Association of Anthropometric Measures with Cardiovascular Risk Factors and Metabolic Syndrome in Normal-Weight Children and Adolescents: The CASPIAN III Study

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Key Words
Anthropometric · Cardiovascular · Metabolic syndrome · Children · Adolescents

Abstract
Objective: This nationwide study was conducted to determine the association of anthropometric measures with cardiovascular risk factors and metabolic syndrome (MetS) in Iranian normal-weight children and adolescents. Methods: We analyzed the data of 3,565 children and adolescents (50.3% boys), aged 10–18 years, with a normal BMI (5th–84th percentile) obtained from the third survey of ‘Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable Disease’ (CASPIAN III) study. The diagnostic criteria for MetS were defined by the International Diabetes Federation consensus. Results: The prevalence of MetS for 10- to 13.9-year-old boys, 14- to 18-year-old boys, 10- to 13.9-year-old girls, and 14- to 18-year-old girls were 1.4, 2.8, 2.3, and 3.3%, respectively. After adjustment for age and sex, each unit increase in BMI (within normal range) and waist circumference increased the odds of MetS from 6 to 72% and from 1 to 20%, respectively. The dominant pattern of dyslipidemia among the participants was high triglycerides and low high-density lipoprotein cholesterol. Conclusion: This study complements recent research about the high frequency of metabolic risk factors among normal-weight individuals in the pediatric age group.

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Introduction

Obesity is reaching pandemic levels and has been shown to have a significant association with metabolic syndrome (MetS), which is one of the major risk factors of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).

Recent studies have documented that the high prevalence of obesity among adults extends to the adolescent population as well, and childhood obesity has become a new type of challenge for pediatric care [1]. Declining levels of physical activity and escalating caloric intake have been proposed as an explanation for the increasing rate of obesity in children and adolescents [2–3]. Childhood obesity is associated not only with important implications for the risk of childhood diseases but also with increased risk of chronic disease and decreased life expectancy in adult life [4].

The association between childhood obesity and MetS has been evaluated in recent years [5]. Many studies have compared the prevalence of cardiometabolic risk factors across weight categories among children and it has been documented that the prevalence of risk factor clustering increases across weight categories [6]. However, in these articles, there is a group of normal-weight children and adolescents with metabolic risk factors predisposing them to the development of the MetS [6–11].

More than three decades ago, the concept of a ‘metabolically obese normal-weight’ (MONW) phenotype was introduced in the adult population [12]. Since then, a large body of evidence has suggested a high prevalence of this phenotype in the general population. It has been shown that these individuals have a higher proportion of visceral fat and a lower lean body mass and respond favorably to caloric restriction [12–13].

In the previous study of this series, we introduced the existence of MONW phenotype in Iranian school children [11]. The present study aimed to determine the association of anthropometric measures with risk factors of CVD as well as MetS in a nationally representative sample of Iranian normal-weight children and adolescents.

Subjects and Methods

We have previously published the methodology in detail [14], and here we present it in brief.

Study Subjects

The data for this study derives from the third survey of ‘Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable Disease’ (CASPIAN) study conducted in 2009 and 2010. The CASPIAN is a national longitudinal school-based program for the surveillance of risk behaviors due to as well as risk factors of chronic diseases among children and adolescents and is a joint collaboration of the Iranian National Ministries of Health and Education. We have previously described detailed information about this project [11].

For the third survey of the CASPIAN study [14], overall 5,088 students aged 10–18 years were selected by multistage random cluster sampling from urban and rural areas of 27 provinces located in diverse parts of the country. Of these, 3,565 subjects who had complete records and normal weight according to the BMI cutoffs (5th–84th percentile) of the Centers for Disease Control and Prevention (CDC) were included in this study. We used the cutoffs of the CDC [15] because the first survey of the CASPIAN study, conducted among 21,111 children and adolescents, revealed a strong agreement of cutoffs obtained for Iranian children and adolescents with cutoffs of the CDC, though not with those of the International Obesity Task Force (IOTF) [16].

The study objectives and protocols were completely explained to the students and their parents. Written informed consent and verbal consent were obtained from the parents and the students, respectively. Approval for the study was granted by the ethics committees and other relevant national regulatory organizations. The Data and Safety Monitoring Board of the project closely supervised the quality control and quality assurance of the survey at the national level.
Anthropometric and Biochemical Measurements

Trained research assistants measured the adolescents' height and weight according to standardized protocols. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with the children wearing only underwear and no shoes. Height and weight measurements were used to calculate BMI (kg/m²). Waist circumference (WC) was measured to the nearest 0.1 cm with a flexible tape at a point midway between the lower border of the ribcage and the iliac crest at the end of normal expiration. We measured blood pressure (BP) before blood sampling and in a calm situation using mercury sphygmomanometers after at least 5 min of rest in the sitting position. The subjects were seated with the heart, cuff, and zero indicators on the manometer at the observer's eye level. All readings were taken in duplicate in the right arm. Appropriate size cuffs were used with a cuff width 40% of the mid-arm circumference as well as cuff bladders covering 80–100% of the arm circumference and approximately two-thirds of the length of the upper arm without overlapping. The procedure was explained to the students and the cuff inflated and deflated once; the first BP measured was not used in the analysis of this study.

The readings at the first and the fifth Korotkoff phase were taken as the systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. The average of the two time measurements was recorded and included in the analysis [17].

Venous blood samples were collected from all study participants after 12 h of overnight fasting and delivered to the laboratory on the day of blood collection. The blood samples were centrifuged for 10 min at 3,000 rpm within 30 min of venipuncture and were immediately transported to the laboratory. Fasting blood sugar (FBS), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured enzymatically by auto-analyzers. HDL-C was determined after dextran sulphate-magnesium chloride precipitation of non-HDL-C. According to the Friedewald equation, low-density lipoprotein cholesterol (LDL-C) was calculated in serum samples with TG \( \leq 400 \text{ mg/dl} \) [18].

Definition of Terms

Subjects were classified as having MetS if they fulfilled three out of the following criteria: i) TG concentration of 150 mg/dl or greater; ii) HDL-C concentration of 40 mg/dl or less; iii) fasting blood glucose concentration of 100 mg/dl or greater; iv) WC in the 90th percentile for their age and sex in the population; and v) either SBP or DBP in the 90th percentile for their age, sex, and height from cut-point recommended by the National Heart, Lung, and Blood Institute. This is based on criteria analogous to the definition of the International Diabetes Federation for MetS in the pediatric age group [19].

Three main parameters of high BP, dyslipidemia, and impaired fasting glucose (IFG) were included in this study as cardiovascular risk factors. Dyslipidemia was defined according to the recent recommendation of the American Heart Association; i.e. TC \( \geq 200 \text{ mg/dl} \) (5.2 mmol/l) and/or TG \( \geq 150 \text{ mg/dl} \) (1.70 mmol/l) and/or LDL-C \( \geq 130 \text{ mg/dl} \) (3.38 mmol/l) and/or HDL-C <40 mg/dl (1.04 mmol/l). IFG was defined as having a fasting blood glucose concentration of 100 mg/dl or greater. High BP was defined as a SBP or DBP value at or above the 90th percentile for age, sex, and height. The definition of pre-hypertension was considered as SBP > 120 and/or DBP > 80 mm Hg [20].

Statistical Analyses

Data are presented as mean ± standard deviation (SD). Independent t-test was used to compare BMI and WC between the subjects with and those without risk factors. Multiple logistic regression analyses were applied to evaluate the association between measures of adiposity (BMI and WC) and potential risk factors, incorporating age and gender in each model as possible confounders. All statistical analyses were performed using programs available in the SPSS version 15.0 statistical package for Windows (SPSS Inc., Chicago, IL, USA).

Results

This national survey comprised 3,565 participants (50.3% boys) aged 10–18 years, with a mean age of 14.86 (2.66) years and with 45.3% of the subjects belonging to the age group of 10–13.9 years. Table 1 presents the demographic and metabolic characteristics of the participants. The lipid profiles of two age groups of boys were similar. However, there was a significant decline in TC and LDL-C with increasing age in girls. TC and LDL-C of 10-
The clustering of components of dyslipidemia, MetS, and risk factors of CVD in different age and sex categories is presented in Table 2. The pattern of risk factor clustering was similar for 10- to 14-year-old boys and girls. More than half of the 10- to 14-year-old boys had none of the components of MetS (54%); however, more than half of the girls at the same age had at least one abnormal metabolic component (53.4%). In the subjects aged 14–18 years, normal-weight adolescent boys were more likely to have no risk factors than were adolescent girls. While more than half of the boys in this range of age (51.2%) had none of the components of MetS, 64.9% of the girls had one or more components of MetS.

Table 3 shows the differences between BMI and WC of the participants with and without risk factors. Individuals with an abnormal level of metabolic characteristics showed a significantly higher level of adiposity (BMI and WC) than those with normal metabolic characteristics. However, mean WC was not significantly different among those individuals with and without three risk factors of CVD. Likewise, mean BMI and WC did not differ among participants with hypercholesterolemia and elevated LDL-C and those without these risk factors.

As presented in Table 4, after adjustment for age and sex, each unit increase in BMI (within normal range) increased the odds of abnormal metabolic characteristics from 6 to 72%. The least increase is observed in low HDL-C and the highest increase occurs for MetS. On the other hand, each centimeter increase in WC increased the odds of abnormal metabolic characteristics from 1 to 20%. Similar to BMI, the greatest and the smallest odds ratio is observed for MetS and low HDL-C, respectively. When both BMI and WC were included in the model, the BMI remained a predictor for some of the risk factors (except for TC, TG, HDL-C, IFG, and dyslipidemia and 3 risk factors of CVD), whereas WC was no longer a predictor risk factors of CVD.
Discussion

This study presents the prevalence of metabolic risk factors in Iranian children and adolescents with normal weight. Along with a few studies in the past, the results of the present study showed that there are children and adolescents with MetS and risk factors of CVD who are not obese according to the BMI percentiles. Although subjects with normal BMI were selected for this survey, the adiposity indices (BMI and WC) were significantly different in subjects with and without metabolic risk factors. Similar to our previous study, the prevalence of high TG and low HDL-C levels was high in this survey, and this seems to be the dominant pattern of dyslipidemia among normal-weight children of our community.

Although the recognition of the MetS can be dated to some decades ago, it has attracted more attention in recent years. The emerging epidemic of T2DM and CVD drew a lot of attention to the MetS as a major factor in the management of these diseases. The relationship between obesity and developing metabolic risk factors has been acknowledged for many years. Adipose tissue has been shown to play an important role regarding the impact on insulin resistance, which is the underlying cause and essential component of MetS. However, more studies documented that adipose tissue can also play a destructive role in subjects who are not obese according to standard weight tables. This concept extended the definition of MetS beyond the boundaries of obesity. In fact, metabolic risk factors associated with adipose
tissue can develop in people with normal weight, and regarding the global pandemic of these risk factors, we should extend the screening programs to include the normal-weight population. Although for a long time there has been the concept of MONW in adults, such experience is limited in population-based studies conducted among youths. However, studies establishing a prevalence of metabolic risk factor clustering within children and adolescent weight groups suggested that the concept of MONW can be extended to pediatrics. In recent years, numerous studies have focused on childhood obesity as a new challenge for pediatric care and human health in the future. It has been documented that obese adolescents are more likely to have abnormal metabolic risk factors than their normal-weight counterparts. However, this does not mean that normal-weight children and adolescents are necessarily on the safe side. Cook et al. [7] reported the prevalence of MetS in US normal-weight children and adolescents to be 0.1% from 1988 to 1994. A similar study, which was conducted from 1999 to 2002, reported a prevalence of 1% for the same group [8]. Camhi et al. [6] evaluated the prevalence of cardiometabolic risk factors within US adolescent BMI groups using the data from 2001/2002, 2003/2004, 2005/2006, and 2007/2008 surveys. They reported the

**Table 3. Mean of BMI and waist circumference relating to dyslipidemia, metabolic syndrome, and cardiovascular risk factors of normal-weight participants according to gender and age group**

<table>
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| WC = Waist circumference; TC = total cholesterol; LDL = low-density lipoprotein; TG = triglyceride; HDL = high-density lipoprotein; DLP = dyslipidemia; IFG = impaired fasting glucose; Pre-HTN = pre-hypertension; SBP = systolic blood pressure; DBP = diastolic blood pressure; HBP = high blood pressure; RF of CVD = risk factors of cardiovascular disease; MetS = metabolic syndrome.
prevalence of cardiometabolic risk factor clustering to be approximately 9% among US
normal-weight children and adolescents. Of course, in the latter study, the authors did not
include WC in the definition of risk factor clustering in order to understand cardiometabolic
risk and obesity as separate entities and to prevent overestimation of prevalence in over-
weight and obese adolescents. In a study on secondary school adolescents, Xu et al. [9]
reported the prevalence of the risk factors of MetS to be 18.5% (for one or more risk factors),
2.1% (for two or more risk factors), 0.2% (for three or more risk factors), and 0.0% (for four
or more risk factors) among subjects with normal BMI. Comparing the relative risks of MetS
in overweight and obese Chinese children with their normal-weight counterparts, Li et al.
[10] reported the prevalence for MetS as 15.5% among normal-weight boys and as 18.8%
among normal-weight girls. In our previous study, which was conducted to estimate the pre-
vance and distribution of the MetS in children with different types of obesity, the prevalence
of MetS was less than 2% among normal-weight subjects. In the present study, overall, more
than half of the study population had at least one risk factor of MetS [11]. Results from a
recent study [21] showed that lipids, lipoproteins, the markers of inflammation and oxidative
stress, as well as the carotid intima media thickness of MONW were similar to obese children.
In the study mentioned, children with the same BMI category, but high cardiorespiratory
fitness, had significantly lower WC compared with subjects with low cardiorespiratory fitness.
The authors insisted on the preventive role of cardiorespiratory fitness along with fatness and obesity in developing MetS [21].
The results of this study provide compelling evidence that WC coupled with BMI does not predict an increase in obesity-related health risk better than does BMI or WC alone in the model. The high collinearity between these two measures is responsible. Thus, there is no major advantage of using both measures of obesity for population monitoring as their independent contribution is only marginal [22].

In the present study, the predominant form of abnormal lipid profile was high TG and low HDL-C. This pattern, which is the dominant pattern of dyslipidemia among Asians compared with Western countries, has been documented in other studies on adults and children [11]. Lower average HDL-C and hypertriglyceridemia is the predominant pattern observed in South Asians in British cities [23]. Also, Asian Indians exhibit an adverse lipid pattern consisting of low HDL-C and high TG [24]. A similar pattern has been observed in pediatric studies. Comparing the prevalence of cardiometabolic risk factors according to weight status among children and adolescents from Quebec, Lambert et al. [25] found the percentage of high levels of TC, LDL-C, HDL-C, and TG to be 16.9, 18.0, 11.4, and 1.0% for boys, respectively. The respective values for girls were 31.0, 31.2, 5.5, and 3.7%. In their evaluation of cardiovascular risk factors among French children, Botton et al. [26] reported the percentage of children with high levels of TC, LDL-C, HDL-C, and TG to be 10, 5.9, 0.5, and 3.7% among normal-weight subjects, respectively. In a study on children in a rural Georgia community, 26% showed high TC, 20% had high LDL-C, 13% had high TG, and 43% had low HDL-C [27]. In contrast, the lipid profile of youths in Eastern countries is different. Serum HDL-C levels of Turkish postpubertal adolescents, as in the adult population, are profoundly lower than in Europeans and North Americans [28]. A high level of hepatic lipase activity and protein mass has been proposed to explain the low HDL-C levels among Turkish people [28]. In a study which was designed to evaluate serum lipid profiles and the prevalence of dyslipidemia in school children in Eastern Iran, the most common form of dyslipidemia was a low HDL-C level and hypertriglyceridemia [29]. In the previous article of this series, the age- and sex-adjusted prevalence of high TC, LDL-C, low HDL-C, and high TG levels were 3.4, 3.2, 22.1, and 22.6% in participants with normal BMI and WC, respectively [11]. High TG and low HDL, which is characteristic of the insulin resistance lipid phenotype, is the dominant pattern of dyslipidemia among normal-weight children of our community. This can be a cause for concern regarding a re-evaluation of cardiovascular risk estimation in our community.

The large sample size of this study allowed us to identify the metabolic risk factors among normal-weight children and adolescents. The cross-sectional nature of the study and the lack of determining the pubertal status of the participants were the major limitations of this survey.

The findings of this study demonstrated that metabolic risk factors are frequent among normal-weight children and adolescents, and normal BMI does not necessarily exclude children from screening programs for MetS. We found that small increases in adipose tissue, even within normal BMI values, can place children at an increased risk of developing MetS. The considerable prevalence of high TG and low HDL-C in normal-weight children may be due to an ethnic predisposition to MetS and lifestyle factors. Therefore, in addition to an emphasis on controlling childhood overweight for the primary prevention of non-communicable diseases, the importance of a healthy lifestyle and fitness in normal-weight children and adolescents should be underscored.

Acknowledgement

The authors are thankful of the large team working on this study and all participants in different provinces.
Disclosure Statement

None to declare.

References


