Elevated Serum Concentrations of Remnant Cholesterol Associate with Increased Carotid Intima-Media Thickness in Children and Adolescents

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Objective To evaluate the relationship between remnant cholesterol and carotid intima-media thickness (cIMT), a surrogate marker for atherosclerosis, in children and adolescents.

Study design Anthropometric, laboratory, liver, and carotid ultrasonographic data were obtained from 767 youths (594, overweight/obese; 173, normal weight). Fasting remnant cholesterol was calculated from the standard lipid profile. cIMT ≥0.56 mm (corresponding to the 90th percentile of values observed in normal-weight children) was chosen to define elevated cIMT. Logistic regression analysis was used to estimate the risk of elevated cIMT according to tertiles of remnant cholesterol levels.

Results In the entire cohort, the mean concentration of remnant cholesterol was 17.9 ± 10.3 mg/dL and mean cIMT value was 0.51 ± 0.8 mm. Remnant cholesterol significantly correlated with age, sex, body mass index, waist circumference, blood pressure, lipids, liver enzymes, and insulin resistance. cIMT value increased progressively with rising remnant cholesterol tertiles ($P_{for\ trend} < .001$). Compared with subjects in the lowest remnant cholesterol tertile, those in the middle and highest remnant cholesterol tertiles had a 2.3- and 2.4-fold increased risk of elevated cIMT, independently of age, sex, pubertal stage, body mass index, and apolipoprotein B (all $P_{adj} \leq .003$). When the effects of overweight/obesity on the association between remnant cholesterol and cIMT were determined, normal-weight as well as overweight/obese subjects in the highest remnant cholesterol tertile had a 3.8- and 2.3-fold increased risk to have elevated cIMT compared with the respective study groups in the lowest tertile, after adjustment for conventional risk factors ($P_{adj} = .038$ and $P_{adj} = .003$, respectively).

Conclusions In youths, elevated levels of remnant cholesterol might represent a marker of early atherosclerotic damage. *(J Pediatr 2021;232:133-9)*.

Over the past years, the prevalence of atherogenic dyslipidemia in children and adolescents has increased.[1,2] Atherogenic dyslipidemia is characterized by increased serum concentrations of triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), increased small dense low-density lipoprotein cholesterol (LDL-C) particles, and accumulation of TG-rich remnant lipoproteins.[3] Remnant cholesterol is the cholesterol content of the triglyceride-rich lipoproteins (TRLs), which are formed when TRLs are partly depleted of TG by lipoprotein lipase and are composed of very-low density and intermediate-density lipoproteins in the fasting state, and by these 2 lipoproteins together with chylomicron remnants in the nonfasting state.[4]

Studies in the adult population have found observational and genetic associations between high concentrations of remnant cholesterol and high risk of ischemic heart disease,[5,6] myocardial infarction,[7,8] and all-cause mortality in the general population.[9] Remnant cholesterol also has been found to be a mediator of obesity and ischemic heart disease. That is, part of the greater risk of ischemic heart disease seen in individuals with obesity was explained by greater remnant cholesterol.[10] Moreover, it has been reported that, beyond traditional risk factors of adiposity and insulin resistance, remnant cholesterol also may contribute to risk of cardiovascular disease in people with fatty liver.[11,12]

Whether high remnant cholesterol levels associate with subclinical atherosclerosis in children and adolescents remains a question. Intima-media thickness of the carotid artery (cIMT) is recognized as a strong predictor of subclinical atherosclerosis in adults and is also considered an indicator of early atherogenesis in children and adolescents.[13,14] The aim of the present study

ALT	Alanine aminotransferase		assessment of insulin resistance
apoB	Apolipoprotein-B	hs-CRP	High-sensitivity C reactive protein
BMI	Body mass index	LDL-C	Low-density lipoprotein cholesterol
BP	Blood pressure	TR	Triglyceride
cIMT	Carotid intima-media thickness	TRL	Triglyceride-rich lipoprotein
γGT	Gamma-glutamyl transferase	WC	Waist circumference
HDL-C	High-density lipoprotein cholesterol		
HOMA-IR	Homeostasis model		

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was to evaluate the association of remnant cholesterol with early signs of morphologic vascular changes as well as with cardiometabolic risk factors in a large cohort of children and adolescents.

Methods

This observational cross-sectional study included 594 children and adolescents with overweight/obesity who were consecutively recruited at the outpatient Clinics of the Department of Maternal and Child Health, Sapienza University of Rome, Italy. All children were of European ancestry. Exclusion criteria were the presence of any condition known to influence body composition, insulin action, or insulin secretion (eg, glucocorticoid therapy, hypothyroidism, and Cushing disease); a history of pre-existing heart disease; a history of type 1 or 2 diabetes; familial or secondary dyslipidemia other than that due to the state of obesity; any laboratory or clinical evidence of chronic liver disease (other than that due to the state of obesity) including hepatic viral infections, autoimmune hepatitis, metabolic hepatic disease, α-1-antitrypsin deficiency, cystic fibrosis, Wilson disease, hemochromatosis, and celiac disease; and history of alcohol consumption and smoking. The study also consisted of a random sample of 173 apparently healthy primary and middle school students recruited from the Rome area. Every student was invited to participate in a pilot study aimed at preventing cardiovascular disease in childhood. Eligibility criteria included body mass index (BMI) appropriate for age and sex; no history of familial dyslipidemia; and no history of alcohol consumption and smoking.

All study participants underwent physical examination, including measurements of weight and standing height (from which BMI was calculated), waist circumference (WC), determination of the pubertal status, and systolic and diastolic blood pressure (BP), as previously reported in detail.[15-18] The degree of obesity was quantified by the Cole least mean square method, which normalizes the skewed distribution of BMI and expresses BMI as SD score.[19] Systolic and diastolic BP were measured twice at the right arm after a 10-minute rest in the supine position by using an automated oscillatory system (Dinamap Vital Signs Monitor, Model 1846 SX; Criticon Incorporated).

The study protocol was reviewed and approved by the Ethics Committee of Policlinico Umberto I Hospital, Rome, Italy. Informed consent was obtained from the parents, or guardians of the children included in this study, in accordance with principles of Helsinki Declaration.

Blood samples were taken from each subject after an overnight fast for the measurement of circulating concentrations of glucose, insulin, TGs, total cholesterol, HDL-C, LDL-C, apolipoprotein A, apolipoprotein B (apoB), aspartate aminotransferase, alanine aminotransferase (ALT), gamma-glutamyl transferase (γGT), and high-sensitivity C reactive protein (hs-CRP). Insulin resistance was determined by a homeostasis model assessment of insulin resistance (HOMA-IR). As previously proposed,[12,20,21] fasting remnant cholesterol was calculated as total cholesterol minus HDL-C minus LDL-C and expressed as mg/dL.

Hepatic and carotid ultrasonography were performed in all patients by a single experienced radiologist who was blinded to the participants' details. Hepatic steatosis was diagnosed on the basis of characteristic sonographic features, eg, increased echogenicity (brightness) of the liver parenchyma in comparison with the renal cortex and spleen, attenuation of the ultrasound beam by liver, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture.

Measurement of cIMT was performed as previously described.[15,16] In brief, longitudinal ultrasonographic scans of the carotid artery included the evaluation of the right and left common carotid arteries near the bifurcation during end diastole. We measured 4 values on each side, and the mean cIMT was calculated. The coefficient of variation was less than 3%.

Data are reported as means and SDs for normally distributed variables or as medians (25th-75th percentiles) for non-normally distributed variables. When appropriate, non-normally distributed variables were transformed into natural logarithms before statistical analysis.

The study participants were stratified into tertiles of remnant cholesterol. Differences among groups were assessed with ANOVA (for parametric variables) or the Kruskal–Wallis test (for nonparametric variables). The χ^2 test was used to compare proportions. Pearson correlation and linear regression coefficients were used to evaluate the relationship between cardiometabolic risk factors and remnant cholesterol concentrations. To assess the risk of elevated cIMT across tertiles of remnant cholesterol, we performed multiple logistic regression analysis. For this purpose, a cut off value ≥0.56 mm (corresponding to the 90th percentile of values observed in children with normal weight) was used to define elevated cIMT. A basic model (model 1) was adjusted for age, sex, pubertal stage, BMI, and apoB levels. A second model (model 2) included adjustments for WC, BP, insulin resistance, and hs-CRP. Statistical significance was defined as $P < .05$. Statistical analyses were performed using SPSS version 24 (IBM Corp).

Results

In the whole cohort of 767 subjects (of whom 53% were males), mean age was 10.9 ± 2.9 years. The mean BMI was 24.4 ± 4.9 kg/m^2. Seventy-seven percent of children were classified as overweight/obese (BMI ≥85th percentile for age and sex), and 23% as normal weight (BMI <85th percentile for age and sex). Overall, 311 (40.5%) subjects had hepatic steatosis. The mean concentration of remnant cholesterol was 17.9 ± 10.3 mg/dL, and the mean cIMT value was 0.51 ± 0.8 mm.

The demographic and clinical characteristics of the study participants according to tertiles of remnant cholesterol are

summarized in Table I. Across the remnant cholesterol tertiles, BMI, WC, BP, lipids (TGs, total cholesterol, LDL-C), fasting serum insulin, HOMA-IR, ALT, γGT, and hs-CRP values gradually and significantly increased, whereas the concentrations of HDL-C significantly and progressively declined (all $P \leq .001$). We also observed a striking increase in circulating apoB concentrations from children in the lowest tertile (0.59 [0.49-0.70] g/L) to those in the greatest remnant cholesterol tertile (0.79 [0.64-0.95] g/L; $P < .001$). The correlation analysis revealed significant positive associations between remnant cholesterol levels and anthropometric and metabolic variables such as age, BMI, WC, systolic and diastolic BP, serum lipid status, aspartate aminotransferase, ALT, γGT, serum glucose, and insulin levels as well as HOMA-IR (all $P < .001$) (Table II; available at www.jpeds.com). In multivariate stepwise linear regression analyses, TGs ($P_{adj} < .001$), HOMA-IR ($P_{adj} = .003$), and BMI values ($P_{adj} = .038$) best explained variation in remnant cholesterol levels in our children cohort (Table II).

As depicted in Figure 1, cIMT increased gradually with rising remnant cholesterol tertiles (P for trend $< .001$). After adjustments for age, sex, pubertal stage, BMI, and apoB concentrations, remnant cholesterol levels were found to be significantly associated with increased cIMT ($P_{adj} < .001$).

Across the remnant cholesterol tertiles, the prevalence of children with elevated cIMT was 15.6%, 27.7%, and 32.5%, respectively ($\chi^2 = 17.07$; $P < .001$). As shown in Table III, children in the middle and highest remnant cholesterol tertiles had an increased risk for elevated cIMT (OR 2.1; 95% CI 1.2-3.5 and OR 2.6; 95% CI 1.6-4.1; $P = .007$ and $P < .001$, respectively) compared with those in the lowest tertile. This association remained statistically significant after adjustments for age, sex, pubertal stage, BMI, and apoB (model 1: $P_{adj} = .003$ and $P_{adj} = .001$, respectively). Further adjustments for systolic and diastolic BP, HOMA-IR, and hs-CRP (model 2), or for WC instead of BMI or fatty liver (data not shown) did not change the independent association between remnant cholesterol concentrations and elevated cIMT. In the stepwise regression analysis, remnant cholesterol tertiles (OR 1.4; 95% CI 1.1-1.7; $P_{adj} = .006$) and BMI (OR 1.1; 95% CI 1.0-1.1; $P_{adj} < .001$) were found to be the best predictors of increased cIMT. Regression analysis showed that remnant cholesterol was better associated with increasing cIMT ($\beta = 0.22$, $P < .001$) as compared with TG ($\beta = 0.20$, $P < .001$), HDL ($\beta = -0.19$, $P < .001$), TC ($\beta = -0.04$, $P = .19$), and LDL-C ($\beta = -0.04$, $P = .24$). After adjustment for age, sex, BMI, and pubertal stage, still remnant cholesterol tertiles were superior to both TC (OR 1.40; 95% CI 1.12-1.75, $P_{adj} = .003$) and LDL-C (OR 1.39; 95% CI 1.11-1.74, $P_{adj} = .003$) levels in predicting high cIMT. Due to the strong intimate correlation between TG and remnant cholesterol, TG levels were omitted from the model.

Based on the observation that the percentage of children with elevated cIMT was significantly greater in the group with overweight/obesity (31.5%) compared with the one with normal weight (14.2%; $\chi^2 = 19.8$; $P < .001$), we evaluated whether overweight/obesity could influence the association between remnant cholesterol and cIMT. Children with elevated cIMT in the middle and highest remnant cholesterol tertiles more frequently belonged to the overweight/obese (27.6%) than to the normal-weight group (11.8%; $\chi^2 = 12.6$, $P < .001$) (Figure 2). Nonetheless, increased cIMT was significantly associated with remnant cholesterol tertiles among children with overweight/obesity (P for trend = .01) (Figure 2, B) as well as children with normal weight (P for trend = .02) (Figure 2, A). After adjustments for age, sex, pubertal stage, and apoB levels, children with normal weight as well as those with overweight/obesity in the highest remnant cholesterol tertile had a 3.8- and 2.3-fold increased risk to have elevated cIMT compared with the respective study children in the lowest tertile ($P_{adj} = 0.038$ and $P_{adj} = 0.003$, respectively, Figure 2). When an additional adjustment for WC was made, children with normal weight as well as those with overweight/obesity within the highest remnant cholesterol tertile still had an increased risk of elevated cIMT (OR 3.8; 95% CI 1.1-13.6; $P_{adj} = .04$ and OR 2.3; 95% CI 1.3-4.0; $P_{adj} = .004$, respectively).

Discussion

Very few data are available on the clinical utility of remnant cholesterol measurement in predicting cIMT in pediatric population. One previous study has described a significant correlation between increasing cIMT and remnant lipoprotein cholesterol in adolescents with extreme obesity.[22] However, visceral fat but not remnant cholesterol emerged as a key predictor of arterial wall thickening in these subjects. Our findings extend these observations and for the first time suggest a possible role of remnant cholesterol in predicting cIMT independently from other cardiometabolic risk factors in children and adolescents. Studies in the adult population have found elevated fasting plasma apoB48, a biomarker of intestinal-derived remnant cholesterol as well as of postprandial dyslipidemia, to be positively associated with cIMT.[23] The atherogenicity of remnant cholesterol has been demonstrated in many experimental studies.[24-31] Remnants enter the arterial intima and, due to their large size, get trapped in the intima by attachment to proteoglycans.[27] In the intima, remnants are taken up by macrophages without any need for previous modification, and thereby converting such cells into foam cells, which are the hallmark of atherosclerotic lesions.[28] In addition, remnants have been shown to promote the aggregation of platelets and to stimulate the adhesion of monocytes to vascular endothelial cells, thus generating local inflammation in the arterial wall.[29] Finally, remnants have been found to up-regulate the expressions of both intracellular adhesion and vascular molecules in cultured human endothelial cells, which could contribute to atherogenesis.[31]

Table I. Clinical and biochemical characteristics of the study cohort across tertiles of remnant cholesterol concentrations

Characteristics	Tertile I (<10.9)	Tertile II (10.9-14.6)	Tertile III (≥14.7)	*P* value
Number of subjects	174	174	419	
Age, y	10.7 (8.1-13.0)	11.0 (9.0-13.0)	11.0 (9.1-13.0)	.10
Male sex, %	56.9	46.8	56.4	.078
BMI, kg/m^2	22.7 (20.1-25.2)	22.7 (19.6-26.4)	25.3 (22.5-28.8)	<.001
BMI-SDS	1.6 (0.8-1.9)	1.6 (0.8-1.9)	1.9 (1.5-2.2)	<.001
Normal weight, %	32	33.3	14.3	<.001
Overweight/obese, %	68.4	66.7	85.7	
Fatty liver, %	26.4	30.5	49.9	<.001
WC, cm	77.8 ± 12.7	77.8 ± 14.9	86.0 ± 14.6	<.001
Systolic BP, mm Hg	110 (100-116)	110 (100-115)	110 (100-120)	<.001
Diastolic BP, mm Hg	65 (60-70)	65.5 (60-70)	70 (60-70)	<.001
TGs, mg/dL	45.2 (37.8-49.6)	62 (58-67)	105 (84.1-136)	<.001
Total cholesterol, mg/dL	147.6 (126.9-169.1)	159.3 (139-181.5)	171 (149-196)	<.001
HDL-C, mg/dL	57 (51-64)	55.1 (47.4-62.4)	46.4 (38.7-53.7)	<.001
LDL-C, mg/dL	81.1 (62.4-101.6)	90.1 (76.4-111.1)	99 (79.7-122.7)	<.001
Apolipoprotein AI, g/L	1.43 (1.30-1.59)	1.44 (1.32-1.60)	1.38 (1.25-1.54)	<.001
apoB, g/L	0.59 (0.49-0.70)	0.66 (0.57-0.78)	0.79 (0.64-0.95)	<.001
AST, U/L	24 (20-28)	23 (19-27)	24 (20-31)	.017
ALT, U/L	18 (14-24)	17.5 (13.7-22)	20 (16-40)	<.001
γGT, U/L	11 (9-14)	12 (9.7-14)	13 (11-19)	<.001
Blood glucose, mmol/L	4.6 (4.3-4.9)	4.6 (4.4-4.8)	4.7 (4.4-5.0)	.008
Insulin, μU/mL	9.1 (6-12.8)	10.1 (6.7-15.8)	15.2 (10.3-22.4)	<.001
HOMA-IR	1.8 (1.2-2.7)	2.0 (1.3-3.1)	3.1 (2.1-4.7)	<.001
hs-CRP, μg/L	1038 (500-2250)	1100 (579-2900)	1498 (767.5-3022.5)	.001

AST, aspartate aminotransferase.
Data are presented as means ± SD or median (25th-75th) or n (%). *P* values by ANOVA or Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables are given.

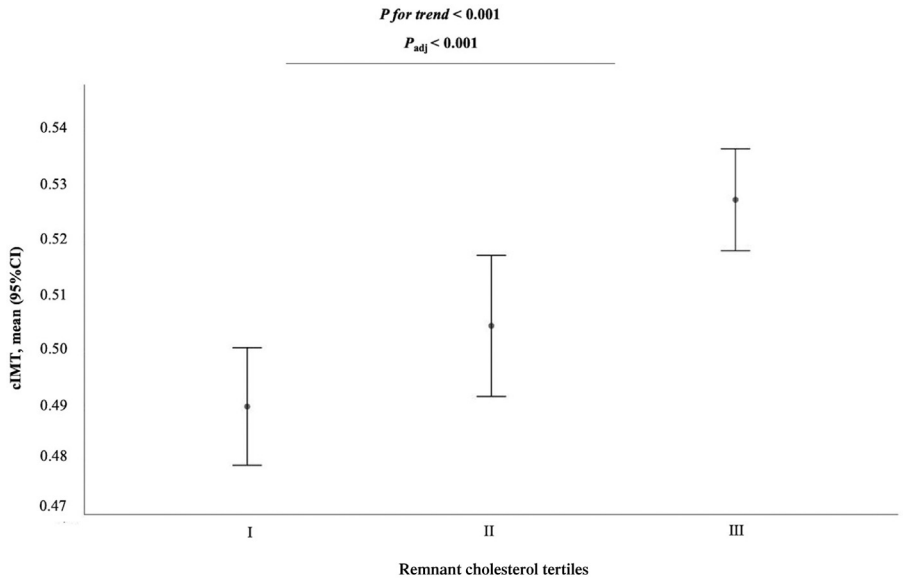

Figure 1. Mean (95% CI) cIMT values across tertiles of remnant cholesterol concentrations. P_{adj} for age, sex, pubertal stage, BMI, and apoB.

Table III. Unadjusted and adjusted ORs (95% CI) for elevated cIMT in the second and third remnant cholesterol tertiles compared with the first tertile

	Tertiles of remnant cholesterol		
	Tertile I	Tertile II	Tertile III
Remnant cholesterol median values	9.01 (7.5-9.9)	12.4 (11.6-13.4)	21 (17-27.3)
Unadjusted model	Reference	2.1 (1.2-3.5)	2.6 (1.6-4.1)
Elevated cIMT		$P = .007$	$P < .001$
Adjusted model 1	Reference	2.3 (1.3-4.0)	2.4 (1.4-4.1)
Elevated cIMT		$P = .003$	$P = .001$
Adjusted model 2	Reference	2.6 (1.4-4.6)	2.3 (1.3-4.0)
Elevated cIMT		$P = .001$	$P = .003$

Elevated cIMT was defined on the basis of a cut off of ≥0.56 mm (corresponding to the 90th percentile of cIMT in children with normal weight).
Model 1: age, sex, pubertal stage, BMI, and apoB levels.
Model 2: age, sex, pubertal stage, BMI, apoB, systolic BP and diastolic BP, HOMA-IR, and hs-CRP.

Obesity is an important cause of high remnant cholesterol concentrations and has been reported to increase very-low density lipoprotein synthesis in the liver, resulting in elevated remnant lipoprotein particles.[32] Several observational studies have clearly shown that remnant cholesterol is significantly greater in children with high BMI values.[33-35] In the work by Choi et al, the proportion of children with remnant cholesterol levels >7.5 mg/dL was about twice in the high-BMI group compared with the other groups.[33] Also, in the work by Wang et al, apoB48 concentrations were 2-fold greater in obese children than in age- and sex-matched normal weight controls.[34] In addition, a recent cross-sectional study involving 1045 adolescents has demonstrated that fasting plasma apoB48 concentrations are associated with measures of adiposity and features of the metabolic syndrome.[35] Like visceral obesity and other insulin-resistant conditions, it also has been reported that fatty liver independently associates with increasing remnant cholesterol concentrations in adults[12] and children,[36] thus further suggesting that the increase of remnant cholesterol is representative of a proatherogenic metabolic profile.

We also observed a striking increase in BMI values in children with the greatest remnant cholesterol concentrations, which, in turn, positively associated with obesity-related risk factors including BP, serum lipid status, markers of liver injury, fatty liver, insulin resistance, and inflammation. Overall, these data suggest that the clustering of cardiometabolic risk factors may result in increased fasting concentrations of remnant cholesterol. It is also important to consider that 50% of our children had nonalcoholic fatty liver disease, which is known to be associated with increased production of TRLs and delayed removal of remnant particles.[37]

Despite a significant correlation between remnant cholesterol concentrations and measures of adiposity, we found

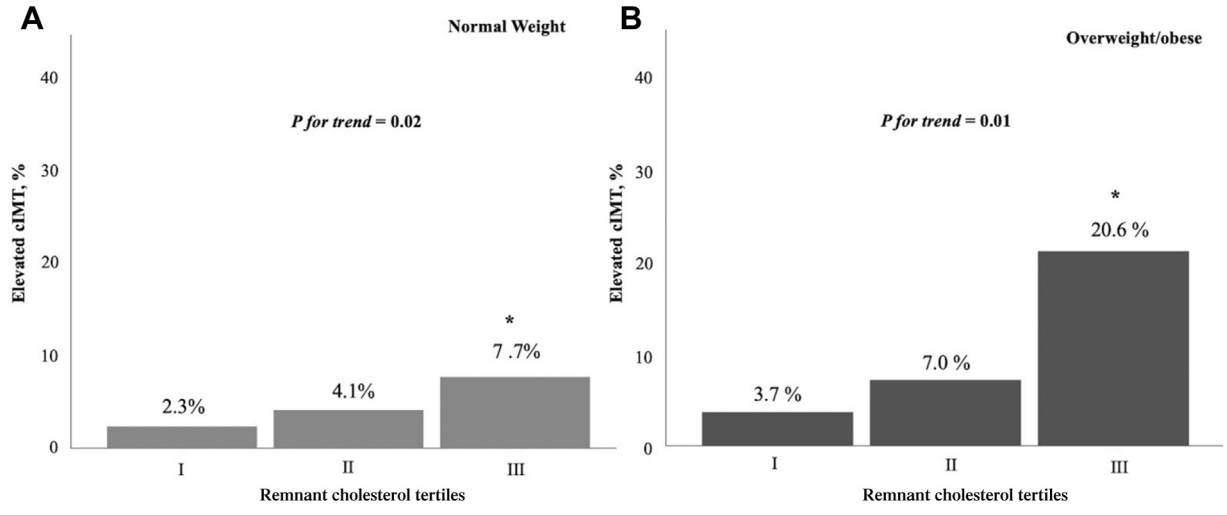

Figure 2. Association between cIMT and remnant cholesterol concentrations according to weight status. Percentage of children with **A,** normal weight and **B,** overweight/obesity with elevated cIMT across remnant cholesterol tertiles. *Significant *P* values for comparisons of the highest vs the lowest remnant cholesterol tertile adjusted for age, sex, pubertal stage, and apoB levels (P_{adj} = .038 for normal weight; and P_{adj} = .003 for overweight/obese).

that the association between elevated cIMT and increased concentrations of circulating remnants appeared to be independent of overweight/obesity status. Indeed, among youths of normal weight as well as those with overweight/obesity, children with the greatest remnant cholesterol values had a 3.8- and 2.3-fold increased risk to have elevated cIMT, respectively. This is not a surprising finding because in adults a causal association between elevated nonfasting remnant cholesterol and low-grade inflammation coupled with increased risk of ischemic heart disease has been found, even in participants without diabetes mellitus and obesity.[6] Yet, in a study involving 106 216 individuals from the general population of Denmark, concentrations of calculated remnant cholesterol were positively correlated with BMI, with 12% of the variation in remnant cholesterol explained by variation in BMI.[8] However, the association between high remnant cholesterol concentrations and high risk of myocardial infarction was similar for individuals with normal weight, overweight, and obesity, suggesting that the association might not necessarily be driven solely by adiposity. Our results may suggest that among the normal-weight group with increased concentration of remnant cholesterol there were also children with genetically determined delay in the lipolysis of TGs. Our previous findings demonstrated that children with atherogenic dyslipidemia (a lipid phenotype in which remnants accumulate) have a strong familial aggregation and an increased cumulative prevalence of loss-of-function mutations in lipoprotein lipase, the crucial enzyme in the lipolytic degradation of TG-rich lipoproteins.[3]

Some limitations of our study should be acknowledged. First, we were not able to directly measure circulating concentrations of remnant particles. This might explain the differences between the mean values of remnant cholesterol found in our population and those reported by Choi et al.[33] However, a consensus method of measuring remnant-like particle-cholesterol concentrations levels has not yet been established.[38] Second, we were not able to evaluate remnant cholesterol during the postprandial state, which is recognized as important as this is when the concentration of remnants is regulated. Third, the cross-sectional nature of our study prevents insights into the causal relationship between elevation of remnant cholesterol and increased cIMT. Further longitudinal studies are needed to validate the use of remnant cholesterol in childhood, and more importantly, to identify earlier in life reliable cut off values to predict adult atherosclerosis-related ischemic complications. The potential impact of lowering levels of remnant cholesterol in children on cardiovascular risk also should be evaluated. The appropriate strategy to reach this target in children is still an open question. One might speculate that dietary interventions aimed at obtaining weight loss may represent a reasonable approach, but no clinical trials have yet provided evidence to support this strategy in children. Also, future studies about the potential effect of food with added plant sterols/stanols in attenuating the atherogenicity of remnant cholesterol would be of special interest. ■

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Data statement

Data sharing statement available at www.jpeds.com.

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Table II. Pearson correlation coefficients and linear regression analysis of variables associated with remnant cholesterol levels

Variables	r	$\beta \pm$ SE	*P* value
Age, y	0.10*		
BMI, kg/m^2	0.31*	0.012 $\pm$ 0.015	.038
WC, cm	0.31*		
Systolic BP, mm Hg	0.19*		
Diastolic BP, mm Hg	0.14*		
TGs, mg/dL	0.98*	0.99 $\pm$ 0.005	<.001
Total cholesterol, mg/dL	0.24*		
HDL-C, mg/dL	−0.42*		
LDL-C, mg/dL	0.13*		
Apolipoprotein AI, g/L	−0.18*		
apoB, g/L	0.35*		
AST, U/L	0.21*		
ALT, U/L	0.31*		
γGT, U/L	0.32*		
Glucose, mmol/L	0.19*		
Insulin, μU/mL	0.39*		
HOMA-IR	0.39*	−0.19 $\pm$ 0.004	.003
hs-CRP, μg/L	0.15*		

Pearson correlation analysis. Only significant associations were reported. Linear regression analysis (stepwise) was applied to analyze best associations. Skewed variables were logarithmically transformed before analysis.
*$P \leq .001$.