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Cardiovascular Risk

Risk Factors Associated With Aortic and Carotid Intima-Media Thickness in Adolescents and Young Adults

The Muscatine Offspring Study

Jeffrey D. Dawson, ScD,* Milan Sonka, PHD,† Mary Beth Blecha, RVT,‡ Wenjiao Lin, MS,*§ Patricia H. Davis, MD‡

Iowa City, Iowa; and Los Angeles, California

Objectives	This study sought to determine whether cardiovascular risk factors are associated with aortic intima-media thickness (aIMT) and carotid intima-media thickness (cIMT) in adolescents and young adults.
Background	Atherosclerotic lesions begin developing in youth, first in the distal abdominal aorta and later in the carotid ar- teries. Knowledge of how risk factors relate to aIMT and cIMT may help in the design of early interventions to prevent cardiovascular disease.
Methods	Participants were 635 members of the Muscatine Offspring cohort. The mean aIMT and cIMT were measured using an automated reading program.
Results	The mean (SD) values of alMT and clMT were 0.63 (0.14) and 0.49 (0.04) mm, respectively. In adolescents (age 11 to 17 years), alMT was associated with triglycerides, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and waist/hip ratio, after adjusting for age, sex, and height. In young adults (age 18 to 34 years), alMT was associated with those same 5 risk factors, plus high-density lipoprotein cholesterol and pulse pressure. In adolescents, clMT was associated with SBP, pulse pressure, heart rate, BMI, and waist/hip ratio. In young adults, clMT was associated with total cholesterol, low-density lipoprotein cholesterol, triglycerides, SBP, DBP, BMI, waist/hip ratio, and glycosylated hemoglobin. In both age groups, alMT and clMT were significantly correlated with the Pathobiological Determinants of Atherosclerosis in Youth coronary artery risk score.
Conclusions	Both aIMT and cIMT are associated with cardiovascular risk factors. Using aIMT in adolescents gives information beyond that obtained from cIMT alone. Measurement of aIMT and cIMT may help identify those at risk for pre- mature cardiovascular disease. (J Am Coll Cardiol 2009;53:2273-9) © 2009 by the American College of Cardiology Foundation

Atherosclerosis begins in childhood with the accumulation of lipid in the intima of arteries to form fatty streaks. Fatty streaks occur in the aorta in almost every child over the age of 3 years (1). Data from the PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study, an autopsy study of individuals ages 15 to 34 years, showed a propensity to develop atherosclerotic lesions within certain segments of the affected arteries. In the abdominal aorta, lesions were most likely to develop in the dorsolateral vessel just proximal to the bifurcation (2). Atherosclerotic lesions occur later in life in the coronary and carotid arteries than in the aorta, but there is a strong association between atherosclerosis in the abdominal aorta and coronary arteries (3). In the PDAY study, several risk factors were strongly associated with atherosclerotic lesions of all grades (2).

See page 2280

Early atherosclerotic lesions may also be detected in living asymptomatic individuals noninvasively by using ultrasound to measure the intima-media thickness (IMT) of the affected vessel. In older adults, this method has been widely used to assess the carotid arteries, and increased carotid intima-media thickness (cIMT) predicts the risk of developing myocardial infarction (MI), stroke, and peripheral vascular disease (4). In young and middle-aged adults, increased cIMT is associated with cardiovascular risk factors

From the Departments of *Biostatistics, †Electrical and Computer Engineering, and ‡Neurology, University of Iowa, Iowa City, Iowa; and the §Center for Health Policy Research, University of California–Los Angeles, Los Angeles, California. Dr. Sonka is a cofounder of Medical Imaging Applications, LLC. All authors received financial support from National Institutes of Health Award HL54730.

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Abbreviations and Acronyms	hig
aIMT = aortic intima-media thickness BMI = body mass index cIMT = carotid intima- media thickness DBP = diastolic blood pressure HbA1C = glycosylated	pe pe a j na ha co (8) ha
hemoglobin HDL-C = high-density lipoprotein cholesterol	eff dro en
IMT = intima-media thickness LDL-C = low-density lipoprotein cholesterol MI = myocardial infarction SBP = systolic blood pressure	ch do art me
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(5–7). In case-control studies, high-risk children who have hypertension, obesity, familial hyperlipidemia, type 1 diabetes, or a parental history of early coronary artery disease (the cases) have significantly higher cIMT compared with control subjects (8). Serial cIMT measurements have been used to monitor the effects of statin therapy in children with familial hyperlipidemia (9).

Because the atherosclerotic changes occur earlier in the abdominal aorta than in the carotid arteries, it has been suggested that measurement of aortic intimamedia thickness (aIMT) may be a more sensitive indicator in younger individuals. Detection of the earliest manifestations of atherosclero-

sis could allow risk factor modification at an even younger age, when the lesions are less advanced. McGill et al. (2) recently suggested that risk factor control in youth would be the most effective strategy for preventing heart disease in the 21st century. The American Academy of Pediatrics recommends that starting as early as 2 to 10 years of age, children with risk factors or a family history of premature heart disease or hyperlipidemia should be screened using a fasting lipid profile. This approach was recommended because there was no currently available noninvasive method of assessing atherosclerosis in children (10). In the study reported herein, we measured aIMT and cIMT in adolescents and young adults who are members of the Muscatine Study Offspring cohort to identify the relationship of concurrently measured cardiovascular risk factors with both of these ultrasound-derived IMT measures.

Methods

From 1996 to 2001, 788 members of the Muscatine Study Longitudinal Adult Cohort participated in a baseline examination of cIMT at ages 33 to 46 years (5). At the time of the examination, we obtained information about their children, enabling us to ask them to participate in the current study. We invited all eligible offspring of each contacted family, with priority given to children in the age range of 11 to 20 years. Eligibility requirements included being at least 11 years old, not pregnant, and without a medical condition that would preclude examination (2 were excluded because of traumatic neurological disorders). Data were obtained from 635 offspring. This study was approved by the Institutional Review Board of the University of Iowa, and all participants provided signed informed consent. Risk factor measurements. Height was recorded to the nearest 0.5 cm, and weight was recorded to the nearest 0.1 kg. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded for each participant after a 5-min seated rest and by measurement of pulse obliteration pressure. Glycosylated hemoglobin (HbA1C) and lipids were measured in the University of Iowa Core Pathology Laboratory. Total cholesterol and triglycerides were measured by automated colorimetric enzymatic assays using the Spectrum High Performance Diagnostic System (Abbott Laboratories, Abbott Park, Illinois). High-density lipoprotein cholesterol (HDL-C) was measured in the supernatant after dextran sulfate-MgCl2 precipitation of very-lowdensity lipoprotein cholesterol and low-density lipoprotein cholesterol (LDL-C) (Abbott Laboratories). The LDL-C was calculated as: total cholesterol - HDL-C - triglycerides/5. Smoking history was obtained using data from health questionnaires, but pack-years were calculated for young adults only because no adolescents smoked more than 1 cigarette per day. Coronary artery PDAY scores were calculated as a composite measure of cardiovascular disease risk based on age, sex, HDL-C, non-HDL-C, smoking status, blood pressure, body mass index (BMI), and HbA1C (2).

Obtaining and measuring IMT. A Technos/MPX ultrasound system (Biosound, Indianapolis, Indiana) along with a linear and a convex array transducer was used to obtain the images. Fasting for 8 h before the examination was necessary to visualize the aorta. Two images of the far wall IMT were obtained in the distal 10 mm of the abdominal aorta proximal to the iliac artery. For the carotid arteries, the near and far wall of the left and right internal, bifurcation, and common carotid arteries were imaged at 3 angles using a Plexiglas neck collar following published guidelines (11).

Aortic and carotid wall borders were identified in ultrasound B-mode image data using a globally optimal graph search border detection approach within the Carotid Analyzer 5 software system, version 5.6. (Medical Imaging Applications LLC, Coralville, Iowa) (12). For aorta images, aIMT was calculated as the mean thickness along the 10-mm length, and a mean IMT measure was then computed from the 2 images to obtain the overall aIMT value used for analysis. For carotid IMT, the mean across angles of the measures was first calculated to obtain locationspecific means, with the average of these 12 measures computed as the overall cIMT value. If measures were obtained at fewer than 12 locations, the mean of the available locations was used.

Statistical methods. Descriptive statistics were obtained for demographic, risk factor, and IMT measures. For associations between risk factors and IMT measures, mixed effects models were fit to accommodate and estimate within-family correlations, using SAS Proc Mixed Version 9.1.3 (SAS Institute Inc., Cary, North Carolina). Partial correlation coefficients (R) were obtained based on Wald scores, and partial coefficients of determination (R²) were based on likelihood ratio test (13). The Olkin method (14)



was used to compare correlation estimates. In all risk factor analyses, age and sex were included as covariates or stratification variables. Height was also included as a covariate in adolescents as a surrogate for maturity. After examining the adjusted effects of risk factors individually, a manual stepwise procedure was used to build predictive models with multiple risk factors.

Results

Data were obtained for 313 male and 322 female subjects from 365 families. There were 161 families with 1 participating offspring, 155 with 2, and 49 with 3 or more. The average (SD) age was 20.4 (5.8) years, with a range from 11 to 34 years; 228 offspring (36%) were <18 years of age. Nearly all participants (98.5%) were Caucasian, corresponding to the racial composition of the Muscatine Study Longitudinal Adult Cohort. Of the 635 offspring, 606 (95%) had ultrasound images that allowed aIMT measurement. cIMT was measured in all participants, with a mean of 11.5 walls measurable. Mean (SD) values for aIMT were 0.63 (0.14) mm and 0.61 (0.13) mm for male and female subjects, respectively. For cIMT, the mean (SD) was 0.50 (0.04) mm for male and 0.49 (0.04) mm for female subjects. Figure 1 shows box plots illustrating the sample distributions of aIMT and cIMT for adolescents (ages 11 to 17 years) and young adults (ages 18 to 34 years). Note that compared with cIMT, aIMT tends to be higher, has more variability, and increases more with age. A partial correlation of 0.35 was observed between aIMT and cIMT values. Stratifying by sex and age group, descriptive statistics for demographic, risk factor, and IMT measures were calculated (Table 1). As expected, the older offspring have higher levels of most risk factors, as well as higher IMT.

Partial correlations of individual risk factors and IMT are shown in Table 2. In adolescents, aIMT was associated with triglycerides, SBP, DBP, BMI, and waist/hip ratio. In young adults, aIMT was associated with those same 5 risk

Table 1 Demographic,	, Risk Factor, and Intima-Media Thic	kness Measures by Sex	and Age Group		
	Male	Male		Female	
	Age 11–17 Yrs (n = 127)	Age 18–34 Yrs (n = 186)	Age 11–17 Yrs (n = 101)	Age 18–34 Yrs (n = 221)	
Age (yrs)	14.8 (2.0)	24.0 (3.6)	14.7 (2.0)	24.6 (3.8)	
Height (cm)	170.9 (12.4)	179.4 (6.5)	162.3 (7.6)	164.6 (6.0)	
Weight (kg)	68.4 (22.1)	84.8 (17.3)	60.1 (15.1)	73.7 (19.3)	
Total cholesterol (mg/dl)	149.0 (27.3)	163.2 (30.7)	158.8 (24.7)	174.9 (32.4)	
LDL-C (mg/dl)	83.3 (22.2)	97.5 (27.7)	86.7 (21.4)	101.2 (29.6)	
HDL-C (mg/dl)	51.2 (11.9)	49.2 (12.6)	55.4 (10.1)	56.6 (13.4)	
Triglycerides (mg/dl)	72.7 (36.6)	82.5 (47.3)	83.5 (44.2)	85.6 (43.5)	
SBP (mm Hg)	111.1 (10.5)	117.0 (12.7)	107.2 (9.0)	110.8 (10.0)	
DBP (mm Hg)	69.1 (8.2)	76.5 (9.1)	69.0 (7.4)	72.4 (8.7)	
Pulse pressure (mm Hg)	42.0 (9.9)	40.5 (9.6)	38.2 (9.2)	38.3 (7.6)	
Heart rate (beats/min)	67.4 (10.1)	64.4 (8.7)	70.1 (10.6)	67.9 (9.5)	
BMI (kg/m ²)	23.1 (6.1)	26.3 (5.1)	22.7 (5.0)	27.2 (6.9)	
Waist/hip ratio	0.82 (0.07)	0.84 (0.07)	0.74 (0.06)	0.76 (0.07)	
HbA1C (%)	5.3 (0.7)	5.3 (0.4)	5.3 (0.3)	5.4 (0.3)	
Smoking (pack-yrs)	NA	0.66 (1.8)	NA	0.92 (2.3)	
Ever smoked	5.5%	25.8%	9.9%	23.5%	
PDAY coronary artery score	6.9 (3.2)	17.5 (5.2)	4.6 (2.2)	15.9 (4.7)	
alMT (mm)	0.57 (0.1)	0.68 (0.1)	0.55 (0.1)	0.64 (0.1)	
cIMT (mm)	0.48 (0.03)	0.52 (0.05)	0.46 (0.03)	0.50 (0.03)	

Values are mean (SD) or %.

alMT = aortic intima-media thickness; BMI = body mass index; clMT = carotid intima-media thickness; DBP = diastolic blood pressure; HbA1C = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; PDAY = Pathobiological Determinants of Atherosclerosis in Youth; SBP = systolic blood pressure.

Table 2

Partial Correlations of Risk Factors Individually Predicting alMT and cIMT, Adjusting for Age, Sex, and (in Adolescents) Height

	aIMT		cll	ИТ
Risk Factors	Age 11–17 Yrs (n = 220)	Age 18–34 Yrs (n = 386)	Age 11–17 Yrs (n = 228)	Age 18–34 Yrs (n = 407)
Total cholesterol	0.047	0.068	0.027	0.256*
LDL-C	0.007	0.089	0.081	0.217†
HDL-C	-0.151	-0.166‡	-0.148	0.053
Triglycerides	0.328*	0.200†	0.067	0.144‡
DBP	0.240†	0.155‡	0.009	0.311*
SBP	0.284*	0.250*	0.249†	0.263*
Pulse pressure	0.088	0.164‡	0.232†	0.027
Heart rate	-0.018	0.051	-0.123‡	-0.031
BMI	0.550*	0.404*	0.173‡	0.335*
Waist/hip ratio	0.517*	0.290*	0.310*	0.207*
HbA1C	0.083	0.026	0.149	0.154†
Smoking, pack-yrs	NA	0.018	NA	-0.096
Ever smoked	0.046	-0.017	-0.023	-0.088
PDAY coronary artery score	0.299*	0.130‡	0.182‡	0.247*

*p < 0.001. †p < 0.01. ‡p < 0.05.

Abbreviations as in Table 1.

factors, plus HDL-C and pulse pressure. In adolescents, cIMT was associated with SBP, pulse pressure, BMI, and waist/hip ratio. In young adults, cIMT was associated total cholesterol, LDL-C, triglycerides, SBP, DBP, BMI, waist/ hip ratio, and HbA1C. All of these associations were in the anticipated direction. There was a borderline indication (p = 0.045) of an unexpected negative association between heart rate and cIMT in adolescents. Both aIMT and cIMT were positively correlated with the PDAY coronary artery risk score. Additional analysis showed that aIMT was associated with the PDAY score in adolescents after adjusting for cIMT (R = 0.283, p < 0.001), whereas cIMT was associated with the PDAY score in young adults after adjusting for aIMT (R = 0.199, p = 0.001). Triglycerides, DBP, BMI, and waist/hip ratio had stronger correlations with aIMT than with cIMT in adolescents, whereas HDL had a stronger correlation with cIMT than with aIMT in young adults (p < 0.05).

The association analyses summarized in Table 2 assumed no interaction between risk factors and sex. This assumption was tested and found to be violated in 4 cases (p < 0.05). Table 3 shows the sex-specific associations for those 4 models. Note that in each case, the association between the risk factor and cIMT was estimated to be higher in male than in female subjects.

Finally, we examined the simultaneous effects of multiple risk factors, while still adjusting for age, sex, and (in adolescents) height (Table 4). The BMI and waist/hip ratio tended to be the predominant risk factors in multivariable models. However, blood pressure was significant in 3 of the 4 models, and cholesterol was significant in 1 model, even while including body size as a predictor. In these 4 models, within-family correlations were estimated to be higher for cIMT versus aIMT in adolescents (0.22 vs. 0.15), as well as in young adults (0.30 vs. 0.00).

Discussion

Both aIMT and cIMT were found to be associated with several cardiovascular risk factors, suggesting that both methods may be effective in detecting atherosclerosis in adolescents and young adults. In adolescents, triglycerides, DBP, BMI, and waist/hip ratio had significantly stronger associations with aIMT than with cIMT. In young adults, HDL-C had a significantly stronger association with cIMT than with aIMT. Although not significant, the correlation of PDAY scores with aIMT appeared higher than with cIMT in adolescents, with a reverse trend in young adults. Hence, stronger risk factor associations seem to be present with aIMT in adolescents, and with cIMT in young adults.

We (5,15) previously reported the association of childhood risk factors with subclinical atherosclerotic disease measured as a young or middle-aged adult in the parents of this cohort. Elevated childhood BMI was associated with coronary artery calcification in both sexes and with increased carotid IMT in women. In the Bogalusa Study (16), childhood BMI was associated with adult cIMT and persisted after adjusting for the adult BMI, although the association was reduced. The current study provides further support for the importance of childhood obesity in premature atherosclerosis.

There are only a few other studies that measured aIMT, and these were predominantly conducted in neonates and children. Using abdominal ultrasound, increased aIMT has been associated with low birth weight (17), intrauterine growth restriction (18), and maternal smoking (19) in studies of neonates. One case-control study of aIMT and cIMT has been conducted in children at high risk for atherosclerosis. Sixteen children with hypercholesterolemia and 44 with type 1 diabetes were compared with 28 healthy control subjects. There was a greater increase in aIMT than cIMT in high-risk children, although both were significantly thicker than in the control children. Age and DBP

Table 3	Sex-Specific Partial Correlations of Risk Factors Individually Predicting cIMT, Where Sex–Risk Factor Interactions Were Significant, Adjusting for Age and (in Adolescents) Height			
Partial Correlation Coefficient (R)				
Age Group	Risk Factor	Male	Female	
11-17 yrs	LDL-C (*)	0.14	-0.09	
	PDAY coronary artery score (†)	0.37‡	-0.01	
18-34 yrs	DBP (*)	0.36‡	0.17*	
	BMI (†)	0.32‡	0.25†	

Footnote symbols in parentheses indicate significance of interaction with sex. *p < 0.05. †p < 0.01. ‡p < 0.001.

Abbreviations as in Table 1

Table 4	Partial Correlation Coefficients of Risk Factors Modeled Simultaneously, Adjusting for Age, Sex, and (in Adolescents) Height				
		alMT		cIMT	
Risk Fac	tor	Age 11–17 Yrs (n = 201) R ² = 0.432	Age 18–34 Yrs (n = 308) R ² = 0.260	Age 11-17 Yrs (n = 209) $R^2 = 0.246$	Age 18–34 Yrs (n = 325) R ² = 0.454
DBP		0.16*	_	—	0.18†
SBP		_	—	0.19*	—
Total choles	terol	—	—	—	0.20†
BMI		0.37‡	0.40‡	—	0.21‡
Waist/hip ra	atio	0.36‡	_	0.26‡	_

*p < 0.05. †p < 0.01. ‡p < 0.001.

Abbreviations as in Table 1.

were associated with aIMT in the children with diabetes or hyperlipidemia (20). In a second case-control study, seropositivity to C. pneumoniae was significantly associated with aIMT but not cIMT in healthy children ages 7 to 11 years (21). Finally, in 512 healthy 13-year-old Finnish children, the mean aIMT was associated with BMI, blood pressure, C-reactive protein, and triglycerides on univariate analysis. The mean cIMT was significantly associated with blood pressure, total cholesterol, LDL-C, and male sex (22). We found that aIMT is associated with BMI, waist/hip ratio, blood pressure, and triglycerides in adolescents. In addition, aIMT is associated with HDL-C and pulse pressure in the young adult group. However, in the current study, the cIMT in those under age 18 years was associated only with blood pressure, BMI, and waist/hip ratio, and an association with total cholesterol and LDL-C was seen only in the young adults. Both the Finnish study and our study suggest that there are differences in risk factors according to the vascular bed studied. Although both aIMT and cIMT are related to blood pressure and BMI, aIMT seems to have a stronger association with risk factors associated with the metabolic syndrome, such as abdominal obesity, high triglycerides, and low HDL-C, whereas cIMT is more strongly related to total and LDL-C. The mechanisms underlying these differences are unclear.

In older populations, different imaging modalities have been used to detect more advanced atherosclerosis in the aorta, with the results compared with the measurement of carotid IMT (23,24). In a sample of the Framingham Heart Study offspring cohort (23), the correlation between aortic plaque found on cardiovascular magnetic resonance imaging and cIMT was low, but the proportion of subjects with positive results on multiple tests of subclinical atherosclerosis increased as the Framingham risk score increased. In the Rotterdam Study (24), the presence of aortic atherosclerosis as identified by calcifications on lateral abdominal radiographs was correlated with carotid IMT, but aortic atherosclerosis remained a significant predictor of subsequent MI even after adjustment for cIMT. These findings suggest that additional prognostic information may be obtained by imaging the aorta as well as the carotid artery.

There are a limited number of studies of cIMT measurement in adolescents from the general population (25-28). In 247 individuals ages 10 to 20 years, cIMT increased with height and age. In univariate analysis, cIMT was associated with BMI, SBP, pulse pressure, and smoking, whereas on multivariable analysis, only pulse pressure and BMI were significant (27). In the Stanislaus cohort (28) of 193 participants ages 10 to 24 years, cIMT was not associated with sex or BMI. In male subjects only, there was a borderline significant association with SBP. In 60 Japanese children age 5 to 14 years (26), cIMT was not associated with any cardiovascular risk factors but did increase with age. In a study of 216 children all age 9 years (25), cIMT was associated with sex, BMI, SBP, and a lower maternal energy intake during pregnancy on univariate analysis. Our study further confirms the association of blood pressure and BMI with carotid IMT in adolescents. In prior studies of young adults (ages 18 to 30 years) in the general population, cIMT was significantly associated with male sex (30), BMI (29,30), blood pressure (29,30), LDL-C (30), and smoking (31) and inversely with HDL-C (31) and alcohol intake (31). In our current study, in those over age 18 years, cIMT was associated with total cholesterol, LDL-C, triglycerides, SBP, DBP, BMI, waist/hip ratio, and HbA1C. The lack of association with smoking in our cohort may be attributable to the low number of pack-years.

One limitation of our study is that we did not examine the participants in a manner that would enable us to obtain Tanner stages of maturity, which may be a confounder in the relationship between risk factors and IMT in adolescents. However, in our analyses we adjusted for age and height as surrogates for maturity. Furthermore, we found an association between DBP and aIMT, even after additional adjustment for BMI and waist/hip ratio. This result suggests that our associations between risk factors and aIMT are not just caused by the maturation process.

Our study had other limitations as well. Our list of potential risk factors was not comprehensive, and did not include such variables as birth weight, maternal smoking, or intrauterine growth retardation. Conversely, we did evaluate a number of risk factors, so that some spurious results could have occurred because of multiple comparisons (e.g., perhaps the negative association involving heart rate). Finally, the associations we saw were based on cross-sectional data, which weakens the argument for causality. We have previous risk factor data, obtained 4 to 7 years before the current study, on 342 of our 635 participants (mostly current young adults, with mean age 24.6 years). Preliminary analysis of these data (details not shown) found that cIMT was associated with previous values of total cholesterol, LDL-C, triglycerides, DBP, SBP, BMI, and waist/hip ratio, whereas aIMT was associated with previous levels of BMI and waist/hip ratio.

One advantage of aIMT over cIMT is that the time involved in scanning and in measuring the vessels is much shorter because only 2 images are used. The procedure was well accepted by this offspring cohort. There is a low rate of missing data even though our cohort included obese participants, a group that is at high risk of early atherosclerosis. A disadvantage is that participants must be fasting and must be scanned early in the morning for images of adequate quality to be obtained.

We found that aIMT is changing more rapidly than cIMT in the age range we studied, and the observed correlation (R = 0.35) between aIMT and cIMT was moderate. These findings are consistent with either the pathological evidence that atherosclerotic lesions begin in the aorta or physiologic differences with more rapid growth of the aorta. The former hypothesis is supported by the stronger associations of aortic IMT with risk factors in adolescents compared with cIMT. As in older adults, additional prognostic information may be found by measuring aIMT in addition to cIMT in adolescents, but long-term follow-up until clinical end points occur would be needed to confirm this.

Conclusions

Our results suggest that measurement of aIMT should be considered along with cIMT as a noninvasive method for objectively detecting early atherosclerosis in adolescents. These could be important complementary tools to identify those at high risk, given the recent emphasis on prevention of atherosclerosis beginning in childhood (2,10). Further studies are needed to assess aIMT in other population-based studies of adolescents, and to see whether aIMT progression can be measured, so that the effect of interventions to retard the atherosclerotic process can be monitored.

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