Original article

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Association between metabolically healthy obesity and carotid intima-media thickness in Korean adolescents with overweight and obesity

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Purpose: Data regarding the association between metabolically healthy obesity (MHO) and preclinical atherosclerosis in childhood are lacking. Carotid intima-media thickness (cIMT) is a noninvasive method used to assess cardiovascular risk. This study examined the relationships among cIMT, metabolic phenotypes, and cardiometabolic risk factors (CMRFs) in overweight and obese adolescents.
Methods: Anthropometric, biochemical, and cIMT data were collected. The study participants were categorized as MHO or metabolically unhealthy obesity (MUO) based on insulin resistance. CMRFs were assessed using blood pressure (BP); levels of triglycerides, high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose; or a diagnosis of diabetes mellitus. Differences in cIMT values were evaluated according to the metabolic phenotype and factors associated with cIMT.
Results: Among the 111 participants (80 boys, 72.1%), 23 (20.7%) were classified as MHO and 88 (79.3%) as MUO. The MHO group exhibited lower glycated hemoglobin and triglyceride levels and higher HDL-C levels compared to those exhibited by the MUO group (all $P<0.01$). The cIMT values did not differ significantly between the MHO and MUO groups. The high cIMT tertile group revealed higher systolic BP compared to that exhibited by the low cIMT tertile group (123.7±2.1 mmHg vs. 116.9±1.6 mmHg, $P=0.028$). Mean cIMT was positively correlated with age ($\beta=0.009$) and body mass index (BMI) ($\beta=0.033$) after adjusting for covariates (both $P<0.05$).
Conclusion: In overweight and obese Korean adolescents, cIMT was associated with age and BMI but not with metabolic phenotype or CMRFs. Further research is warranted to determine the relationship between cIMT during adolescence and cardiovascular outcomes during adulthood.

Keywords: Pediatric obesity, Overweight, Obesity, Metabolically benign, Cardiometabolic risk factors, Carotid intima-media thickness, Adolescent, Korea

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Highlights

- This study examined the relationship between carotid intima-media thickness (cIMT) and metabolic health in overweight and obese adolescents.
- cIMT was associated with age and BMI but did not differ significantly between metabolically healthy and unhealthy obesity groups.

Introduction

In recent decades, the prevalence of pediatric obesity has increased globally, as well as in Korea.[1,2] Pediatric obesity is an important health issue associated with several cardiometabolic risk factors (CMRFs), including abdominal obesity, impaired fasting glucose or type 2 diabetes

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mellitus (T2DM), high blood pressure (BP), and dyslipidemia.[3-5] Furthermore, children exhibiting obesity are more likely to be obese in adulthood, with the relative risk of adult obesity exceeding 5 times that in nonobese children.[6] Since obesity and its associated CMRFs persist into adulthood, early intervention for management of childhood obesity and screening for comorbidities are crucial.

Obesity is increasingly recognized as a heterogeneous condition, with a subset of obese individuals not exhibiting CMRFs.[7] Metabolically healthy obesity (MHO) individuals have preserved insulin sensitivity with normal BP and lipid profiles despite being obese.[8,9] According to the 2011–2019 Korea National Health and Nutrition Examination Survey, the overall prevalence of MHO, defined as the absence of any CMRFs, was 39.2% among overweight and obese Korean adolescents.[10] Previous studies in adults have revealed that MHO individuals demonstrate an increased risk of cardiovascular events compared to the risks in metabolically healthy normal-weight individuals.[11-13] However, information regarding the association between childhood metabolic phenotype and potential risk of cardiovascular disease (CVD) is lacking.

Assessing cardiovascular risk in pediatric populations is difficult because CVDs, such as myocardial infarction and ischemic stroke, rarely occur during this period. Carotid intima-media thickness (cIMT) is one of the various markers of cardiovascular risk even though it is a noninvasive indicator.[14] A meta-analysis of randomized controlled trials in adults revealed that interventions reducing cIMT progression also lower the risk of cardiovascular events.[15] A systematic review that mainly included pediatric population-based observational studies reported a significant association between adiposity and cIMT in adolescents.[16] Additionally, a single-center study of healthy Korean adolescents identified a positive relationship between systolic BP (SBP) and cIMT.[17]

However, the correlation between elevated cIMT and metabolic alterations in children and adolescents remains controversial. While mean cIMT values and prevalence of high cIMT varied by weight and metabolic status categories in 5 pediatric population-based studies, another study observed no significant difference in mean cIMT values between MHO and metabolically unhealthy obesity (MUO) individuals.[18,19] The present study investigated whether cIMT was related to the MHO phenotype or metabolic alterations in overweight and obese Korean adolescents.

Materials and methods

1. Participants and anthropometric and biochemical assessments

Available cIMT data were retrospectively reviewed in 111 adolescents aged 10–18 years who were overweight (n=1) or obese (n=110) and visited the Seoul National University Bundang Hospital (SNUBH) between January 2017 and April 2022.

Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 0.1 kg using an electronic scale. Body mass index (BMI) was calculated by dividing the weight (kg) by height squared (m^2). Height, weight, and BMI were converted into standard deviation scores (SDS) based on the 2017 Korean National Growth Charts.[20] Overweight and obesity were defined as BMI in the 85-<95th and ≥95th percentiles, respectively. Waist circumference was measured to the nearest 0.1 cm at the midpoint between the lowest point of the rib and uppermost edge of the iliac crest during exhalation. The waist-to-height ratio was calculated by dividing the waist circumference in centimeters by height in centimeters.[21] BP was measured 3 times after the participants rested for at least 5 minutes in a seated position.

Blood samples were collected from participants after a 12-hour fast. Plasma glucose, serum insulin, serum triglyceride (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, aspartate aminotransferase, alanine aminotransferase, and glycated hemoglobin (HbA1c) levels were measured using an automated analyzer. The homeostatic model assessment of insulin resistance (HOMA-IR) values were calculated using the following formula: fasting insulin (mIU/L) × fasting glucose (mg/dL)/405.[22]

2. Definition of metabolic phenotype and CMRFs

Overweight and obese adolescents were classified into 2 groups, MHO and MUO, based on the presence of T2DM and/or insulin resistance using Korean reference data.[23] MUO was defined as a HOMA-IR value in the 95th percentile or above or diagnosis of T2DM, whereas MHO was defined as a HOMA-IR value below the 95th percentile. Other CMRFs were defined as follows: SBP or diastolic BP at or above the 90th percentile based on Korean reference data[24] or treatment with antihypertensive drugs; fasting plasma glucose ≥100 mg/dL or diagnosis of T2DM; TG ≥150 mg/dL; and HDL-C <40 mg/dL.[25] Hypertension and prehypertension were defined as BP at or above the 95th percentile and between the 90th and 95th percentiles, respectively, based on Korean reference data.[24] Prediabetes was defined as a fasting plasma glucose level of 100–125 mg/dL or HbA1c of 5.7%–6.4%.[26]

3. Measurement of cIMT

The right and left common carotid arteries were scanned by a radiologist using a color Doppler ultrasonography system (EPIQ 7; Philips Medical Systems, Andover, MA, USA) equipped with a linear high-frequency transducer (5–12 MHz). Participants were scanned in the supine position with the head slightly tilted contralateral to the side being examined. The cIMT measurements were recorded from the far wall, 1 cm proximal to the carotid bulb, and over a length of 1 cm. The cIMT values were calculated using a semiautomated method (Automated; QLAB, Phillips, Crawley, UK), which averaged 3 values from each artery and provided results in micrometers.

4. Statistical analysis

Statistical analyses were conducted using the Stata 17.0 (StataCorp LP, College Station, TX, USA). Continuous variables were presented as mean±standard deviation, while skewed variables were log-transformed and presented as geometric mean with standard error. Categorical variables are expressed as the number of cases and percentage. Differences in anthropometric, cardiometabolic, and cIMT parameters between the MHO and MUO groups were assessed using Student *t*- and chi-square tests for continuous and categorical variables, respectively. To compare the metabolic parameters according to the cIMT tertile or the number of CMRFs, an analysis of variance was conducted. Linear and logistic regression analyses were performed to identify factors associated with cIMT values. $P<0.05$ was considered statistically significant.

5. Ethical statement

This study was approved by the Institutional Review Board (IRB) of SNUBH (IRB No. B-2205-757-104).

Results

1. Characteristics of the study participants

Among the 111 overweight and obese adolescents (80 males and 31 females), the mean and maximal cIMT values were 470.1±46.2 μm and 515.4±66.0 μm, respectively. Twenty-three (20.7%) were classified as MHO and 88 (79.3%) as MUO. The clinical characteristics of the participants according to their metabolic phenotypes are presented in Table 1. Compared to the MUO group, participants in the MHO group were younger (12.5±1.4 years vs. 14.4±2.2 years) and exhibited lower HbA1c and TG levels, and higher HDL-C levels (all $P<0.01$). The cIMT values did not differ between the MHO and MUO groups (mean, 459.7±9.7 μm vs. 470.1±5.8 μm; maximum 506.8±13.6 μm vs. 512.7±6.7 μm). Among the 88 adolescents with MUO, 23 (20.7%) were prediabetic, 48 (43.2%) had T2DM, 53 (47.8%) had elevated BP, 38 (34.2%) had elevated TG levels, while 48

Table 1. Clinical characteristics of participants according to metabolic phenotype

Characteristic	MHO (n=23)	MUO (n=88)	*P*-value
Age (yr)	12.5±1.4	14.4±2.2	<0.001
Male sex	19 (82.6)	61 (69.3)	0.206
Weight SDS	2.2±0.7	2.5±0.7	0.063
Height SDS	0.7±0.8	1.0±1.3	0.319
BMI (kg/m^2)	29.7±3.7	31.0±4.2	0.107
BMI SDS	2.2±0.5	2.4±0.6	0.246
Waist circumference SDS	2.5±0.5	2.8±0.6	0.128
WHtR SDS	2.6±0.5	2.7±0.7	0.741
Systolic blood pressure (mmHg)*	120.5±2.5	120.9±1.3	0.892
Diastolic blood pressure (mmHg)*	66.4±1.6	68.3±1.1	0.390
Fasting glucose (mg/dL)	99.3±3.5	104.8±2.9	0.252
HbA1c (%)*	5.4±0.1	7.4±0.3	<0.001
HOMA-IR*	3.2±0.1	8.1±0.7	<0.001
Total cholesterol (mg/dL)*	163.2±8.7	172.0±4.1	0.334
LDL-C (mg/dL)	103.4±30.0	110.6±29.9	0.309
HDL-C (mg/dL)*	47.8±1.9	41.0±0.9	0.001
Triglyceride (mg/dL)*	100.5±10.0	137.2±7.3	0.001
Uric acid (mg/dL)	6.8±0.2	6.9±0.2	0.787
AST (IU/L)*	39.2±5.5	42.3±3.0	0.634
ALT (IU/L)*	48.8±10.4	64.5±6.2	0.204
cIMT mean (μm)*	459.7±9.0	470.1±5.8	0.321
cIMT max (μm)*	506.8±13.6	512.7±6.7	0.688
Normal/prehypertension /hypertension	10:4:9 (43.5:17.4:39.1)	48:12:28 (54.6:13.6:31.8)	0.638
Normal/prediabetes/T2DM	16:7:0 (69.6:30.4:0)	24:16:48 (27.3:18.2:54.6)	<0.001
Elevated triglyceride	4 (17.4)	34 (38.6)	0.056
Low HDL-C	6 (26.1)	42 (47.7)	0.062

Values are presented as mean±standard deviation or number (%) except for log-transformed variables.
MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; SDS, standard deviation score; BMI, body mass index; WHtR, waist-to-height ratio; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine aminotransferase; cIMT, carotid intima-media thickness; T2DM, type 2 diabetes mellitus.
*Log-transformed values were used for the analysis and expressed as geometric mean±standard error.

(43.2%) had decreased HDL-C levels. There was no significant difference in the mean cIMT values according to the presence of prediabetes or T2DM: Normal, 462.0±35.8 μm, prediabetes, 467.0±49.2 μm, T2DM, 478.3±51.7 μm, *P*=0.245). Atheromatic plaques in the carotid arteries were not observed.

2. Comparison of metabolic parameters according to the cIMT category

Table 2 shows the anthropometric and metabolic parameters according to the cIMT category. The participants were categorized into 3 groups based on tertiles of mean cIMT values: 40 (36.0%) low tertile (≤ 445.0 μm), 34 (30.6%) mid tertile (456.7–480.0 μm), and 37 (33.3%) high tertile (≥481.0 μm). The high cIMT tertile group exhibited higher SBP than that demonstrated by the low cIMT tertile group (123.7±2.1 mmHg vs. 116.9±1.6 mmHg, *P*=0.028). The other metabolic parameters did not differ among the 3 cIMT groups. Among the 23 MHO individuals, 10 (43.5%), 6 (26.1%), and 7 (30.4%) were classified in the low, mid, and high cIMT tertiles, respectively. The proportion of patients with MHO did not significantly differ among the 3 cIMT categories.

3. Factors associated with cIMT

Mean cIMT was positively associated with age and BMI SDS in univariable analysis (all *P*<0.05), both of which remained significant in the multivariate analysis (age: β=0.009, *P*=0.022; BMI SDS: β=0.033, *P*=0.040). cIMT was not associated with CMRFs or MHO in either univariate or multivariate analysis (Table 3). In addition, cIMT did not differ according to number of accompanying CMRFs (Fig. 1).

Discussion

In this study, cIMT values did not differ according to metabolic phenotype or presence of CMRFs. However, participants in the high cIMT category exhibited a higher SBP compared to those participants in the low cIMT category. Among overweight

Table 2. Anthropometric and metabolic parameters according to the cIMT categories

Characteristic	Low cIMT tertile (n=40)	Mid cIMT tertile (n=34)	High cIMT tertile (n=37)	*P*-value
cIMT mean (μm)*	426.3±2.3	464.0±1.7	521.4±5.7	<0.001
cIMT max (μm)*	452.1±4.4	509.4±4.9	575.4±9.1	<0.001
Age (yr)	13.7±2.3	13.6±2.2	14.7±2.1	0.060
Male sex	27 (67.5)	26 (76.5)	27 (73.0)	0.685
Weight SDS	2.3±0.8	2.5±0.6	2.5±0.8	0.219
Height SDS	0.7±1.1	1.0±1.2	1.0±1.2	0.623
BMI (kg/m^2)	30.0±4.2	31.2±3.0	31.6±4.8	0.187
BMI SDS	2.2±0.6	2.4±0.5	2.4±0.6	0.319
Waist Circumference SDS	2.7±0.7	2.8±0.5	2.7±0.7	0.839
WHtR SDS	2.7±0.6	2.7±0.6	2.6±0.7	0.689
Systolic blood pressure (mmHg)*	116.9±1.6	122.5±2.2	123.7±2.1†	0.028
Diastolic blood pressure (mmHg)*	66.2±1.4	67.9±1.7	70.1±1.6	0.202
Fasting glucose	102.6±3.6	101.1±4.2	105.0±4.1	0.789
HOMA-IR*	6.4±0.7	6.7±0.8	7.1±1.3	0.874
HbA1c (%)*	7.0±0.4	6.7±0.4	7.2±0.4	0.678
Total cholesterol (mg/dL) *	167.7±6.5	172.5±6.7	170.6±6.2	0.867
LDL-C (mg/dL)	104.6±30.0	111.0±31.7	112.2±28.6	0.495
HDL-C (mg/dL)*	43.8±1.5	40.8±1.5	42.1±1.3	0.317
Triglyceride (mg/dL)*	128.1±11.9	132.9±10.6	125.5±9.6	0.894
Uric acid (mg/dL)	6.8±1.7	7.0±1.3	6.8±1.9	0.931
AST (IU/L)*	44.6±5.1	40.0±4.1	40.0±4.7	0.718
ALT (IU/L)*	64.7±10.4	58.7±8.3	58.8±9.2	0.827
Normal/prehypertension /hypertension	24:6:10 (60:15:25)	15:6:13 (44.1:17.7:38.2)	19:4:14 (51.4:10.8:37.8)	0.594
Normal/prediabetes/T2DM	16:8:16 (40:20:40)	14:7:13 (41.2:20.6:38.3)	10:8:19 (27.0:21.6:51.4)	0.710
Elevated triglyceride	14 (35.0)	13 (38.2)	11 (29.7)	0.746
Low HDL-C	14 (35.0)	20 (58.8)	14 (37.84)	0.086
MHO	10 (43.5)	6 (26.1)	7 (30.4)	0.700

Values are presented as mean±standard deviation or number (%) except for log-transformed variables.
cIMT, carotid intima-media thickness; SDS, standard deviation score; BMI, body mass index; WHtR, Waist-to-height ratio; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine aminotransferase; T2DM, type 2 diabetes mellitus.
*Log-transformed values were used for the analysis and expressed as geometric mean±standard error. †*P*<0.05 compared with lower cIMT tertile group.

and obese Korean adolescents, age and BMI were independent predictors of increased cIMT.

Atherosclerosis is hypothesized to begin during childhood and results in CVD in adulthood.[27] cIMT is considered a surrogate marker of atherosclerosis, allowing assessment of vascular changes at an early stage.[28] Increased cIMT has been reported in obese children compared to children of normal weight.[29,30] cIMT measurements are recommended for CVD prevention in children with obesity.[31] Several studies have reported normative values in children and adolescents.[32-35] A study involving 1,155 children aged 6–18 years reported 50th percentiles of cIMT between 360 μm (at 6 years) and 400 μm (at 18 years old),[33] while another large study of 263 healthy adolescents aged 15–20 years revealed the 75th percentile of cIMT at 449 μm (at 15 years of age).[34] In our study, the mean cIMT in adolescents aged 10–18 years who were overweight and obese (470.1 μm) was higher than the previously reported normative values in the same age group.[31]

Growing evidence suggests a positive relationship between adiposity and cIMT in pediatric populations. A systematic review of 5 population-based observational studies in children aged 5–15 years reported that adiposity may be associated with cIMT in adolescents but not in preadolescents, suggesting that obesity-related thickening of the carotid artery may only become detectable in late childhood, and that age-related arterial changes may be accelerated by adiposity.[16] In the present study, cIMT was positively associated with age and BMI SDS, in line with previous studies in pediatric populations. Furthermore, a study investigating cIMT reference values in children aged 6–18 years reported a positive correlation between age and cIMT.[33] Additionally, a study involving 291 healthy children and adolescents aged 6–18 years demonstrated a positive correlation between BMI and cIMT.[36] Moreover, a study of 204 pediatric participants with obesity revealed that cIMT was significantly higher in obese patients, even in those without metabolic alterations, compared to those in normal-weight children.[19] These findings suggest that the duration and degree of adiposity, rather than metabolic phenotype, may have an important effect on vascular changes.

Nevertheless, overweight and obese adolescents in the high cIMT tertile group exhibited significantly higher SBP compared to those demonstrated by participants in the low cIMT tertile group. Moreover, hypertension and obesity were associated with a higher risk of cIMT above the 75th percentile in an 11-year follow-up study of 4,709 German subjects aged 14–28 years.[37] In a systematic review of 8 population-based studies in healthy children, BP and cIMT revealed an independent positive association even after adjusting for other CMRFs in 6 studies.[38] Although a positive linear association between cIMT and SBP was observed in our study participants, it was not significant after adjusting for other CMRFs. This may be partly explained by the strong correlation between multiple CMRFs, which could result in overadjustment.[38] Although the underlying mechanism associating BP with cIMT remains unclear, BP, and especially SBP, may contribute to pressure overload in the vascular beds, leading to vascular endothelial changes. Overall, cIMT measurements can provide insights into early signs of atherosclerosis in the pediatric population in a noninvasive manner and help assess the risk of CVD.[39]

This study had several limitations. First, as it was conducted at a single tertiary center and included only overweight and obese individuals who underwent cIMT measurements, selection bias may have occurred. Second, owing to the retrospective and cross-sectional study design involving a limited number of subjects with a relatively short obesity duration, the temporal relationship between obesity duration and cIMT remains uncertain. Third, due to the lack of normal-weight control subjects and normative values for Korean adolescents, we could only evaluate the relative associations between cIMT and metabolic parameters. Nevertheless, this is the first study to explore the associations between cIMT and metabolic phenotypes, as well as the accompanying CMRFs, in overweight and obese Korean adolescents.

In conclusion, cIMT is related to age and adiposity rather than to the metabolic phenotype or the accompanying CMRFs in overweight and obese Korean adolescents. Further studies are warranted to determine the long-term effects of increased cIMT on cardiovascular events later in life, using cIMT reference

Table 3. Factors associated with carotid intima-media thickness

Variable	Univariate		Multivariate	
	β±SE	*P*-value	β±SE	*P*-value
Age	0.010±0.004	0.019	0.009±0.004	0.022
Male sex	0.013±0.020	0.528	-	-
BMI SDS	0.035±0.016	0.036	0.033±0.016	0.040
Hypertension	0.015±0.018	0.405	-	-
Elevated triglyceride	0.007±0.019	0.714	-	-
Low HDL-C	0.000±0.018	0.990	-	-
Dysglycemia	0.024±0.019	0.200	-	-
MHO	-0.022±0.022	0.321	-	-

SE, standard error; BMI, body mass index; SDS, standard deviation score; HDL-C, high-density lipoprotein cholesterol; MHO, metabolically healthy obesity.

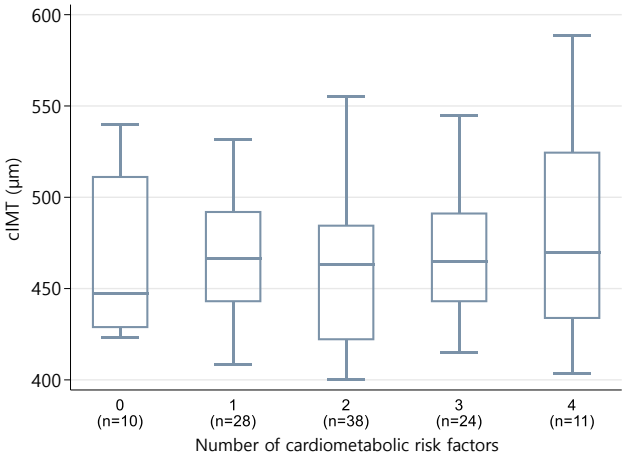

Fig. 1. Carotid intima-media thickness according to the number of cardiometabolic risk factors. cIMT, carotid intima-media thickness.

values derived from the healthy Korean pediatric population.

Notes

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Data availability: The data that support the findings of this study can be provided by the corresponding author upon reasonable request.

Author contribution: Conceptualization: SS, JL, JK; Data curation: SS, JL; Formal analysis: SS; Methodology: SS, HYK, JL; Project administration: JK; Visualization: SS; Writing - original draft: SS, YJR; Writing - review & editing: HYK, JYK, JK

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References

1. Di Cesare M, Sorić M, Bovet P, Miranda JJ, Bhutta Z, Stevens GA, et al. The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. BMC Med 2019;17:212.
2. Kim JH, Moon JS. Secular trends in pediatric overweight and obesity in Korea. J Obes Metab Syndr 2020;29:12-7.
3. Lee J, Kim JH. Endocrine comorbidities of pediatric obesity. Clin Exp Pediatr 2021;64:619-27.
4. Yoo SE, Lee JH, Lee JW, Park HS, Lee HA, Kim HS. Increasing prevalence of fasting hyperglycemia in adolescents aged 10-18 years and its relationship with metabolic indicators: the Korea National Health and Nutrition Examination Study (KNHANES), 2007-2018. Ann Pediatr Endocrinol Metab 2022;27:60-8.
5. Kim M, Kim J. Cardiometabolic risk factors and metabolic syndrome based on severity of obesity in Korean children and adolescents: data from the Korea National Health and Nutrition Examination Survey 2007-2018. Ann Pediatr Endocrinol Metab 2022;27:289-99.
6. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obes Rev 2016;17:95-107.
7. Phillips CM. Metabolically healthy obesity across the life course: epidemiology, determinants, and implications. Ann N Y Acad Sci 2017;1391:85-100.
8. Blüher M. Metabolically healthy obesity. Endocr Rev 2020;41:bnaa004.
9. Videira-Silva A, Freira S, Fonseca H. Metabolically healthy overweight adolescents: definition and components. Ann Pediatr Endocrinol Metab 2020;25:256-64.
10. Kim HY, Kim JH. Temporal trends in the prevalence of metabolically healthy overweight and obesity in Korean youth: data from the Korea National Health and Nutrition Examination Survey 2011-2019. Ann Pediatr Endocrinol Metab 2022;27:134-41.
11. Hinnouho GM, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care 2013;36:2294-300.
12. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: a systematic review and meta-analysis. Ann Intern Med 2013;159:758-69.
13. Opio J, Croker E, Odongo GS, Attia J, Wynne K, McEvoy M. Metabolically healthy overweight/obesity are associated with increased risk of cardiovascular disease in adults, even in the absence of metabolic risk factors: a systematic review and meta-analysis of prospective cohort studies. Obes Rev 2020;21:e13127.
14. George JM, Bhat R, Pai KM, S A, Jeganathan J. The carotid intima media thickness: a predictor of the clincal coronary events. J Clin Diagn Res 2013;7:1082-5.
15. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, et al. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. Circulation 2020;142:621-42.
16. Park MH, Skow Á, De Matteis S, Kessel AS, Saxena S, Viner RM, et al. Adiposity and carotid-intima media thickness in children and adolescents: a systematic review. BMC Pediatr 2015;15:161.
17. Lim SM, Kim HC, Lee HS, Lee JY, Suh M, Ahn SV. Association between blood pressure and carotid intima-media thickness. J Pediatr 2009;154:667-71.
18. Zhao M, López-Bermejo A, Caserta CA, Medeiros CCM, Kollias A, Bassols J, et al. Metabolically healthy obesity and high carotid intima-media thickness in children and adolescents: international childhood vascular structure evaluation consortium. Diabetes Care 2019;42:119-25.
19. Farello G, Antenucci A, Stagi S, Mazzocchetti C, Ciocca F, Verrotti A. Metabolically healthy and metabolically unhealthy obese children both have increased carotid intima-media thickness: a case control study. BMC Cardiovasc Disord 2018;18:140.
20. Kim JH, Yun S, Hwang SS, Shim JO, Chae HW, Lee YJ, et al. The 2017 Korean National Growth Charts for children and adolescents: development, improvement, and prospects. Korean J Pediatr 2018;61:135-49.
21. Lee J, Kang SC, Kwon O, Hwang SS, Moon JS, Kim J. Reference Values for Waist Circumference and Waist-Height Ratio in Korean Children and Adolescents. J Obes Metab Syndr. 2022 Sep 30;31:263-71.

22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
23. Yi KH, Hwang JS, Kim EY, Lee SH, Kim DH, Lim JS. Prevalence of insulin resistance and cardiometabolic risk in Korean children and adolescents: a population-based study. Diabetes Res Clin Pract 2014;103:106-13.
24. Kim SH, Park Y, Song YH, An HS, Shin JI, Oh JH, et al. Blood pressure reference values for normal weight Korean children and adolescents: data from the Korea National Health and Nutrition Examination Survey 1998-2016: The Korean Working Group of Pediatric Hypertension. Korean Circ J 2019;49:1167-80.
25. Damanhoury S, Newton AS, Rashid M, Hartling L, Byrne JLS, Ball GDC. Defining metabolically healthy obesity in children: a scoping review. Obes Rev 2018;19:1476-91.
26. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37 Suppl 1:S81-90.
27. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation 2006;114:2710-38.
28. de Groot E, Hovingh GK, Wiegman A, Duriez P, Smit AJ, Fruchart JC, et al. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. Circulation 2004;109(23 Suppl 1):III33-8.
29. Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. J Am Coll Cardiol 2006;48:1865-70.
30. Abellaneda Millán M, Morillas-Ruiz JM, Ballester Sajardo R, Guillén Martínez D, Morales Moreno I, Hernández Morante JJ. Sonographic markers are useful for detection of early vascular deterioration in children with overweight/obesity: effect of a 1-year combined nutritional education and physical exercise program. Nutrients 2023;15:894.
31. Dalla Pozza R, Ehringer-Schetitska D, Fritsch P, Jokinen E, Petropoulos A, Oberhoffer R. Intima media thickness measurement in children: a statement from the Association for European Paediatric Cardiology (AEPC) Working Group on Cardiovascular Prevention endorsed by the Association for European Paediatric Cardiology. Atherosclerosis 2015;238:380-7.
32. Jourdan C, Wühl E, Litwin M, Fahr K, Trelewicz J, Jobs K, et al. Normative values for intima-media thickness and distensibility of large arteries in healthy adolescents. J Hypertens 2005;23:1707-15.
33. Doyon A, Kracht D, Bayazit AK, Deveci M, Duzova A, Krmar RT, et al. Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. Hypertension 2013;62:550-6.
34. Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S. Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. Eur Heart J 2013;34:2368-80.
35. Dalla Pozza R, Greil S, Januszewska K, Netz H, Kozlik-Feldmann R. Carotid intima media thickness and cardiac allograft vasculopathy after heart transplantation in childhood. Transplantation 2011;91:e46-7.
36. Gooty VD, Sinaiko AR, Ryder JR, Dengel DR, Jacobs DR Jr, Steinberger J. Association between carotid intima media thickness, age, and cardiovascular risk factors in children and adolescents. Metab Syndr Relat Disord 2018;16:122-6.
37. Neuhauser HK, Büschges J, Schaffrath Rosario A, Schienkiewitz A, Sarganas G, Königstein K, et al. Carotid intima-media thickness percentiles in adolescence and young adulthood and their association with obesity and hypertensive blood pressure in a population cohort. Hypertension 2022;79:1167-76.
38. Ferreira JP, Girerd N, Bozec E, Machu JL, Boivin JM, London GM, et al. Intima-Media Thickness Is Linearly and Continuously Associated With Systolic Blood Pressure in a Population-Based Cohort (STANISLAS Cohort Study). J Am Heart Assoc 2016;5:e003529.
39. Day TG, Park M, Kinra S. The association between blood pressure and carotid intima-media thickness in children: a systematic review. Cardiol Young 2017;27:1295-305.