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PAPER

The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study

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OBJECTIVE: Although obese children are at increased risk for coronary heart disease in later life, it is not clear if this association results from the persistence of childhood obesity into adulthood. We examined the relation of adiposity at various ages to the carotid intima-media thickness (IMT) at age 35 y.
DESIGN: Prior to the determination of IMT by B-mode ultrasound, subjects (203 men, 310 women) had, on average, six measurements of body mass index (BMI) and triceps skinfold thickness (TSF) between the ages of 4 and 35 y. Mixed regression models for longitudinal data were used to assess the relation of these characteristics to adult IMT.
RESULTS: Overall, adult IMT was associated with levels of both BMI and TSF ($P<0.001$), with the magnitudes of the associations with childhood adiposity comparable to those with adult levels of BMI and TSF. Furthermore, adult obesity modified the association between childhood adiposity and IMT: high IMT levels were seen only among overweight (BMI ≥95th percentile) children who became obese (BMI $\geq 30\,\mathrm{kg/m^2}$) adults ($P<0.01$ for linear trend). In contrast, IMT levels were not elevated among (1) overweight children who were not obese in adulthood, or among (2) thinner children who became obese adults.
CONCLUSIONS: These results emphasize the adverse, cumulative effects of childhood-onset obesity that persists into adulthood. Since many overweight children become obese adults, the prevention of childhood obesity should be emphasized.
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Keywords: atherosclerosis; carotid arteries; children; longitudinal; triceps skinfold thickness; ultrasound; intima-media thickness

Introduction

Although the clinical manifestations of coronary heart disease (CHD) are not typically seen until the sixth decade of life, several risk factors for CHD and ischemic stroke promote the development of atherosclerosis in early life. Maternal hypercholesterolemia is associated with fatty streaks among neonates,[1] and obesity is associated with fatty streaks and fibrous plaques among children.[2] Obese children are also at increased risk for coronary artery calcification [3] and CHD [4–6] in adulthood. The three-fold increase in the prevalence of childhood obesity over the last 30 y [7] will likely increase the incidence of CHD in the near future.

Persons at high risk for CHD can be identified through the measurement of carotid intima-media thickness (IMT), a marker of generalized atherosclerosis, using B-mode ultrasonography. Despite its limitations,[8,9] carotid IMT among adults is associated with obesity and other CHD risk factors,[10–14] arteriographically documented lesions,[15] and subsequent myocardial infarction and stroke.[16–19] Childhood obesity is also cross-sectionally associated with carotid IMT,[20–23] and predicts IMT in adulthood.[24] However, because obese children are likely to become obese adults,[25] this longitudinal association may reflect the importance of adult, rather then childhood, obesity.

This study examines the relative importance of childhood *vs* adult obesity as predictors of adult carotid IMT among 513

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persons. On average, subjects had six measurements of body mass index (BMI) and triceps skinfold thickness (TSF) between the ages of 4 and 35 y, with carotid IMT measured approximately 3 y after the last risk-factor examination.

Methods

Sample

Bogalusa is a semirural community in Washington Parish ($n \sim 30\,000$), Louisiana, and is 70 miles north of New Orleans. Seven cross-sectional studies of schoolchildren were conducted between 1973 and 1994 in this biracial (1/3 black) community, and four studies of adults (previously examined as children) were conducted between 1983 and 1996.[26] Several substudies have also been conducted, and more than 12 500 persons have been examined in the Bogalusa Heart Study. Most subjects have participated in multiple screenings, resulting in approximately 34 000 examinations.

Of 1420 adults (ages 20–37 y) examined in the 1995–1996 risk-factor examination, 518 underwent carotid ultrasound examinations in 1998–1999.[14] The current analyses exclude five subjects who did not participate in a risk-factor examination by age 18 y, resulting in 513 persons with 3065 measurements of weight, height, and TSF. Of these persons, 448 (87%) were initially examined in the first (1973–1974) cross-sectional examination in Bogalusa.

General examinations

All protocols were approved by appropriate institutional review boards, and informed consent was obtained from all participants. Schoolchildren were examined while wearing underpants, an examination gown, and socks; young adults wore street clothes (excluding sweaters, jackets, belts, and shoes). Height was measured to the nearest 0.1 cm with an Iowa Height Board, and weight to the nearest 0.1 kg using a balance beam metric scale.[26]

As levels of BMI (kg/m^2) vary by age among children, sex- and age-specific *Z*-scores and percentiles (P) were calculated from national US data collected from 1963 to 1994.[27,28] These *Z*-scores and P would therefore represent a child's BMI relative to those children of the same age and sex who were examined between 1963 and 1994. As suggested,[29] childhood overweight is defined as a BMI $\geq$95th P and adult obesity as a BMI ≥ 30 kg/m^2. The TSF was measured three times in succession to the nearest millimeter with Lange Skinfold Calipers.

The total cholesterol and triglycerides were determined enzymatically on an Abbott VP analyzer (Abbott Laboratories, North Chicago, IL, USA), and lipoprotein cholesterols were measured by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis.[30] Relaxed, sitting, right arm systolic, and diastolic blood pressures were measured in triplicate by trained observers with a mercury sphygmomanometer.[26]

Carotid ultrasonography

Ultrasonography was performed by trained technicians using a Toshiba Sonolayer (SSH160A, Diagnostic Ultrasound Equipment) with a 7.5 MHz linear array transducer as previously described.[14] The carotid artery was divided into three segments according to arterial geometry: (1) the distal common carotid, which is the 1 cm segment below the origin of the arterial dilatation; (2) the carotid bifurcation, which is between the arterial dilatation and the flow divider; and (3) the proximal internal carotid artery, which is the 1 cm internal carotid segment above the flow divider.

All examinations were conducted in a physician's office in Bogalusa, and subjects were examined in supine position with the head slightly extended and turned. During the examination, the sonographer concentrated on the boundary interfaces between the adventitia/media and intima/lumen. Images were excluded from the study if the artery was extremely tortuous or did not have an anatomic reference, or if advanced lesion(s) obscured the interfaces for valid IMT measurements.

Each ultrasound examination was recorded on super-VHS tapes and sent to the Division of Vascular Ultrasound Research at Wake Forest University School of Medicine for off-line analysis by a certified reader. IMT was semiautomatically measured with software that was originally developed by the California Institute of Technology/Jet Propulsion Laboratory.[31] While reviewing the ultrasound exam, the reader searched for and took measurements of the maximum IMT of the far and near walls of each carotid segment.

Few subjects were missing far-wall measurements for both sides (right and left) of the common carotid (0), carotid bifurcation (1%), or internal carotid (3%). The ultrasound end point was the mean of the maximum IMT of the far walls of the three arterial segments, bilaterally. Since the clinical relevance of the near-wall IMT has yet to be confirmed,[32] we restricted our analyses to the far-wall IMT. In addition, measurements from the near wall were much more likely to be missing and were less reproducible in the current study.

Statistical analyses

Prior to the single measurement of adult IMT, subjects had (on average) six measurements of BMI and TSF. To use these repeated longitudinal data, the analyses were somewhat similar to those for a case–control study,[33] with disease status based on the mean IMT of the far wall. Several analyses contrasted BMI and TSF levels at various ages among persons with relatively high ($\geq$90th P, 'cases') IMT, those with intermediate (10th–89th P) IMT, and those with relatively low ($<$10th P, 'controls') IMT. These IMT cutpoints were calculated within each race, sex, and age (<35 *vs* ≥ 35 y) group. Smoothed levels of BMI and TSF by age were examined within each IMT group using lowess.[34]

Longitudinal models for repeated (clustered) data were fit using SAS PROC MIXED, with a spatial power law for the covariance of the unequally spaced examinations.[35] Subjectspecific effects (intercepts and age at examination) were treated as random effects in these models. The mean BMI and TSF levels were estimated within each IMT group after adjusting for race, sex, and age (linear and higher-order terms), and statistical significance was assessed in models that treated IMT as a continuous variable. Effect modification by race, sex, age, or obesity was examined by including product terms in the regression models. Although we used the mean IMT in most analyses, the use of location-specific IMT measurements in models for clustered data (six locations per subject) yielded similar results.

Results

Levels of various characteristics are shown in Table 1. The mean carotid IMT was 736 μm, while the 90th P varied from 823 μm (white women) to 885 μm (black men). On average, subjects had six measurements of BMI and TSF before the IMT determination. The mean age at the initial risk-factor examination was 11 y, and the mean BMI *Z*-score during childhood was close to 0. The mean BMI levels at the final risk-factor examination, which occurred 3 y before the IMT determination, were ≥25 kg/m^2 in all race–sex groups, and were highest among black women (30 kg/m^2).

Figure 1 shows smoothed levels of BMI (top panels) and TSF (bottom panels) by age for persons with high (>90th P) or low (<10th P) levels of carotid IMT in adulthood. By age 10 y, BMI levels were 2–3 kg/m^2 higher among both boys and girls who subsequently had high levels of carotid IMT in adulthood than among those who had low adult levels of IMT. These BMI differences tended to increase with age, reaching ~5 kg/m^2 among men between the ages of 20 and 25 y, and ~4 kg/m^2 among women by age 15 y. Similar patterns were seen for TSF (bottom panels), but the magnitude of the difference between the two IMT groups remained fairly constant after age 10 y.

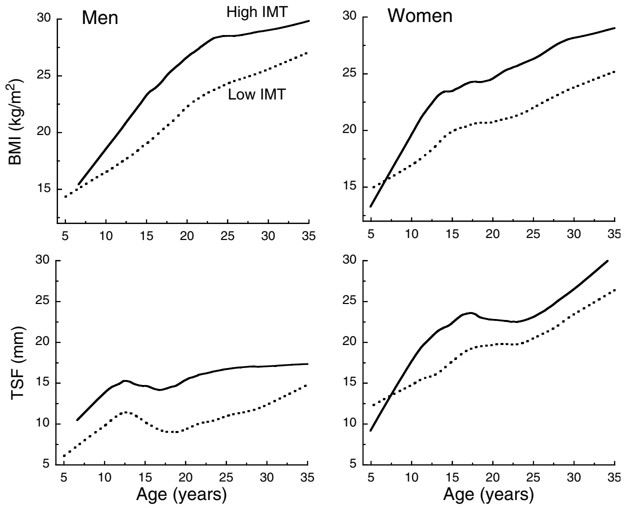

Figure 1 Smoothed levels of BMI (top panels) and TSF (bottom levels) throughout life according to adult IMI; data for men are shown on the left, and for women, on the right. High IMT levels were those ≥90th P, and low IMT levels were below the 10th P. Within each IMT group, levels of BMI and TSF were smoothed using lowess.

Longitudinal analyses, accounting for the repeated nature of the data, confirmed these findings (Table 2). Based on all measurements, adjusted mean BMI levels were 21.8 kg/m^2

Table 1 Descriptive characteristics

	Overall	*White men*	*White women*	*Black men*	*Black women*
N	513	141	223	62	87
Intima-media thickness[a]					
Age at measurement (y)	35±3[b]	35±3	35±3	36±3	35±3
Mean (μm)	736±100[c]	759±103	707±90	777±109	754±87
10th P (μm)	632	658	612	647	630
90th P (μm)	858	884	823	885	872
Number of risk factor examinations	6±2	6±2	6±2	6±2	6±2
2–4 exams (%)	24%	30%	24%	21%	16%
5–7 exams (%)	53%	50%	53%	57%	56%
≥8 exams (%)	23%	20%	23%	22%	28%
Initial risk factor examination					
Age (y)	11±3	11±3	11±3	11±3	11±3
BMI (kg/m^2)	18±4	18±4	18±4	18±4	18±4
BMI *Z*-score	0	0	0	–0.3	0.1
TSF (mm)[d]	13	11	15	9	12
Final risk factor examination					
Age (y)	33±3	33±3	32±3	33±3	32±3
BMI (kg/m^2)	28±7	28±5	27±7	27±7	30±8
TSF (mm)[d]	21	15	27	11	26

[a] Carotid IMT was assessed between the ages of 23 and 40 y, 3 y (mean) after the last risk factor examination. This end point was the mean of the maximum IMT of the far walls of the common carotid, carotid bifurcation, and internal carotid, bilaterally [b] Values are mean±s.d. [c] The mean IMTs of the three segments were 665 μm (common carotid), 859 μm (carotid bifurcation), and 683 μm (internal carotid). [d] Geometric means are shown for TSF.

(low IMT), 22.6 kg/m^2 (intermediate IMT), and 24.2 kg/m^2 (high IMT); $P = 0.002$ for the association between BMI levels and IMT. Similarly, the mean levels of the BMI *Z*-score ranged from –0.2 (low) to 0.5 (high), and the mean levels of TSF ranged from 13 to 17 mm (BMI *Z*-scores were available only for subjects <20 y of age at a risk-factor examination.) Stratified analyses suggested that IMT was more strongly associated with BMI levels among women than men, and among white subjects than black subjects, but the examined interaction (product) terms in regression models were not statistically significant. BMI *Z*-scores and TSF showed statistically significant associations with IMT in all four groups.

These associations were then examined within various age groups (Table 3). Adult IMT tended ($P = 0.053$) to be associated with BMI levels before age 11 y, and the observed associations with BMI *Z*-scores and TSF measurements before age 11 y were statistically significant at the 0.05 level. The levels of the adiposity measures in each of the four older age groups were also significantly associated with adult IMT, with the strongest associations seen among 15–18 y olds. Although the magnitudes of the correlations were relatively low (maximum $r = 0.22$), correlations among 11–14 y olds were comparable to those seen after age 25 y. Furthermore, several of the differences between the low and high IMT groups were substantial, with a 3.3 kg/m^2 difference in mean BMI levels seen among 11–14 y olds.

We then examined if childhood levels of BMI and TSF, measured at the initial risk-factor examination, were related to adult IMT independently of adult (final examination) levels of adiposity. After adjustment for race, sex, and age, a 1-s.d. unit difference in childhood BMI was associated with a 14 μm difference in adult IMT, whereas a 1-s.d. unit difference in childhood TSF was associated with a 16 μm difference ($P < 0.01$ for each association). Controlling for adult levels of both BMI and TSF reduced the magnitudes of

Table 2 Mean levels of BMI and TSF by race, sex, and IMT group

			Sex		*Race*	
Variable	*MT Group*[a]	*Overall (n = 513)*[b]	*Men (n = 203)*	*Women (n = 310)*	*Whites (n = 364)*	*Blacks (n = 149)*
BMI (kg/m^2)	Low	21.8	21.2	22.3	21.7	21.6
	Intermediate	22.6	22.3	22.8	22.3	22.5
	High	24.2**	24.4***	24.3	23.3	25.9***
BMI *Z*-score[c]	Low	−0.2	−0.4	0	−0.2	−0.2
	Intermediate	0	−0.1	0.1	0	0
	High	+0.5***	0.6**	0.5*	0.4*	0.9***
TSF[d]	Low	13	9	18	14	12
	Intermediate	14	11	18	16	13
	High	17***	14***	21*	18**	17*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ as assessed in mixed longitudinal models. [a]IMT groups are based on race-, sex-, and age-specific cutpoints: >90th P (high IMT), 10th–89th P (intermediate IMT and <10th P(low IMT). [b]Adjusted (for race, sex, and age) mean levels were calculated using linear mixed models. [c]BMI *Z*-scores are available only from examinations conducted before the subject was 20 y of age. [d]Geometric means are shown for the TSF.

Table 3 Mean levels of BMI and TSF by age and IMT group

		Age group (y)				
Variable	*IMT group*[a]	*<11 (n = 246)*	*11–14 (n = 429)*	*15 –18 (n = 396)*	*19 –24 (n = 367)*	*≥25 (n = 512)*
BMI (kg/m^2)	Low	16.6[b]	18.7	20.9	23.3	26.4
	Intermediate	16.8	19.6	21.7	24.2	26.9
	High	17.3	22.0**	24.7***	26.7***	29.2***
		($r = 0.12$)[c]	($r = 0.15$)	($r = 0.22$)	($r = 0.16$)	($r = 0.17$)
BMI *Z*-score	Low	–0.1	–0.3	–0.2	—	—
	Intermediate	–0.1	0	0	—	—
	High	+0.4*	+0.6**	+0.6***	—	—
		($r = 0.10$)	($r = 0.15$)	($r = 0.22$)		
TSF[d]	Low	11	12	13	14	16
	Intermediate	11	14	14	15	17
	High	13*	16*	17**	17*	20**
		($r = 0.12$)	($r = 0.10$)	($r = 0.17$)	($r = 0.07$)	($r = 0.10$)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ as assessed in mixed longitudinal models. [a]IMT groups are based on race-, sex-, and age-specific cutpoints: >90th P (high IMT), 10th to 89th P(intermediate IMT, and <10th P(low IMT). [b]Adjusted (for race, sex, and age) mean levels were calculated using linear mixed models. [c]Values in parentheses represent correlation between IMT and the first measurement of BMI or TSF within each age group. [d]Geometric means are shown for TSF.

Table 4 Mean IMT (μm) by childhood and adult levels of BMI and TSF

Childhood age (y)	*Childhood characteristic*[a]	*Category*	*Overall*	*Adult BMI*[a]	
				<30 kg/m^2 (n = 359)	*≥30 kg/m^2 (n = 154)*
≤18 y	BMI percentile	<50 P	735	742[b] (234)	729 (33)
		50–85 P	734	735 (96)	733 (60)
		85–94 P	746	734 (20)	759 (34)
		≥95 P	786	738 (9)	834** (27)
	TSF quartile	1 (low)	716	735 (117)	696 (11)
		2	753	750 (98)	755 (30)
		3	733	733 (89)	733 (40)
		4 (high)	759*	746 (55)	772** (73)
<11 y[c]	BMI percentile	<50 P	695	722 (117)	668 (12)
		50–85 P	696	703 (48)	688 (28)
		85–94 P	745	728 (11)	763 (15)
		≥95 P	734	727 (4)	742** (11)
	TSF quartile	1 (low)	675	719 (54)	631 (5)
		2	713	723 (55)	704 (9)
		3	703	705 (43)	700 (22)
		4 (high)	723	714 (28)	731* (30)

*$P<0.05$, **$P<0.01$ for the relation of childhood levels of BMI or TSF to adult IMT. These associations were examined in regression models that treated BMI and TSF as continuous variables, and also included adult levels of BMI and TSF as covariates. [a]The BMI level at the final risk-factor examination, along with the first childhood measurement of BMI or TSF, was used in the analyses. [b]Mean levels of adult IMT (μm) adjusted for race, sex, age. Number of persons in each cell is shown in parentheses. [c]Restricted to the 246 subjects who had a childhood examination before age 11 y.

these associations, but the association between childhood TSF and IMT remained significant ($P=0.03$).

Regression analyses also indicated that adult obesity modified the relation of IMT to childhood levels of BMI ($P=0.02$ for interaction term) and TSF ($P=0.03$), with the effect of childhood adiposity most pronounced among the 154 obese adults. As seen in analyses stratified by adult obesity (Table 4), with increasing levels of childhood BMI (<50 P to ≥95 P) the mean IMT increased by 105 (834–729) μm among obese adults, but did not vary among nonobese adults. In addition, the relation of adult obesity to IMT was most evident among persons who had a childhood BMI ≥95 P, and the highest mean IMT (834 μm) was seen among the 27 overweight children who became obese adults. Similar trends were seen with childhood levels of TSF, with the highest mean IMT (772 μm) seen among obese adults who had relatively high levels of TSF in childhood.

We also examined the relation of childhood levels of BMI and TSF to IMT among the 246 subjects who participated in a risk-factor examination before age 11 y (Table 4, bottom). Adult obesity also modified the relation of adult IMT to levels of BMI ($P=0.01$) and TSF ($P=0.02$) measured before age 11 y, with childhood adiposity significantly associated with adult IMT only among obese adults.

Discussion

There are limitations in the use of carotid IMT as an index of generalized atherosclerosis,[8,9] but IMT is correlated with coronary artery disease [15] and is predictive of myocardial infarction and stroke. [16–19] We found that carotid IMT at age 35 y was correlated with BMI and TSF levels measured throughout life. In addition, there was an interaction between childhood and adult adiposity: childhood levels of BMI and TSF were associated with carotid IMT only among obese adults. These findings emphasize the long term, cumulative effects of childhood-onset obesity.

Many of our results agree with those of other studies. Men had higher levels of IMT than did women, and as reported by D'Agostino *et al*,[36] we also found that the higher IMT levels among black subjects was largely due to the differences in the common carotid. Cross-sectional studies have also shown that carotid IMT is associated with BMI levels in childhood [20–23] and adulthood,[10–14] and weight loss has been found to slow the rate of IMT progression.[37] Furthermore, overweight children are at increased risk for CHD in adulthood,[4–6] and among boys, this association may be independent of adult weight.[5] Although the sex interaction was not statistically significant, we also found that BMI levels tended to be more strongly associated with IMT among men than women; there was, however, little difference in the magnitudes of the associations with BMI *Z*-scores and TSF.

Although the associations that we observed with carotid IMT were statistically significant, they were relatively weak. This is, in part, due to the interaction between childhood and adult adiposity. For example, the correlation between BMI levels before age 11 y and adult IMT was $r=0.12$ (Table 3), but additional analyses indicated that among obese adults, the correlation was $r=0.26$. These associations are likely to be clinically important. For example, the mean IMT of obese adults who had been overweight in childhood was ∼100 μm higher than levels among thinner persons (Table 4), and a difference of this magnitude has been associated with CHD rate ratios of 2.7 (women) and 1.6 (men).[17]

Other findings have also emphasized the long term, cumulative effects of various CHD risk factors.[38–41] For example, as compared with concurrent levels of cholesterol and blood pressure, the extent of carotid stenosis in the Framingham Heart Study was more strongly associated with time-integrated (over 34 y) and baseline levels of these characteristics.[39] The importance of the cumulative effects of long-term obesity is also emphasized by studies that have found (1) an increased CHD risk among obese adults only after long periods of follow-up[40] and (2) that both the degree and duration of obesity increase the risk for type II diabetes.[41] Our findings indicate that the duration of obesity may also influence the extent of atherosclerosis.

We considered the possibility that the relation of childhood obesity to adult IMT was mediated by other characteristics, including premature familial CHD.[42] However, in agreement with the results of other studies,[43,44] additional analyses (not shown) indicated that levels of lipids and blood pressure could not account for the observed associations. In addition, although only self-reported data were available, we found that physical activity and parental histories of myocardial infarction, stroke and diabetes could not explain the associations between obesity and IMT. It is possible, however, that the effects of childhood obesity may be mediated by other characteristics such as insulin resistance, or levels of fibrinogen or homocysteine.

A previous report [24] also found that childhood adiposity was associated with adult (ages, 33–42 y) IMT, but the observed correlations were relatively weak. The stronger associations that we observed may be due to differences in the estimation of IMT. Whereas our analyses were based on the far-wall IMT, Davis *et al*[24] calculated the mean IMT using both the near and far walls. It has been suggested that the clinical relevance of measurements from the near wall, which is difficult to visualize, is uncertain,[32] and childhood BMI was not associated with near-wall IMT in the current study. The somewhat contrasting findings of the two studies, however, may also be due to the relatively high prevalence of obesity (30%) among young adults in the current study.

Several limitations of the current study should be considered. There are errors in the measurement of IMT,[45] and we found that replicate IMT determinations made within 30 days were only moderately ($r = 0.68$, $n = 46$) correlated. However, random measurement errors would have biased the observed associations towards 0. In addition, the IMT of the carotid bifurcation and internal carotid segments could not be determined for a few subjects, and these individuals had relatively high BMI levels. However, because of the small numbers involved and the lack of any missing data for the common carotid, it is unlikely that this substantially influenced our results. We also found that as compared with TSF, adult levels of BMI were more strongly associated with IMT (Table 3). Although this difference could reflect the importance of central obesity, it may be due to the larger measurement errors associated with skinfold thicknesses.

Previous studies have shown that overweight children have elevated risk-factor levels,[46] and are at risk for severe obesity[47] and CHD[4–6] in adulthood. Although some findings[48] suggest that this increased risk may be due to the persistence of childhood obesity into adulthood, few studies have been able to examine the possible interaction between measured levels of childhood and adult adiposity. Our results suggest that childhood-onset obesity may be associated with more extensive atherosclerosis in adulthood. It is likely that the recent secular trends in childhood obesity, along with the persistence of this obesity into adulthood, will lead to higher rates of CHD in the future. The prevention and treatment of childhood obesity should be emphasized.

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