Metabolically Healthy Obesity and High Carotid Intima-Media Thickness in Children and Adolescents: International Childhood Vascular Structure Evaluation Consortium

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OBJECTIVE

It has been argued that metabolically healthy obesity (MHO) does not increase cardiovascular disease (CVD) risk. This study examines the association of MHO with carotid intima-media thickness (cIMT), a proxy of CVD risk, in children and adolescents.

RESEARCH DESIGN AND METHODS

Data were available for 3,497 children and adolescents aged 6–17 years from five population-based cross-sectional studies in Brazil, China, Greece, Italy, and Spain. Weight status categories (normal, overweight, and obese) were defined using BMI cutoffs from the International Obesity Task Force. Metabolic status (defined as "healthy" [no risk factors] or "unhealthy" [one or more risk factors]) was based on four CVD risk factors: elevated blood pressure, elevated triglyceride levels, reduced HDL cholesterol, and elevated fasting glucose. High cIMT was defined as cIMT ≥90th percentile for sex, age, and study population. Logistic regression model was used to examine the association of weight and metabolic status with high cIMT, with adjustment for sex, age, race/ethnicity, and study center.

RESULTS

In comparison with metabolically healthy normal weight, odds ratios (ORs) for high cIMT were 2.29 (95% CI 1.58–3.32) for metabolically healthy overweight and 3.91 (2.46–6.21) for MHO. ORs for high cIMT were 1.44 (1.03–2.02) for unhealthy normal weight, 3.49 (2.51–4.85) for unhealthy overweight, and 6.96 (5.05–9.61) for unhealthy obesity.

CONCLUSIONS

Among children and adolescents, cIMT was higher for both MHO and metabolically healthy overweight compared with metabolically healthy normal weight. Our findings reinforce the need for weight control in children and adolescents irrespective of their metabolic status.

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The prevalence of obesity in children and adolescents has increased dramatically worldwide in recent decades (1). It is well-documented that childhood obesity is associated with several cardiometabolic disorders including elevated blood pressure (BP), impaired glucose metabolism, dyslipidemia, and insulin resistance (2). However, not all obese individuals have metabolic disorders at a certain point in time, and these individuals have been described as "metabolically healthy obesity" (MHO) (3).

Some earlier studies in adults suggested that MHO was not associated with an increased risk of cardiovascular disease (CVD) compared with metabolically healthy normal weight (4,5). However, accumulating data, including meta-analyses, indicate that MHO is associated with increased CVD risk and mortality compared with metabolically healthy normal weight in adults (6–9), suggesting that MHO is not a benign condition.

Atherosclerosis-related CVD events rarely develop early in life (i.e., among children and adolescents), but intermediary cardiovascular outcomes can occur and be detected in young populations (10). Carotid intima-media thickness (cIMT), as one measure of early atherosclerosis and vascular remodeling, has been widely shown to predict CVD events in adults (11,12), although findings have not always been consistent (13).

To our knowledge, limited studies have investigated the association of MHO with preclinical markers of CVD in children and adolescents. Therefore, we aimed to examine the association between MHO and high cIMT in children and adolescents using population-based data from five countries (Brazil, China, Greece, Italy, and Spain).

RESEARCH DESIGN AND METHODS

Study Populations

Data were available for 3,497 children and adolescents aged 6–17 years from five population-based cross-sectional studies in Brazil, China, Greece, Italy, and Spain. Detailed information of four studies has previously been published (14–17), while data from the recently completed Chinese study have not yet been published. Detailed information on the study samples and measurements of BP and carotid artery ultrasound in each of the five centers is presented in Supplementary Data. Briefly, at each center, height and weight were measured in light clothes without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist-to-height ratio (WHtR) was calculated as waist in centimeters divided by height in centimeters. BP was measured using clinically validated devices. The mean values of three consecutive BP readings were used for data analyses. Blood samples were taken after a fast of at least 10 h. HDL cholesterol (HDL-C), triglycerides (TG), and fasting blood glucose (FBG) were measured using an automatic analyzer in each center except in the Spain study, where FBG was measured using the hexokinase method, TG by the glycerol-phosphate oxidase method, and HDL-C by a homogenous method of selective detergent with accelerator. Ultrasound examination of cIMT was performed using a clinically validated ultrasound device in each center. The mean value of the left and right cIMT was used for data from Brazil, China, and Italy. However, cIMT was available for the right side only in the study in Spain and maximum bilateral cIMT was used in the Greek study. In sensitivity analysis, exclusion of the two studies from Spain and Greece only marginally changed the results. Thus, we included all five studies in the final analysis. All studies were approved by the corresponding institutional review boards, and written informed consent was obtained from all the study participants and their parents or guardians.

Definitions of Weight and Metabolic Status

Normal weight, overweight, and obesity were defined using the International Obesity Task Force (IOTF) criteria (18). The IOTF criteria were established based on data from six large nationally representative surveys from six countries/regions (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the U.S.). Of note, the IOTF BMI percentile cutoffs by sex and age for overweight and obesity in children and adolescents are linked to the 25 and 30 kg/m^2 cutoffs for overweight and obesity at the age of 18 years. The IOTF criteria have been widely used to assess the prevalence of overweight and obesity in children and adolescents worldwide.

We used two criteria to define metabolic status in the current study: the modified National Cholesterol Education Program (NCEP) criteria and the modified International Diabetes Federation (IDF) criteria, which have been widely used to define metabolic syndrome in children and adolescents worldwide. In the modified NCEP criteria (19), metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) is based on four CVD risk factors: elevated BP (systolic/diastolic BP $\geq$90th percentile for sex, age, and height using the international child BP reference [20]), elevated TG ($\geq$110 mg/dL), low HDL-C ($<$40 mg/dL), and elevated FBG ($\geq$110 mg/dL). In the modified IDF criteria (21), metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) is based on the same four CVD risk factors but using slightly different risk factor cutoffs: elevated BP (systolic/diastolic BP $\geq$120/80 mmHg for those aged $<$10 years [22] and systolic/diastolic BP $\geq$130/85 mmHg for those aged $\geq$10 years), elevated TG ($\geq$150 mg/dL), low HDL-C (at age $<$16 years, $<$40 mg/dL, and at age $\geq$16

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years, <40 mg/dL in males and <50 mg/dL in females) and elevated FBG (≥100 mg/dL).

Participants were divided according to their weight status (normal weight, overweight, or obesity) and metabolic status (healthy or unhealthy), which resulted in six categories: metabolically healthy normal weight, metabolically unhealthy normal weight, metabolically healthy overweight, metabolically unhealthy overweight, MHO, and metabolically unhealthy obesity.

In sensitivity analyses, we used WHtR ≥0.50 to define central obesity (23). Participants were divided according to WHtR categories (normal [no central obesity] or increased [central obesity]) and metabolic status (healthy or unhealthy), which resulted in four categories: metabolically healthy normal WHtR, metabolically unhealthy normal WHtR, metabolically healthy central obesity, and metabolically unhealthy central obesity.

Definition of High cIMT

High cIMT was defined as cIMT ≥90th percentile values for sex, age, and study population using our current data—similar to previous studies in adults (24,25). In sensitivity analyses, we used cIMT ≥75th, 80th, or 95th percentile values for sex, age, and study population to define high cIMT. In addition, we also performed a sensitivity analysis using cIMT ≥90th percentile values for sex and age, based on 1,051 European children and adolescents aged 6–17 years (26).

Statistical Analysis

Linear regression models were used to examine associations between the continuous variables and six categories of weight and metabolic status. Covariance analyses were used to compare mean cIMT across categories of weight and metabolic status with adjustment for sex, age, race/ethnicity, and study center. Logistical regression models were used to assess the association between categories of weight and metabolic status and cIMT with adjustment for sex, age, race/ethnicity, and study center. Analyses were performed using data pooled from the five study centers, since numbers were low for some categories when stratified by study center. All statistical analyses were performed with SAS 9.3, and a two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Among the 3,497 children and adolescents in our study, 158 (4.5%) were classified as MHO based on the NCEP criteria, while 287 (8.2%) were classified as MHO based on the IDF criteria. Table 1 shows the characteristics of each study population stratified by weight and metabolic status based on the NCEP criteria. BMI, systolic BP, diastolic BP, and TG increased, while HDL-C decreased across weight and metabolic status categories (all $P < 0.0001$).

Mean cIMT levels increased similarly across weight and metabolic status categories based on either the NCEP or IDF criteria (both $P < 0.0001$) (Table 2). The results were similar when stratified by sex (Table 2). There was also an upward trend in the prevalence of high cIMT across weight and metabolic status categories based on either the NCEP or IDF criteria (both $P < 0.0001$) (Fig. 1*A* and *B*). Based on the NCEP criteria, the prevalence of high cIMT was 6.2% among participants with metabolically healthy normal weight and 19.0% among participants with MHO (Fig. 1*A*). Using the IDF criteria, the corresponding proportions were 6.0 and 25.1%, respectively (Fig. 1*B*).

Based on the NCEP criteria, MHO was associated with high cIMT (odds ratio [OR] 3.91 [95% CI 2.46–6.21]) compared with metabolically healthy normal weight (Table 3). MHO was also associated with high cIMT (OR 5.59 [95% CI 3.96–7.91]) using the IDF criteria (Table 3). The results were similar when stratified by sex using either criterion for metabolic status (Table 3). Being metabolically unhealthy normal weight was also associated with high cIMT (NCEP criteria OR 1.44 [95% CI 1.03–2.02] and IDF criteria OR 1.65 [95% CI 1.12–2.42]). In addition, overweight was also associated with high cIMT regardless of metabolic status categories (Table 3).

In sensitivity analyses using alternative cIMT percentile values to define high cIMT (Supplementary Table 1), and using WHtR ≥0.50 in place of BMI to define obesity (Supplementary Table 2), results were similar to those from the primary analyses. We also performed a sensitivity analysis after exclusion of children aged <10 years using the modified IDF criteria, and we also obtained similar results (Supplementary Table 3).

CONCLUSIONS

To our knowledge, this is the largest study investigating the association between MHO and high cIMT in children and adolescents. Using pooled data from ~3,500 children and adolescents from five countries in three continents, we found that MHO was associated quite strongly with high cIMT compared with metabolic healthy normal weight.

Comparison With Other Studies

In adults, the association between MHO and disease outcomes has repeatedly been examined. Early reports suggested that individuals with MHO were not at increased risk of CVD compared with individuals with metabolically healthy normal weight (4,5). However, several recent prospective cohort studies have found an increased CVD risk associated with MHO (3,27–32). A prospective cohort study in the U.K. consisting of 3.5 million adults with a median follow-up time of 5.4 years showed that MHO was associated with CVD compared with metabolically healthy normal weight (30). The large European Prospective Investigation into Cancer and Nutrition study (EPIC-CVD), which included 520,000 European adults, also found increased risk of coronary heart disease among MHO individuals (32). There are several possible explanations for the controversial early results in adults. First, there is no consensus definition of MHO. The prevalence of MHO was reported to range from 3 to 32% in men and from 11 to 43% in women using different MHO definitions (33). It is believed that MHO is a transitional stage to a metabolically unhealthy status among obese persons over time, and, hence, a person with MHO at a single point of time would develop risk factors later (resulting in unhealthy obesity) (34). Indeed, as many as one-half of participants with MHO at baseline of one cohort study developed metabolic syndrome after a median follow-up of 12.2 years (29). As expected, MHO has been described more often in cohort studies with a relatively short (<10 years) versus long (≥10 years) follow-up (3,6,8,9), suggesting a transition from MHO to unhealthy obesity over time.

In agreement with most previous studies in adults (6–9,27–32), we found that MHO was associated with high cIMT in

Table 1—Characteristics of the study populations

	Normal weight		Overweight		Obese		
	Metabolically healthy	Metabolically unhealthy	Metabolically healthy	Metabolically unhealthy	Metabolically healthy	Metabolically unhealthy	*P*
Brazil							
N	143	227	15	43	1	12	
Boys, %	19.6	41.0	6.7	37.2	0	25.0	
Age, years	16.5 (0.8)	16.6 (0.8)	16.5 (0.7)	16.4 (0.8)	17.0	16.7 (0.8)	0.8603
BMI, kg/m^2	19.7 (2.1)	20.2 (2.1)	26.3 (1.3)	26.0 (1.3)	40.1	32.4 (2.5)	<0.0001
WC, cm	67.2 (4.7)	68.9 (4.9)	78.9 (5.3)	81.8 (5.0)	105	93.1 (9.2)	<0.0001
WHtR	0.41 (0.03)	0.42 (0.03)	0.50 (0.03)	0.50 (0.03)	0.63	0.58 (0.05)	<0.0001
SBP, mmHg	104.1 (7.0)	112.9 (10.2)	108.8 (6.5)	118.2 (10.2)	112.7	120.4 (5.0)	<0.0001
DBP, mmHg	63.6 (5.3)	68.7 (7.0)	67.3 (4.8)	69.7 (6.7)	77.0	75.2 (4.7)	<0.0001
TG, mg/dL	63.0 (51.0–78.0)	77.0 (58.0–104.0)	64.0 (52.0–93.0)	89.0 (72.0–136.0)	69	140.5 (79.5–153.5)	<0.0001
HDL-C, mg/dL	47.7 (5.8)	38.6 (8.5)	48.2 (7.2)	39.1 (7.6)	52.0	38.5 (6.9)	<0.0001
FBG, mg/dL	75.2 (6.8)	75.8 (7.3)	75.9 (6.6)	79.3 (7.1)	78.0	74.3 (4.7)	0.0535
China							
N	650	285	157	153	47	124	
Boys, %	50.2	44.9	60.5	56.9	59.6	69.4	
Age, years	8.7 (1.5)	9.3 (1.4)	9.0 (1.5)	9.5 (1.3)	8.6 (1.6)	8.8 (1.5)	0.0105
BMI, kg/m^2	15.9 (1.4)	16.8 (1.5)	20.4 (1.6)	21.3 (1.7)	23.4 (2.2)	24.9 (2.9)	<0.0001
WC, cm	56.9 (4.7)	59.7 (5.4)	69.1 (7.0)	71.7 (6.7)	75.5 (7.9)	80.0 (8.3)	<0.0001
WHtR	0.43 (0.03)	0.43 (0.03)	0.50 (0.03)	0.50 (0.03)	0.55 (0.04)	0.57 (0.04)	<0.0001
SBP, mmHg	101.6 (6.4)	113.1 (8.0)	104.2 (6.0)	115.0 (7.9)	106.6 (4.9)	115.7 (7.8)	<0.0001
DBP, mmHg	60.9 (5.3)	66.6 (6.4)	63.2 (5.3)	68.8 (6.3)	64.5 (5.1)	68.9 (7.0)	<0.0001
TG, mg/dL	61.1 (51.4–76.2)	81.5 (57.6–116.9)	72.6 (62.0–89.5)	101.0 (71.7–135.5)	78.8 (59.3–93.9)	110.7 (73.1–143.5)	<0.0001
HDL-C, mg/dL	66.7 (12.9)	65.8 (15.7)	61.9 (10.7)	62.2 (13.3)	57.8 (9.8)	56.9 (12.5)	<0.0001
FBG, mg/dL	81.9 (9.5)	87.1 (12.6)	85.3 (8.3)	88.6 (11.1)	82.9 (8.9)	85.6 (10.8)	<0.0001
Greece							
N	162	94	37	92	11	43	
Boys, %	34.6	45.7	54.1	60.9	54.6	60.5	
Age, years	13.5 (2.1)	13.6 (2.3)	12.3 (2.2)	13.6 (2.2)	12.6 (2.8)	13.3 (1.9)	0.4039
BMI, kg/m^2	18.8 (2.4)	19.5 (2.2)	23.8 (2.1)	24.8 (2.1)	30.2 (4.6)	31.5 (4.1)	<0.0001
WC, cm	72.2 (9.1)	74.5 (8.1)	83.8 (7.6)	88.0 (8.2)	95.0 (11.8)	101.5 (10.6)	<0.0001
WHtR	0.46 (0.05)	0.47 (0.04)	0.54 (0.04)	0.54 (0.05)	0.60 (0.06)	0.63 (0.06)	<0.0001
SBP, mmHg	106.6 (6.8)	117.4 (9.9)	108.3 (7.2)	123.2 (11.9)	111.3 (7.4)	124.7 (11.2)	<0.0001
DBP, mmHg	66.1 (6.3)	74.8 (7.8)	67.7 (5.8)	75.5 (7.7)	69.8 (6.0)	78.8 (7.4)	<0.0001
TG, mg/dL	57.5 (43.0–74.0)	67.0 (48.0–110.0)	64.0 (53.0–84.0)	76.0 (63.0–112.5)	53.0 (45.0–86.0)	109.0 (72.0–141.0)	<0.0001
HDL-C, mg/dL	60.5 (10.4)	54.8 (14.7)	57.0 (9.6)	50.3 (11.2)	52.2 (7.4)	45.0 (10.7)	<0.0001
FBG, mg/dL	90.7 (8.6)	92.3 (7.1)	92.0 (5.4)	94.0 (9.2)	92.1 (9.3)	94.9 (8.8)	0.0004
Italy							
N	237	85	100	78	24	46	
Boys, %	44.3	48.2	51.0	56.4	62.5	60.9	
Age, years	12.3 (0.9)	12.4 (1.0)	12.0 (0.9)	12.2 (0.9)	12.1 (1.0)	12.0 (0.9)	0.0330
BMI, kg/m^2	18.5 (1.9)	18.5 (2.3)	23.5 (1.6)	23.8 (1.6)	28.8 (2.5)	29.6 (2.7)	<0.0001
WC, cm	72.2 (6.5)	72.2 (8.3)	84.7 (7.2)	86.0 (6.7)	97.6 (7.0)	99.4 (7.7)	<0.0001
WHtR	0.46 (0.03)	0.47 (0.04)	0.54 (0.04)	0.55 (0.04)	0.61 (0.04)	0.62 (0.05)	<0.0001
SBP, mmHg	100.3 (9.3)	111.9 (13.3)	103.6 (8.7)	110.1 (13.2)	107.0 (10.3)	112.7 (10.1)	<0.0001
DBP, mmHg	62.3 (6.5)	68.2 (9.2)	64.2 (6.4)	68.6 (9.4)	64.5 (6.7)	70.1 (6.3)	<0.0001
TG, mg/dL	56.0 (44.0–74.0)	72.0 (53.0–95.0)	59.5 (47.5–75.0)	100.0 (66.0–131.0)	73.5 (57.5–92.5)	93.0 (76.0–127.0)	<0.0001
HDL-C, mg/dL	57.0 (10.6)	47.8 (12.9)	51.1 (8.2)	45.2 (11.2)	49.9 (9.0)	40.5 (9.6)	<0.0001
FBG, mg/dL	82.2 (6.1)	84.1 (9.0)	83.4 (6.0)	83.4 (7.7)	82.6 (6.9)	82.5 (6.4)	0.4577
Spain							
N	201	78	79	61	75	137	
Boys, %	53.2	46.2	54.4	54.1	58.7	54.0	
Age, years	8.2 (1.8)	8.1 (1.7)	8.9 (1.7)	9.2 (1.6)	8.8 (1.7)	9.3 (1.9)	<0.0001
BMI, kg/m^2	15.8 (1.8)	16.1 (1.6)	20.8 (2.0)	21.3 (2.0)	24.5 (2.7)	26.1 (3.4)	<0.0001
WC, cm	55.3 (6.4)	55.3 (5.5)	69.8 (8.0)	71.8 (8.3)	77.2 (9.6)	81.9 (10.6)	<0.0001
WHtR	0.43 (0.03)	0.43 (0.03)	0.51 (0.04)	0.52 (0.04)	0.56 (0.05)	0.58 (0.05)	<0.0001
SBP, mmHg	100.1 (7.2)	112.1 (9.4)	103.0 (7.5)	116.2 (10.3)	103.2 (7.9)	117.7 (9.4)	<0.0001
DBP, mmHg	57.2 (5.4)	63.5 (8.4)	58.8 (5.8)	63.5 (8.1)	58.6 (7.0)	67.3 (8.3)	<0.0001
TG, mg/dL	47.0 (37.0–59.0)	49.0 (40.0–68.0)	54.0 (43.0–68.0)	60.0 (47.0–95.0)	58.0 (43.0–85.0)	76.0 (55.0–116.0)	<0.0001
HDL-C, mg/dL	62.2 (12.6)	61.0 (16.0)	56.6 (10.8)	53.7 (13.0)	53.7 (8.5)	47.1 (11.1)	<0.0001
FBG, mg/dL	85.6 (6.8)	86.0 (8.3)	87.6 (6.1)	87.7 (6.2)	87.3 (5.8)	89.1 (6.2)	<0.0001

Data are means (SD) or median (interquartile range) if the variable was not normally distributed, and categorical variables are presented as proportions. DBP, diastolic BP; SBP, systolic BP; WC, waist circumference.

Table 2—cIMT levels across weight and metabolic status categories

	Normal weight		Overweight		Obese	
	Metabolically healthy	Metabolically unhealthy	Metabolically healthy	Metabolically unhealthy	Metabolically healthy	Metabolically unhealthy
NCEP criteria†						
Total	0.410 (0.002)	0.419 (0.003)	0.440 (0.003)	0.449 (0.003)	0.445 (0.005)	0.465 (0.004)
Boys	0.419 (0.003)	0.423 (0.004)	0.459 (0.005)	0.462 (0.005)	0.455 (0.007)	0.478 (0.005)
Girls	0.402 (0.002)	0.413 (0.003)	0.419 (0.005)	0.434 (0.005)	0.438 (0.008)	0.451 (0.005)
IDF criteria‡						
Total	0.404 (0.003)	0.416 (0.002)	0.445 (0.003)	0.445 (0.005)	0.455 (0.004)	0.468 (0.005)
Boys	0.403 (0.006)	0.424 (0.003)	0.461 (0.004)	0.460 (0.007)	0.462 (0.005)	0.487 (0.006)
Girls	0.402 (0.004)	0.407 (0.002)	0.425 (0.004)	0.430 (0.006)	0.449 (0.006)	0.447 (0.007)

Data are means (SE). Adjusted for sex, age, race/ethnicity, and study center. †Based on the NCEP criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional cardiovascular risk factors: elevated BP, elevated TG, reduced HDL-C, and elevated fasting glucose. ‡Based on the IDF criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional cardiovascular risk factors: elevated BP, elevated TG, reduced HDL-C, and elevated fasting glucose.

children and adolescents. For example, the Cardiovascular Risk in Young Finns Study among 1,617 participants aged 9–24 years showed that overweight and metabolic disturbances during youth were associated with an increased risk of metabolic syndrome, high cIMT, and type 2 diabetes 21–25 years later in adulthood (35). These findings, along with ours,

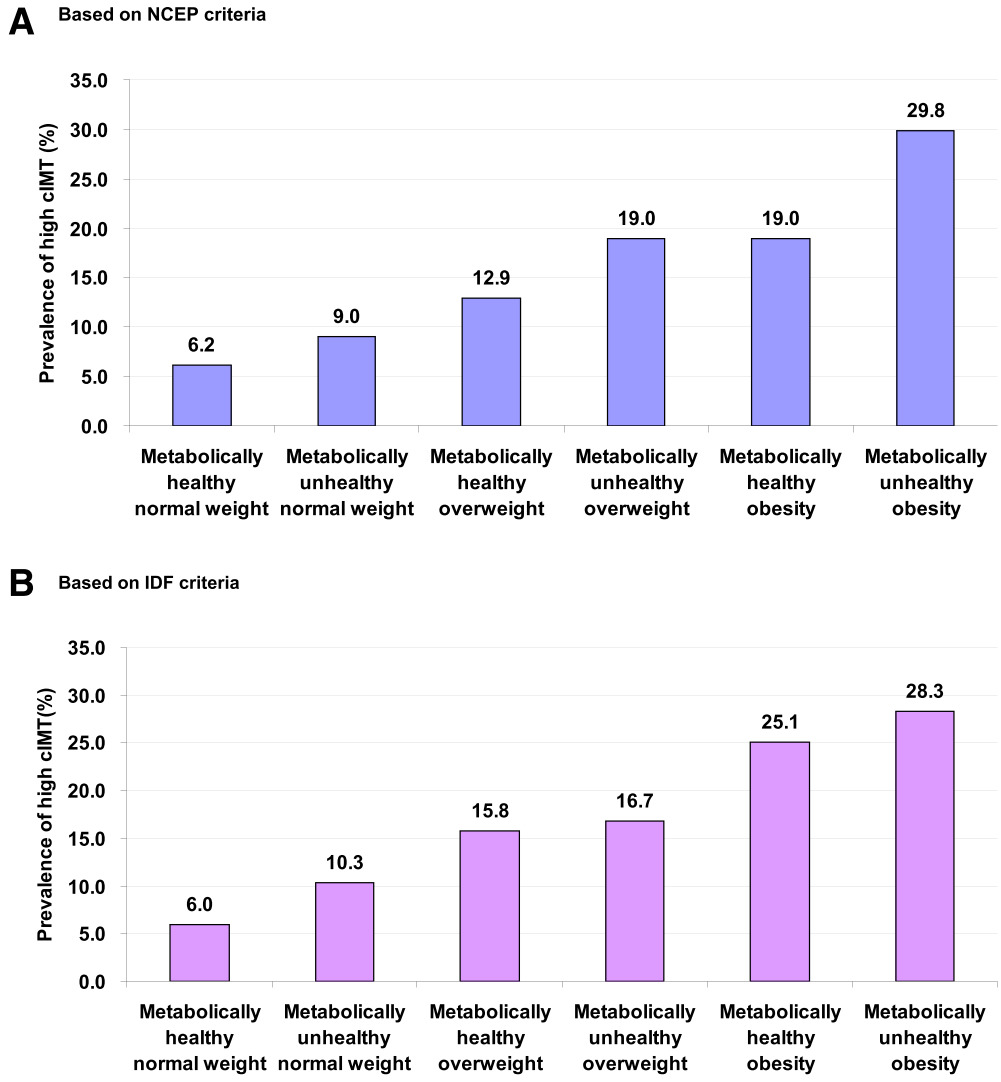

Figure 1—Prevalence of high cIMT across categories of weight and metabolic status: based on NCEP criteria (*A*) and based on IDF criteria (*B*).

Table 3—Odds ratios (95% CI) of high cIMT across weight and metabolic status categories

	Normal weight		Overweight		Obese	
	Metabolically healthy	Metabolically unhealthy	Metabolically healthy	Metabolically unhealthy	Metabolically healthy	Metabolically unhealthy
NCEP criteria†						
Total	1.00 (ref)	1.44 (1.03–2.02)	2.29 (1.58–3.32)	3.49 (2.51–4.85)	3.91 (2.46–6.21)	6.96 (5.05–9.61)
Boys	1.00 (ref)	2.18 (1.23–3.84)	3.36 (1.89–5.97)	5.47 (3.24–9.23)	4.66 (2.33–9.29)	10.97 (6.68–18.02)
Girls	1.00 (ref)	1.18 (0.77–1.80)	1.82 (1.10–3.03)	2.63 (1.67–4.12)	3.88 (2.03–7.42)	4.86 (3.06–7.72)
IDF criteria‡						
Total	1.00 (ref)	1.65 (1.12–2.42)	2.94 (2.15–4.02)	2.97 (1.99–4.43)	5.59 (3.96–7.91)	6.41 (4.47–9.21)
Boys	1.00 (ref)	2.64 (1.42–4.91)	3.90 (2.39–6.39)	5.32 (3.01–9.38)	7.77 (4.67–12.94)	9.53 (5.64–16.11)
Girls	1.00 (ref)	1.20 (0.73–1.98)	2.53 (1.67–3.83)	1.69 (0.91–3.11)	4.48 (2.72–7.39)	4.74 (2.77–8.10)

Adjusted for sex, age, race/ethnicity, and study center. ref, reference. †Based on the NCEP criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional cardiovascular risk factors: elevated BP, elevated TG, reduced HDL-C, and elevated fasting glucose. ‡Based on the IDF criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional cardiovascular risk factors: elevated BP, elevated TG, reduced HDL-C, and elevated fasting glucose.

question the clinical usefulness of stratifying obese into healthy versus unhealthy categories.

We also found that children and adolescents with metabolically unhealthy normal weight had higher cIMT compared with those who were metabolically healthy with normal weight, suggesting that a normal weight does not necessarily imply a healthy metabolic status. Our findings are consistent with previous prospective cohort studies in adults (30,32). Indeed, normal weight individuals may also be metabolically unhealthy (36,37). Thus, while our data provide further support for the need for all individuals to maintain a healthy weight, they also provide evidence for prevention of metabolic risk factors irrespective of weight status.

Strengths and Limitations of Study

Our study has two main strengths. First, we included a large number of participants from several populations (~3,500 children and adolescents from five countries), which enhances generalizability of our findings to different populations. Second, our results were robust in sensitivity analyses, including the use of two different definitions of metabolic health (i.e., the NCEP criteria and the IDF criteria), two different definitions of adiposity (i.e., BMI and WHtR), and different definitions of high cIMT (i.e., 75th, 80th, 90th, and 95th percentiles). However, several limitations should be noted. First, the cross-sectional design precludes causal inference. However, reverse causation for the relation between body weight and cIMT is highly unlikely, which strengthens the significance of our results. Yet, further prospective cohort studies could further help disentangle the respective roles of weight and weight change in the occurrence of CVD risk factors and target organ damage in pediatric populations. Second, the sample size in each country was limited, which impedes data analyses by study site. In addition, because of insufficient statistical power in metabolically unhealthy categories, we were unable to examine which specific metabolic abnormality was particularly associated with high cIMT. Third, our statistical analyses were adjusted for only a limited number of potential confounders (sex, age, race/ethnicity, and study center), which were available from each country. Future studies should also consider adjustment for lifestyle factors, cardiorespiratory fitness, and other potential risk factors (38,39).

Conclusion

In conclusion, we found that children and adolescents with MHO had higher cIMT compared with metabolically healthy normal weight individuals. Our findings provide pediatric evidence that MHO is not a harmless condition, and this reinforces the need for weight control in children and adolescents regardless of their metabolic status.

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