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Childhood Levels of Serum Apolipoproteins B and A-I Predict Carotid Intima-Media Thickness and Brachial Endothelial Function in Adulthood

The Cardiovascular Risk in Young Finns Study

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Objectives The aim of this study was to determine whether apolipoproteins (apo) B and A-I measured in childhood and adolescence predict atherosclerosis in adulthood.

Background Exposure to dyslipidemia in childhood predicts the development of atherosclerosis. Apolipoproteins B and A-I might be good markers of atherogenic dyslipidemia, but there is a paucity of information concerning their importance in childhood.

Methods Apolipoproteins B and A-I, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, blood pressure, obesity, insulin, C-reactive protein, and smoking were assessed in 1980 and 2001 among 879 subjects in the Cardiovascular Risk in Young Finns Study (ages 3 to 18 years at baseline). Carotid artery intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD) were measured in 2001 at the age of 24 to 39 years.

Results In subjects ages 12 to 18 years at baseline, apoB and apoB/apoA-I ratio were directly ($p < 0.001$) related and apoA-I was inversely ($p = 0.01$) related with adulthood IMT. In subjects ages 3 to 18 years at baseline, apoB ($p = 0.02$) and the apoB/apoA-I ratio ($p < 0.001$) were inversely related and apoA-I ($p = 0.003$) was directly related to adulthood FMD. These relations were not altered when the effects of nonlipid risk factors and adulthood apolipoproteins were taken into account. The apoB/apoA-I ratio measured in adolescence was superior to LDL/HDL ratio (c-values, 0.623 vs. 0.569, $p = 0.03$) in predicting increased IMT in adulthood (IMT ≥90th percentile and/or carotid plaque).

Conclusions Apolipoproteins B and A-I measured in children and adolescents reflect a lipoprotein profile predisposing to the development of subclinical atherosclerosis in adulthood. These markers might have value in pediatric lipid risk assessment. (J Am Coll Cardiol 2008;52:293–9) © 2008 by the American College of Cardiology Foundation

Dyslipidemia is a major risk factor for atherosclerotic diseases (1), and serum lipid values are cornerstones in clinical risk stratification. Serum concentrations of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol are mainly used for this purpose. However, the amounts of LDL and HDL particles' major apolipoproteins (apo) B and A-I could be better markers of dyslipidemia risk than their cholesterol concentration (2–8).

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Atherosclerosis begins in childhood (9). Pre-clinical vascular changes can be assessed noninvasively and reliably by ultrasound in young subjects. Increased carotid intima-

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Abbreviations and Acronyms

apo = apolipoprotein
BMI = body mass index
CHD = coronary heart disease
CRP = C-reactive protein
CV = coefficient of variation
FMD = flow-mediated dilation
HDL = high-density lipoprotein
IMT = intima-media thickness
LDL = low-density lipoprotein
ROC = receiver-operating characteristic

media thickness (IMT) is a marker of structural atherosclerosis. It correlates with cardiovascular risk factors (10) and the severity of coronary atherosclerosis (11) and predicts cardiovascular events (12). Vascular endothelial function can be measured by evaluating brachial artery flow-mediated dilation (FMD) (13). Impaired FMD predicts cardiovascular events (14), and preserved FMD response associates with favorable cardiovascular outcome (15).

Exposure to atherogenic lipid profile in early life might induce changes in arteries that contribute to the development of atherosclerosis. We (10) and others (16,17) have shown that elevated LDL-cholesterol levels in childhood predict increased carotid IMT in adulthood. In cross-sectional settings, HDL-cholesterol levels in childhood and early adulthood have been related to decreased IMT and increased FMD (16–20).

In the present study, we aimed to examine the roles of high apoB/LDL cholesterol and low apoA-I/HDL cholesterol in predicting the development of subclinical atherosclerosis. We also tested the hypothesis that serum apoB and apoA-I and their ratio are better indicators of atherogenic/antiatherogenic lipoprotein particles than the conventional measures of LDL cholesterol and HDL cholesterol. To address this, we studied whether childhood/adolescent levels of apoB and apoA-I are predictive of carotid IMT and brachial FMD measured 21 years later in early adulthood among 879 men and women. The study subjects were participants of the prospective Cardiovascular Risk in Young Finns Study (10).

Methods

Subjects. The Cardiovascular Risk in Young Finns Study is a multicenter follow-up study of atherosclerosis precursors of Finnish children and adolescents. The first cross-sectional survey was conducted in 1980, when 3,596 participants, ages 3, 6, 9, 12, 15, and 18 years, were randomly chosen from the 5 study areas on the basis of the national population register. In the 21-year follow-up in 2001, we carried out vascular ultrasound studies in 2,265 of these individuals, ages 24 to 39 years. Apolipoproteins B and A-I were measured in a subcohort of 1,341 subjects in 1980. Due to limited analytical capacity, apolipoproteins were measured only for this subsample of the total cohort (21). Altogether, 879 of these 1,341 subjects with apolipoprotein data gathered in 1980 participated in the 21-year follow-up in 2001, comprising the present study cohort. The study has been approved by the ethics committees of each center, and all subjects and/or their parents have given their written informed consents. The authors have had full access to the data and take full responsibility for their integrity.

Apolipoprotein and lipid measurements. Venous blood samples were drawn after an overnight fast. In 1980, apoB and apoA-I were determined with a radial immunodiffusion method (21). The interassay coefficient of variation (CV) was 5.1% for apoB and 4.0% for apoA-I. In 2001, apoB and apoA-I were analyzed immunoturbidometrically (Orion Diagnostica, Espoo, Finland); interassay CVs were 2.8% for apoB and 3.2% for apoA-I. The details of other lipid determination methods have been previously published (22).

Non-lipid risk factors. Height and weight were measured, and body mass index (BMI) was calculated. Blood pressure was measured from the brachial artery with a standard mercury sphygmomanometer in 1980. From 3-year-old subjects blood pressure was measured with an ultrasound device. In 2001, a random zero sphygmomanometer was used. The mean of 3 measurements was used in the analysis. Serum samples for youth C-reactive protein (CRP) measurements were taken in 1980 and stored in −20°C. These samples were analyzed in 2005 (23). During the storage, the samples were not thawed or refrozen. In 1980, serum insulin was measured with a modification of the immunoassay method of Herbert et al. (24). Smoking habits were determined with a questionnaire in subjects ages ≥12 years. Regular cigarette smoking on a weekly basis or more often was defined as a risk factor for smoking.

Ultrasound imaging. Ultrasound studies of the carotid and brachial arteries were performed with Sequoia512 ultrasound mainframes (Acuson, Mountain View, California) with 13.0 MHz linear array transducer (10,20). To assess intraindividual reproducibility of ultrasound measurements, 57 subjects were re-examined 3 months after the initial visit.

Carotid IMT. Carotid IMT was measured on the posterior (far) wall of the left carotid artery. At least 4 measurements were taken approximately 10 mm proximal to the bifurcation to derive mean carotid IMT. The between-visit CV was 6.4% (10). The far and near walls of the left common carotid artery and carotid bulb area were scanned for the presence of atherosclerotic plaque, defined as a distinct area of the vessel wall protruding into the lumen >50% of the adjacent intima-media layer (25).

Brachial FMD. To assess brachial FMD, the left brachial artery diameter was measured at rest and during reactive hyperemia. Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mm Hg for 4.5 min, followed by a release (20). Arterial diameter was measured at end-diastole at a fixed distance from an anatomic marker at rest and 40, 60, and 80 s after cuff release. The vessel diameter in scans after reactive hyperemia was expressed as the percentage relative to resting scan. The average of 3 measurements at each time

point was used to derive the maximum FMD (the greatest value between 40 and 80 s). The between-visit CV for brachial diameter was 3.2% and for FMD 26.0% (20).

Statistical methods. To examine possible selection bias, the clinical characteristics between subjects of the present 21-year follow-up who had had their serum apolipoproteins measured in 1980 ("study subjects") and those whose apolipoprotein values were not available ("excluded due to missing data") were compared with the *t* test for continuous variables and chi-square test for categorical variables.

To study the relations between apolipoproteins and markers of subclinical atherosclerosis, we first examined the bivariate associations with age- and gender-specific *Z* score values (standardized values) for apolipoproteins. Then, we studied the independent effects of apolipoproteins on subclinical atherosclerosis. Therefore, multivariable models including age- and gender-specific *Z* score values for blood pressure, triglycerides, BMI, CRP, insulin, and brachial diameter (in FMD models) and absence/presence of smoking were constructed. Finally, we investigated whether the effects of childhood apolipoproteins are independent of the adulthood values, by including *Z* score values of adulthood apolipoproteins in multivariable models.

Possible risk factor × gender and risk factor × age interactions were tested with linear regression models. Because there were no significant gender interactions in the associations of apolipoproteins with IMT or FMD, the analyses were performed with genders combined. There were significant apoB × age ($p = 0.002$), apoA-I × age ($p = 0.007$), and apoB/apoA-I ratio × age ($p < 0.001$) interactions when studying their associations with IMT. Therefore, as in our prior report concerning associations between conventional childhood risk factors and adulthood IMT (10), the analyses concerning IMT were performed separately for subjects ages 3 to 9 and 12 to 18 years at baseline. This age stratification paralleled pubertal staging, because approximately 85% of 12- to 18-year-old subjects at baseline were classified having puberty on-going or completed (Tanner staging). The results of the regression analyses were essentially similar with either pubertal stage or age group stratification. The relations between apolipoproteins and FMD showed no interaction with age, but univariate results are shown separately for subjects ages 3 to 9 and 12 to 18 years at baseline and also for the total cohort.

We also studied the utility of different childhood lipid measures in predicting adulthood IMT ≥90th percentile and/or carotid plaque and, separately, brachial FMD ≤10th percentile. Therefore, the receiver-operating characteristic (ROC) curves were generated for the childhood apoB/apoA-I ratio and the LDL/HDL-cholesterol ratio by plotting sensitivity versus 1 − specificity obtained from the multivariable logistic model also including all nonlipid risk factors independently associating with ultrasound variables. The c-value calculated from these models is conceptually analogous to the area under a ROC curve. The statistical comparisons of the ROC curves of different predictive variables were carried out with a Statistical Analysis System (SAS, Cary, North Carolina) macro. This program performs nonparametric statistical test for comparison of ROC curves (26).

The statistical tests were performed with SAS version 9.1. Statistical significance was inferred at a 2-tailed p value <0.05. Values for triglycerides, insulin, and CRP were $\log_{10}$-transformed before analyses due to skewed distributions. All the analyses were repeated after excluding subjects taking lipid-lowering (n = 3) or antihypertensive medications (n = 22), with essentially similar results.

Results

Representativeness of the study population. The present analyses focused on the 879 subjects of the 21-year follow-up study with apolipoprotein data from 1980 ("study subjects"). The comparison of clinical characteristics of study subjects and subjects excluded because of lacking apolipoprotein data is shown in Table 1. The distributions of gender or age did not differ between the groups. The baseline level (in 1980) of LDL cholesterol was slightly lower among study subjects in comparison with those excluded from the present analyses. No statistically signifi-

Table 1 Clinical Characteristics of Study Subjects and Those Excluded Due to Missing Childhood Apolipoprotein Data

	Study Subjects	Excluded	p Value
n	879	1,386	
Male subjects (%)	45.7	44.4	0.56
Baseline characteristics in 1980			
Age (yrs)	10.9 ± 5.0	10.5 ± 5.0	0.08
LDL cholesterol (mmol/l)	3.39 ± 0.78	3.48 ± 0.82	0.01
HDL cholesterol (mmol/l)	1.56 ± 0.31	1.56 ± 0.31	0.91
Triglycerides (mmol/l)	0.66 ± 0.31	0.67 ± 0.31	0.54
Systolic blood pressure (mm Hg)	112 ± 12	113 ± 12	0.19
BMI (kg/m^2)	17.9 ± 3.1	17.9 ± 3.1	0.90
Insulin (mU/l)	9.8 ± 6.0	9.7 ± 5.9	0.39
CRP (mg/l)	0.9 ± 2.7	1.1 ± 3.2	0.80
Smoking (%)*	28.0	24.6	0.19
ApoA-I (g/l)	1.52 ± 0.25		
ApoB (g/l)	0.93 ± 0.21		
Characteristics in 2001			
Age (yrs)	31.9 ± 5.0	31.5 ± 5.0	0.08
LDL cholesterol (mmol/l)	3.27 ± 0.82	3.28 ± 0.86	0.64
HDL cholesterol (mmol/l)	1.29 ± 0.32	1.29 ± 0.32	0.83
Triglycerides (mmol/l)	1.32 ± 0.86	1.35 ± 0.85	0.54
Systolic blood pressure (mm Hg)	117 ± 13	116 ± 13	0.19
BMI (kg/m^2)	25.1 ± 4.6	25.0 ± 4.3	0.58
Smoking (%)	26.9	28.7	0.36
ApoA-I (g/l)	1.51 ± 0.25	1.49 ± 0.26	0.17
ApoB (g/l)	1.07 ± 0.25	1.06 ± 0.27	0.37
Carotid IMT (mm)	0.58 ± 0.09	0.58 ± 0.09	0.50
Brachial FMD (%)	8.12 ± 4.43	7.92 ± 4.42	0.30

*Among subjects ages 12 to 18 years.

Apo = apolipoprotein; BMI = body mass index; CRP = C-reactive protein; FMD = flow-mediated dilatation; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein.

cant differences were seen in the levels of HDL cholesterol, triglycerides, blood pressure, and BMI and smoking rates. There were no differences between the 2 groups in apolipoprotein levels, IMT, and FMD measured in 2001.

Associations between childhood and adolescent apolipoproteins and adulthood carotid IMT. In bivariate analyses (performed for age- and gender-specific Z score values), apoB and the apoB/apoA-I ratio were directly related and apoA-I was inversely related to adulthood IMT in subjects ages 12 to 18 years at baseline. In subjects ages 3 to 9 years at baseline, these associations were nonsignificant (Table 2). In subjects ages 12 to 18 years at baseline, the standardized regression coefficients between apolipoproteins and IMT were approximately 50% higher compared with the regression coefficients between conventional lipid measures and IMT (Table 2).

In multivariable analyses (performed for age- and gender-specific *Z* score values at the age of 12 to 18 years), the direct associations between apoB and the apoB/apoA-I ratio and IMT and the inverse association between apoA-I and IMT were independent of other risk factors (Table 3). In addition, the associations between adolescent apolipoproteins and adulthood IMT remained significant after including adulthood apolipoprotein values in the multivariable models ($p < 0.05$).

When performing the multivariate analyses also with data from those subjects ages 3 to 9 years at baseline, childhood/adolescence (age 3 to 18 years) apoA-I ($p = 0.04$), and the apoB/apoA-I ratio ($p = 0.02$) were independently associated, whereas apoB ($p = 0.09$) was not associated with adulthood IMT.

The c-value for multivariable model predicting carotid IMT ≥90th percentile and/or carotid plaque incorporating also non-lipid risk factors independently associating with IMT (i.e., systolic blood pressure and smoking) was higher for the adolescent apoB/apoA-I ratio compared with the LDL/HDL ratio (0.623 vs. 0.569, $p = 0.03$) (Fig. 1). The difference remained similar when the LDL/HDL ratio was replaced with the non-HDL/HDL ratio ($p = 0.03$).

Table 3 Multivariable Relations Between Adolescent ApoB and ApoA-I and Adulthood Carotid IMT Adjusted With Other Risk Factors in Subjects Ages 12 to 18 Years at Baseline

	β (95% CI)	p Value
ApoA-I*	−11 (−19 to −3)	0.01
ApoB*	17 (8 to 26)	<0.001
Triglycerides	1 (−9 to 11)	0.76
Systolic blood pressure	16 (8 to 24)	<0.001
BMI	3 (−7 to 13)	0.61
Insulin	−2 (−12 to 8)	0.61
CRP	−2 (−12 to 8)	0.65
Smoking	32 (12 to 52)	0.002

N = 472. Values are regression coefficients (expressed in micrometers) for a 1-SD change (specific for age and gender) in continuous variables and for the presence/absence of smoking. *When apoB and apoA-I were replaced with their ratio, the ratio was significantly associated with increased IMT ($\beta = 23$ [15 to 31], $p < 0.001$).
Abbreviations as in Tables 1 and 2.

Associations between childhood and adolescent apolipoproteins and adulthood brachial FMD. In subjects ages 3 to 18 years at baseline, apoB and the apoB/apoA-I ratio were indirectly related and childhood apoA-I was directly related to adulthood FMD (Table 4). Conventional lipids measured in childhood and adolescence were not associated with adulthood FMD (Table 4). The associations between apolipoproteins (analyses performed for age- and gender-specific Z score values) and FMD were independent of other childhood and adolescent risk factors and brachial artery diameter (Table 5). These associations remained significant after including adulthood apolipoprotein values in multivariable models ($p < 0.05$).

The apoB/apoAI ratio had a higher c-value compared with the LDL/HDL ratio (0.613 vs. 0.602) in predicting adult brachial FMD ≤10th percentile, but this difference was not significant ($p = 0.46$).

Discussion

Risk factors operating in early life might have long-term effects on arterial health. At present, however, there are

Table 2 Bivariate Relations Between Childhood/Adolescence Apolipoproteins and Lipids on Adulthood Carotid IMT Measured 21 Years Later

	Carotid IMT			
	Age 3–9 Yrs (n = 407)		Age 12–18 Yrs (n = 472)	
	β (95% CI)	p Value	β (95% CI)	p Value
ApoA-I	−1 (−8 to 8)	0.95	−12 (−22 to −2)	0.01
HDL cholesterol	10 (2 to 18)	0.009	−7 (−17 to 3)	0.11
ApoB	−5 (−13 to 3)	0.16	18 (8 to 28)	<0.001
LDL cholesterol	−4 (−12 to 4)	0.25	11 (1 to 21)	0.02
Non-HDL cholesterol	−5 (−13 to 3)	0.19	12 (2 to 22)	0.009
ApoB/apoA1 ratio	−4 (−12 to 4)	0.26	24 (14 to 34)	<0.001
LDL/HDL ratio	−10 (−18 to −2)	0.01	16 (6 to 26)	0.004
Non-HDL/HDL ratio	−10 (−18 to −2)	0.02	16 (6 to 26)	0.003

Beta values are regression coefficients (expressed in micrometers) for a 1-SD change (specific for age and gender) in continuous variables. p values are from regression analysis testing for linear relationship between risk factors and IMT.
CI = confidence interval; other abbreviations as in Table 1.

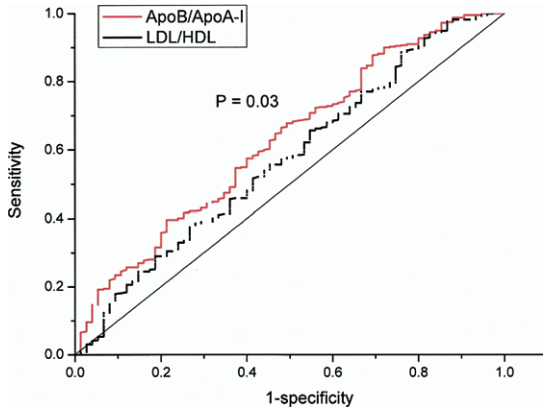

Figure 1 ROC Curves for Adolescent Lipid Measures Predicting Adulthood IMT ≥90th Percentile or Carotid Plaque

Ages 12 to 18 years, n = 472. The **diagonal line** indicates a test with an area under the receiver operating characteristics curve of 0.5. In addition to lipid measures, the models included those risk factors significantly associated with intima-media thickness in multivariate model (blood pressure, smoking). The values for continuous variables were age- and gender-specific *Z* scores. ApoA-I = apolipoprotein A-I; ApoB = apolipoprotein B; HDL = high-density lipoprotein (cholesterol); IMT = intima-media thickness; LDL = low-density lipoprotein (cholesterol); ROC = receiver-operating characteristic.

limited data linking childhood risk factors to cardiovascular disease end points to support this idea. It has been shown—regarding lipid risk factors—that exposure to high levels of LDL cholesterol in childhood and adolescence predicts the development of increased carotid IMT in adulthood (10,16,17). In the present study, we found that apoB and apoA-I levels and their ratio assessed at an early age were predictive of adulthood carotid IMT and brachial FMD. These relations were independent of apolipoprotein levels in adulthood. In addition, we found that a high apoB/apoA-I ratio was superior to conventional lipid measures in predicting abnormal IMT.

Apolipoproteins have been consistently shown to predict cardiovascular morbidity and mortality (2–8,27). In the INTERHEART (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries) study (27), a high apoB/apoA-I ratio was the strongest risk factor for acute myocardial infarction. The population-attributable risk associated with the apoB/apoA1 ratio was approximately 50%, suggesting that the apoB/apoA-I ratio alone accounts for about one-half of the risk of an acute myocardial infarction. In addition, apolipoproteins might be superior to LDL cholesterol and HDL cholesterol in predicting coronary heart disease (CHD) and stroke (2–8). In the EPIC-Norfolk (European Prospective Investigation of Cancer, Norfolk) Study (8), the apoB/apoA-I ratio was associated with future CHD events, independent of conventional lipid measurements. In the AMORIS study (4), the apoB/apoA-I ratio was a stronger marker of CHD risk compared with the total/HDL-cholesterol ratio, LDL/HDL-cholesterol ratio, or non–HDL/HDL-cholesterol ratio. In a recent report from the Framingham Offspring Study (28), apolipoproteins were somewhat better than conventional lipid measures in predicting CHD risk, but the

Table 5 Multivariable Relations Between Childhood and Adolescence ApoB and ApoA-I and Adulthood Brachial FMD Adjusted With Other Risk Factors and Brachial Diameter in Subjects Ages 3–18 Years at Baseline

	β (95% CI)	p Value
ApoA-I*	0.47 (0.17 to 0.77)	0.003
ApoB*	−0.38 (−0.68 to −0.08)	0.02
Baseline brachial diameter	−1.25 (−1.55 to −0.95)	<0.001
Triglycerides	0.31 (−0.01 to 0.63)	0.054
Systolic blood pressure	0.06 (−0.26 to 0.38)	0.69
BMI	0.74 (0.42 to 1.06)	<0.001
Insulin	−0.06 (−0.38 to 0.26)	0.71
CRP	0.07 (−0.23 to 0.37)	0.66
Smoking	−0.06 (−0.90 to 0.78)	0.89

N = 805. Values are regression coefficients (expressed in percents) for a 1-SD change (specific for age and gender) in continuous variables and for the presence/absence of smoking.
*When apoB and apoA-I were replaced with their ratio, the ratio was significantly associated with decreased FMD (β = −0.60 [−0.90 to −0.30], p < 0.001).
Abbreviations as in Tables 1 and 2.

Table 4 Bivariate Relations Between Childhood/Adolescent Apolipoproteins and Lipids on Adulthood Brachial FMD Measured 21 Years Later

	Brachial FMD					
	Age 3–9 Yrs (n = 375)		Age 12–18 Yrs (n = 438)		All (n = 813)	
	β (95% CI)	p Value	β (95% CI)	p Value	β (95% CI)	p Value
ApoA-I	0.48 (0.02 to 0.94)	0.04	0.43 (0.01 to 0.85)	0.04	0.45 (0.13 to 0.77)	0.004
HDL cholesterol	0.03 (−0.43 to 0.49)	0.91	0.17 (−0.25 to 0.59)	0.43	0.10 (−0.22 to 0.42)	0.51
ApoB	−0.36 (−0.82 to 0.10)	0.12	−0.34 (−0.76 to 0.08)	0.11	−0.35 (−0.67 to −0.03)	0.03
LDL cholesterol	−0.09 (−0.55 to 0.37)	0.70	−0.15 (−0.57 to 0.27)	0.49	−0.13 (−0.45 to 0.19)	0.44
Non-HDL cholesterol	−0.05 (−0.51 to 0.41)	0.84	−0.11 (−0.53 to 0.31)	0.62	−0.08 (−0.40 to 0.24)	0.61
ApoB/apoA1 ratio	−0.56 (−1.02 to −0.10)	0.01	−0.55 (−0.99 to −0.11)	0.01	−0.56 (−0.88 to −0.24)	<0.001
LDL/HDL ratio	−0.09 (−0.55 to 0.37)	0.70	−0.16 (−0.58 to 0.26)	0.45	−0.13 (−0.45 to 0.19)	0.41
Non-HDL/HDL ratio	−0.04 (−0.50 to 0.42)	0.85	−0.12 (−0.56 to 0.32)	0.58	−0.09 (−0.41 to 0.23)	0.59

Beta values are regression coefficients (expressed in percents) for a 1-SD change (specific for age and gender) in continuous variables. p values are from regression analysis testing for linear relationship between risk factors and FMD.
Abbreviations as in Tables 1 and 2.

difference was statistically nonsignificant. In that study apoA-I was associated with CHD risk only in men, whereas apoB predicted CHD in both men and women (28). In the PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study (29), apolipoproteins have been associated with postmortem arterial lesions. In a recent cross-sectional analysis from the Bogalusa Heart Study (30) in 1,062 black and white subjects ages 24 to 43 years, apoB was directly related and apoA-I was indirectly related to carotid IMT. However, to our knowledge, there are no prior longitudinal data linking childhood apolipoproteins with later vascular findings. The present results are in line with earlier reports suggesting that both the concentrations of apoB and apoA-I reflect lipoprotein profile predisposing to atherosclerosis.

We found that youth apoB and apoA-I were both consistently superior to conventional LDL cholesterol and HDL cholesterol measurements in predicting abnormal carotid IMT in adulthood. This might suggest that the concentrations of apolipoproteins are better indicators of the function of serum lipoprotein particles than their cholesterol content. Apolipoproteins B and A-I serve as structural proteins for the very-low-density to low-density lipoprotein spectrum (LDL, VLDL, IDL, and lipoprotein [a]) and HDL and act as determinants of the metabolic fate of these lipoproteins (31). In general, apoB-containing lipoproteins carry lipids from liver and gut to the sites of use, whereas apoA-I–containing particles mediate the reverse cholesterol transport and bring excess cholesterol from peripheral tissues to the liver (31). As discussed by Walldius and Jungner (32), there are advantages in measuring apoB and apoA-I. Their concentrations reflect the particle numbers of their respective lipoprotein classes and thus the opposite aspects of the risk. A high apoB/apoA-I ratio indicates the number of atherogenic lipoprotein particles, which are likely to be deposited in the arterial wall. In line, we have previously shown an age-related increase in the content of apoB and a decrease in the apoA-I/apoB ratio in the lesion-free aortic intimas of children and adolescents, changes that could favor the deposition of lipids in the arteries (33).

In cross-sectional settings, HDL cholesterol concentration measured in children (18,19) and young adults (16,17,20) has been shown to associate inversely with carotid IMT. However, in the prior reports from longitudinal studies, childhood HDL cholesterol concentrations have not been predictive of adult carotid IMT (10,17). We observed that concentrations of HDL particles' major apoA-I were predictive of both adulthood carotid IMT and brachial FMD. Thus, this is the first demonstration that childhood HDL metabolism might influence the risk of developing subclinical atherosclerosis in adulthood. The HDL particles have several potential antiatherogenic properties. They promote the efflux of cholesterol from macrophages and form cells in the artery wall and have anti-inflammatory, antithrombotic, profibrinolytic, and antioxidant properties (34). The HDL particles also inhibit adhesion molecule expression and stimulate endothelial nitric oxide production (34). These functions seem to involve apoA-I, which might therefore be central to the role of HDL cholesterol in protecting against vascular disease (35).

In the present study, apolipoprotein measurements became predictive for adulthood carotid IMT only at adolescence. Similarly, we have previously reported that conventional risk factors (i.e., LDL cholesterol, blood pressure, and obesity) are associated with adulthood IMT when assessed in adolescence but not in childhood (10). These findings implicate adolescence as a critical period of time when exposure to risk factors might have measurable long-term effects on atherosclerosis.

Study limitations. Our study has limitations. We had childhood data on apolipoproteins only from a subcohort of the 2,265 subjects participating in the 21-year follow-up study in 2001. Nevertheless, the study cohort still remained substantially large with 879 subjects, and its clinical characteristics were virtually similar to those of the rest of the cohort. Apolipoprotein measurements were performed with radial immunodiffusion method in 1980 and turbidometric method in 2001. However, we have previously shown that these methods are comparable (36). Because our study cohort comprises young adults without clinical atherosclerotic diseases, we are not able to study associations between risk factors and cardiovascular events. Instead, we have used vascular ultrasound measures as indicators of an atherogenic process. Although the apoB/apoA-I ratio was a better marker than the LDL/HDL ratio in predicting abnormal carotid IMT in adulthood, the c-value for the apoB/apoA-I ratio was only 9% greater than for the LDL/HDL ratio. The absolute c-values were comparatively low and clearly lower than achieved with risk factors in adult life in predicting clinical end points (4,8). Nevertheless, our data suggest that apolipoproteins might have additional value over conventional lipid measurements in pediatric cardiovascular risk assessment. Other advantages include methodological issues and the possibility to use non-fasting blood samples (32).

Conclusions

The present data suggest that the concentrations of LDL and HDL particles' major apolipoproteins B and A-I measured in early life are related to subclinical atherosclerosis in adulthood. These findings support the role of serum lipoproteins in the pathophysiology of atherosclerosis. Apolipoproteins B and A-I measured in children and adolescents might have value in pediatric lipid risk assessment.

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