF definition with the adolescent cut-offs were the 83rd percentile for males and the 50th percentile for females. Despite the differences between samples, the method used was the same as ours, and the discrepancy between percentiles allow us to question about a single percentile for children and adolescents. Moreover, although the prevalence differences between IDF criteria and age-specific cut-offs for each MS variable, the MS diagnose was similar, meaning that the percentage of subjects identified as possessing the MS was the same in our sample for both methods. Furthermore, we showed that risk factors clustered in 73 subjects and even if none of the participants had clinical disease, clustered risk is certainly an undesirable condition that has been shown to track into young adulthood (Andersen, Hasselstrøm, Grønfeldt, Hansen, & Karsten, 2004).

Accuracy of dichotomous methods to diagnose the MS in children and adolescents

Once validated the cMSr score for children and adolescents and known that the MS

score has been shown to track from childhood/adolescence into young adulthood (Bao, et al., 1994; Batey, et al., 1997; Katzmarzyk, et al., 2001; Raitakari, et al., 1994), rises the need to test the actually recommended MS criteria for youth, testing out the possibility of linking adult cut-offs to youth data with a sample-specific method.

Despite the utility of our findings for both clinical and research approach, providing a continuous method for the MS, we likewise intended to compare the accuracy of the IDF paediatric definition with the accuracy of the age-specific cut-offs and furthermore with the accuracy of the IDF paediatric definition applying age-specific cut-offs only for WC, compensating for the AO significance in the MS prevalence as Pirkola et al (Pirkola, et al., 2008) findings suggest.

Receiver Operating Characteristics analysis provided specific cut-offs conferring an increased risk for MS presence in our work (1.98). A previous study from Eisenman and colleagues (Eisenmann, et al., 2010) obtained the cut-off of 3.72 as conferring increased risk for the MS diagnose. Sensitivity and specificity were similar, 100% and 99% respectively in our work, and 100% and 93.9% respectively in their study, both with an AUC of 98%, being both highly accurate to identify the presence of the MS for the respective samples.

Also Shafiee and colleagues study (Shafiee, et al., 2013) found a specific cut-off from a continuous MS score as conferring increased risk. They have found the cut-off of 2.93 with a sensitivity of 92% and a specificity of 91%, lower than ours and Eisenman and colleagues (2010). The AUC was 96%, likewise lower (Shafiee, et al., 2013).

Differences in the cut-offs that confer increased risk for the MS were due to the specificity of each sample and the method adopted to validate the continuous score. Eisenman and colleagues (Eisenmann, et al., 2010) data derived from 7- to 9-years-old American children, so a different sample once includes only children. Moreover, in their study was used a different criteria to diagnose the MS, based in age-modified

cut-offs of the ATP III criteria published previously by Cook et al. (Stephen Cook, et al., 2003). Shafiee and colleagues data (Shafiee, et al., 2013) accounted for youth between 10 and 18 years old and the continuous MS score was derived by first standardizing the residuals for WC, mean arterial pressure, HDL-C, TG, and GLU by regressing them on age and sex to account for age- and gender-related differences. Because the standardized HDL-C was inversely related to the MS risk, it was multiplied by -1. The continuous MS score was calculated as the sum of the standardized residuals (*z* scores) for the individual variables.

Until our knowledge our work is the first comparing the accuracy of dichotomous methods to diagnose the MS with a continuous score, fact that compromises comparisons with other investigations. We and some investigators believe that continuous scores, such as the PCA, are statistically more sensitive and less error prone when compared to the dichotomous approach (Brage, et al., 2004; Ragland, 1992), which made us to consider the continuous score as the reference diagnostic tool to test the dichotomous methods.

In our work, the highest AUC was shown by the combination of actual IDF paediatric criteria with the age-specific WC cut-offs (AUC = 0.978), revealing a higher accuracy when age-specific growth curves are applied to WC rather than the 90^{th} percentile. On the other hand, the accuracy of the IDF paediatric criteria was slightly lower (AUC = 0977) and the accuracy of age-specific growth curves applied to all MS components was the lowest (AUC = 0.978). Our results point that when the growth curves were applied to WC the accuracy was the highest, instead of the 90^{th} percentile currently recommended by the IDF for children and adolescents. Such fact suggests that the use of age- and gender-specific growth curves is a most accurate method to diagnose AO in children and adolescents based on its relationship with other MS risk factors. Despite AO being considered a *sine qua non* condition for the MS diagnose by the IDF (Alberti, et al., 2006), their consensus for a specific criteria for children and adolescents recognized that the use of the 90^{th} percentile might be reassessed when more data are available (Zimmet, et al., 2007).

We believe that our data might be considered to reassess AO criteria for children and adolescents, fact that will be discussed deeply in the next chapter "Abdominal obesity diagnose in a different sample: IDF paediatric criteria Vs age-specific growth curves".

Abdominal obesity diagnose in a different sample: IDF paediatric criteria Vs age-specific growth curves

Waist circumference measurement conversion, from NIH to WHO protocol

In order to adjust the data relative to the WC collected in the Portuguese sample frame, we needed to convert the WC values from NIH protocol to WHO protocol.

The comparison between places to measure WC using WHO and NIH protocols as been already made (Patry-Parisien, Shields, & Bryan, 2012), providing specific equations for 3 to 19 years old boys and girls.

Until our knowledge there are no studies using the referred equations to convert NIH to WHO measurements. Once our data was in accordance to NIH protocol we had used the conversion equation in order to enable the further analysis with the IDF criteria, since the IDF criteria for WC is based in the WHO measurement protocol.

In Jennifer Patry-Parisien and colleagues study (Patry-Parisien, et al., 2012), the WC values for Canadian adults and children were significantly greater through the NIH protocol, in comparison to the WHO protocol, as well as we found in our work in children and adolescents where significant differences were found in both genders at all ages. Similarly to the Candian study, in our work the WC mean difference was greatest among girls. These findings add to the limited information about WC measurements taken at different sites (Mason & Katzmarzyk, 2009; Wang, et al., 2003). In a study based on 111 healthy volunteers aged 7 to 83, Wang et al. (Wang, et al., 2003) compared measurements at four sites - immediately below the lowest rib, at the narrowest waist, midway between the lowest rib and iliac crest (WHO), and immediately above the iliac crest (NIH). In their study, males' mean WC at the

narrowest waist was significantly lower than at the other three sites. For females, mean WC at each site differed significantly from means at the others, and WC measurements using the NIH protocol significantly exceeded those using the WHO protocol (1.82 cm) (Wang, et al., 2003).

We consider this conversion equation a practical method to convert WC values from NIH to WHO measurement protocol, allowing comparisons between measurement places and posterior comparative studies between different samples with different methods.

IDF paediatric criteria Vs age-specific growth curves

Waist circumference has attracted much recent attention as an indicator of fatness and health risks in children and adults. The interest in WC stems from research linking accumulated visceral adipose tissue to increased health risks and metabolic disorders in children and adults (Gower, Nagy, & Goran, 1999; Katzmarzyk, et al., 2004).

Compared with BMI, WC in children provides a better estimate of visceral adipose tissue measured with MRI at the level of the fourth lumbar vertebra (65% vs 56% of variance), whereas BMI is better at estimating subcutaneous adipose tissue (89% vs 84% of variance) (Brambilla, et al., 2006). In multivariate regression models, WC is significantly more efficient than BMI in predicting insulin resistance, blood pressure, serum cholesterol levels, and triglyceride levels (Lee, et al., 2006; Maffeis, et al., 2001; Savva, et al., 2000). Consequently, measurements of WC provide unique predictive information regarding health risks, especially for adolescents.

Despite the regular use of age- and gender-specific percentiles to draw WC growth curves for children and adolescent worldwide, Canada (Katzmarzyk, 2004), Great Britain (McCarthy, Jarrett, & Crawley, 2001), Spain (Zaragoza) (Moreno, et al., 1999), Turkey (Hatipoglu, et al., 2008), China (Sung, et al., 2008; Yan, et al., 2008), Cyprus (Savva, et al., 2001), the USA (Fernández, Redden, Pietrobelli, & Allison, 2004), Holland (Fredriks, Van Buuren, Fekkes, Verloove-Vanhorick, & Wit, 2005), Austrália (Eisenmann, 2005), Japan (Inokuchi, Matsuo, Anzo, Takayama, &

Hasegawa, 2007), Poland (Nawarycz, et al., 2010), Germany (Schwandt, Kelishadi, & Haas, 2008), Bolívia (Botti, Pérez-Cueto, Monllor, & Kolsteren, 2010), Iran (Kelishadi, et al., 2007) and Portugal (Sardinha, Santos, Vale, Silva, et al., 2011), our work is until our knowledge the first one that used age and gender-specific WC cut-offs for youth linked to actual IDF criteria for European adults.

Our work provided WC age-specific cut-offs for Portuguese and Danish boys and girls from 10 to 15 years old, matching with the current IDF recommended cut-offs for adults and once we have found no similar data taking in account the protocol used the statistic comparison seems to be needless, once this method is a sample-specific method. However, as we used the same method than Jolliffe and Jansen in 2007 with U.S. adolescents (Jolliffe & Janssen, 2007), it seems appropriate to compare the percentiles founded in both studies. In their study (Jolliffe & Janssen, 2007), the 83rd percentile for males and the 50th percentile for females (12 to 19 years old) were found to intercept the WC cut-offs established by the IDF for adults, showing that the percentile that classifies girls with AO is lower than the boy's percentile, reinforcing our results. Such findings indicate that the 90th percentile recommended by the IDF for both genders might not compensate for phenotypic and metabolic differences caused by pubertal changes (Tfayli & Arslanian, 2007), under or overestimating the number of children and adolescents at risk.

Furthermore, either for boys and girls the percentiles founded by Jolliffe and Jansen (Jolliffe & Janssen, 2007) for U.S. youth were lower than those founded for Portuguese and for Danish youth, indicating not only that American youth have higher mean WC values as also the need for demographic and ethnic-specific growth curves as previously suggested by the IDF (Zimmet, et al., 2007). Once there are other studies supporting the WC mean differences between European and American youth (Sardinha, Santos, Vale, Silva, et al., 2011) (McCarthy, et al., 2001), we believe that it is critical to adopt a method that besides to reduce ethnic differences might be internationally consensual, as the IDF cut-offs for adults (Alberti, et al., 2006).

Comparison between IDF paediatric criteria and age-specific *LMS* growth curves performed in our work showed that the 90th percentile overestimates AO incidence in boys and underestimates AO incidence in girls.

In the IDF expert's consensus statement (P. Zimmet, et al., 2007), the 90th percentile has been suggested as the cut-off for children and adolescents from 10 to 15 years old, adopting the adults criteria at the age of sixteen. The 90th percentile was established based on a study developed with 818 pre-pubertal children aged between 3 and 11 years old which indicates that those children with WC above the 90th percentile had a higher probability to develop multiple risk factors, especially an adverse lipid profile and hypertension (Maffeis, et al., 2001). Since data supporting the previous IDF recommendations was collected in children younger than 11 years old and recognized the hormonal, metabolic and psychological changes caused by puberty (Maffeis, et al., 2001), we consider that a cross-sectional percentile throughout childhood and adolescence might not compensate for metabolic instability, being the MS diagnose doubtful.

Agreeing with other investigators suggestion (Jolliffe & Janssen, 2007) and based in our findings, we also believe that the *LMS* growth curves method to develop age- and gender-specific cut-offs linked to actual IDF adult's criteria might better compensate for the gender differences throughout childhood and adolescence, being a more suitable diagnose method both for clinical practice and research.

Conclusion

In conclusion, facing our general aim:

- the 90th percentile recommended by the IDF to diagnose AO in children and adolescents was shown to overestimate the incidence of AO in boys and underestimate the incidence in girls. This finding was tested in two different sample frames, proving the inadequacy of IDF currently recommended cut-off for WC. Actual IDF paediatric criteria for AO needs to be recessed and we alternatively recommend the use of age-specific growth curves linked to adult cut-offs through the *LMS* method.

Furthermore, and regarding our specific aims:

- our results validate the application of the cMSr score in children and adolescent, proving to be a valuable tool especially, but not exclusively, for research.
- the prevalence of the MS is 0.5% in Danish youth, either according to the IDF paediatric criteria or according to the age-specific growth curves. Moreover, the paediatric IDF criteria overestimates the presence of the MS in boys, being identified 0.8% of boys compared to 0.4% through the growth curves method. On the other hand, the IDF paediatric criteria underestimates the presence of the MS in girls, being identified 0.2% with the MS, when compared to the growth curves method where 0.6% were identified.
- the paediatric IDF criteria were shown to be highly accurate in the MS diagnose when compared to a continuous method, being the age-specific cut-offs developed through the *LMS* growth-curves a moderately accurate method. However, switching the IDF paediatric criteria for WC by age-specific growth curves linked to adult's cut-off resulted to be the most accurate method to diagnose the MS in children and adolescents.
- tested the 90th percentile utility in a different sample frame, we confirmed that the 90th percentile overestimates the incidence of AO in boys and

underestimate the incidence in girls.

General strengths and limitations

We believe to be a strength of our work the fact that we have derived our cMSr score based on a PCA rather than a *z*-score. The *z*-score considers that each selected variable is equally important in defining CVS risk, however despite a child being defined as at risk does not necessarily mean that the child has high levels of CVD risk factors *per se*. The PCA compares the overall relationship between variables and groups that are statistically related. We consider the PCA a more suitable method to apply to biological systems than the *z*-score.

Moreover, we consider that the comparison between dichotomous method's accuracy should be made having a continuous variable as reference (cMSr score) being for us, and in accordance to other researchers (S. r. Brage, et al., 2004; Richard Kahn, John Buse, Ele Ferrannini, & Michael Stern, 2005; David R Ragland, 1992), a fairer approach to apply for health physiological issues.

We also consider a strength the fact that our analysis was the first to provide age-specific cut-offs linked to adult ctuoffs for European paediatric samples.

A major limitation to the cMSr score presented in our work is that is sample specific.

Therefore, the cMSr score derived in one study cannot be compared to other studies unless the demographic characteristics, distribution of data, and the measures of central tendency and variability are similar in the two samples.

It is also important to note that sexual maturation was not accounted for our analysis and the growth curves were age-adjusted rather than maturation-adjusted. In fact, the growth curves are related with changes on decimal age rather than maturation's level, however this approach would not be practical for clinical use as the maturation level would have to be assessed.

Furthermore, our work age span was not completed for the Danish sample frame and despite the *LMS* method adjustment, it would be ideal to have a complete age span between 10 to 16 years old or an overtime longitudinal sample to produce the cut-

offs. Nevertheless, considering this limitation we applied the *LMS* growth curves in a complete age span sample frame (data from Portugal) in order to verify the findings obtained with the Danish sample frame.

Finally, although using cross-sectional data is a common practice to develop growth curves, cross-sectional comparisons between ages might not correctly represent changes over-time in a given individual, owing to individual differences in growth velocity.

Perspectives

Although the present work indicates that MS risk assessed by a continuous score is a more appropriate way to have in account the variability between individuals, the intra-individual variability analysis should represent a step further on the investigation. A more sophisticated analysis of MS variability provides a measure of the integrity of the underlying system that produces the dynamics between risk factors. As the spatial and temporal organization of a complex system define its very nature, changes in the patterns of interconnection between risk factors and patterns of each risk factor variation over time contain valuable information about the state of the overall system, representing an important means with which the diagnose of MS risk is specific for each individual. Thus, measure more times the risk factors in the same subject, allow investigators to assess the variation of the metabolism over time, and afterwards define the entropy for that specific subject, which will give useful information about the levels from which the subject is closer to the pathology. Furthermore, having a longitudinal sample provides the possibility to understand how specific variables and the entire pathophysiological system behave over time and for the different life stages.

This work outcomes supports the inclusion of WC age-specific growth curves linked to adult cut-offs for children and adolescents younger than 16 years old in the current MS diagnose, however further application in different samples should be made in order to widely confirm the accuracy of this method.

Technological progress provides today powerful instruments to measure body composition (e.g. DEXA, MRI, ultrasonography). The idea of applying such instruments to test the accuracy of the different field methods to assess AO kept in our mind after the previous studies. However, financing limitations and the difficulty to widely apply the technological methods limited our horizons, but just for nowadays. Combining actual MS criteria with a high tech accurate method to

measure AO seems to us a starting point to further discuss the most accurate form to widely assess AO risk factor.

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The metabolic syndrome in youth is a contemporary topic in international research, with some studies focusing on the potential benefits of a continuous classification instead of a dichotomous classification. Recently, the International Diabetes Federation has recommended using the 90th percentile as the cutoff point of waist circumference for diagnosing the metabolic syndrome in children and adolescents younger than 15 years of age, keeping the remaining variables with the cutoff values for adults. Some researchers question the adequacy of the cutoff set to identify abdominal obesity and why youth took the reference values from adults, suggesting other methods to identify the cutoffs that best compensate for differences in age and gender at this stage of youth development, such as growth curves. The main objective of this work was to examine the validity of the International Diabetes Federation paediatric criteria to diagnose the metabolic syndrome in children and adolescents, with special attention to waist circumference.

Jorge Bravo Lectures Exercise Physiology at the University of Évora, Portugal. His Ph.D. study focused on the subject of the metabolic syndrome among youth. Jorge has clinical practice on exercise prescription for health.

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