Epidemiologic studies have demonstrated that cardiovascular risk factors are identifiable in childhood and are predictive of adulthood risk for coronary artery disease (CAD). Autopsy studies in youth have also established a strong association between cardiovascular risk factors and early stages of coronary atherosclerosis. Carotid intima-media thickness (IMT) measured by ultrasound is a reliable and valid noninvasive surrogate end point to assess CAD risk as it is related to cardiovascular risk factors, the presence and extent of coronary atherosclerosis, and occurrence of coronary events. However, most studies of IMT have been performed in middle-aged and elderly populations.

In a cross-sectional study, we have previously shown a deleterious trend of increasing carotid IMT with increasing number of risk factors in asymptomatic healthy young adults. It is well recognized that cardiovascular risk factors persist or track over time. Therefore, there may be value to examine different traditional risk factors measured from childhood to adulthood for predicting carotid IMT in young adults.

Context Carotid artery intima-media thickness (IMT) is associated with cardiovascular risk factors and is recognized as an important predictive measure of clinical coronary atherosclerosis events in middle-aged and elderly populations. However, information on the association of carotid IMT in young adults with different risk factors measured in childhood, adulthood, or as a cumulative burden of each of the risk factors measured serially from childhood to adulthood is limited.

Objective To examine the association between carotid IMT in young adults and traditional cardiovascular risk factors measured since childhood.

Design, Setting, and Participants A cohort study of 486 adults aged 25 to 37 years from a semirural black and white community in Bogalusa, La (71% white, 39% men), who had at least 3 measurements of traditional risk factors since childhood, conducted between September 1973 and December 1996.

Main Outcome Measure Association of carotid IMT with risk factors, including systolic blood pressure, lipoprotein levels, and body mass index.

Results Male vs female (0.757 mm vs 0.719 mm) and black vs white (0.760 mm vs 0.723 mm) participants had increased carotid IMT (P<.001 for both). In multivariable analyses, significant predictors for being in top vs lower 3 quartiles of carotid IMT in young adults were childhood measures of low-density lipoprotein cholesterol (LDL-C) level (odds ratio [OR], 1.42, corresponding to 1-SD change specific for age, race, and sex; 95% confidence interval [CI], 1.14-1.78) and body mass index (BMI; OR, 1.25; 95% CI, 1.01-1.54); adulthood measures of LDL-C level (OR, 1.46; 95% CI, 1.16-1.82), high-density lipoprotein cholesterol (HDL-C) level (OR, 0.67; 95% CI, 0.51-0.88), and systolic blood pressure (OR, 1.36; 95% CI, 1.08-1.72); and long-term cumulative burden of LDL-C (OR, 1.58; 95% CI, 1.24-2.01) and HDL-C (OR, 0.75; 95% CI, 0.58-0.97) levels measured serially from childhood to adulthood. An increasing trend in carotid IMT across quartiles of LDL-C level measured in childhood was observed, with a mean value of 0.761 mm (95% CI, 0.743-0.780 mm) for those at the top quartile vs 0.724 mm (95% CI, 0.715-0.734 mm) for those in the lower 3 quartiles (P<.001).

Conclusions Childhood measures of LDL-C level and BMI predict carotid IMT in young adults. The prevention implications of these findings remains to be explored.
CHILDHOOD LDL-C AND ADULT VASCULAR CHANGES

factors measured serially from childhood to adulthood are limited.19

Longitudinal data from the Bogalusa Heart Study, a semirural black and white community-based investigation of cardiovascular risk factors beginning in childhood,20 provide an opportunity to examine the consistency of traditional cardiovascular risk factors measured since childhood in predicting increased carotid IMT in young adults. Such observations may aid in identifying earliest predictors of CAD risk in youth.

METHODS

Study Population
Between September 1973 and December 1996, 7 cross-sectional surveys of children aged 4 to 17 years and 5 surveys of young adults aged 18 to 38 years, who participated earlier as children and remained accessible, were conducted in the biracial (65% white, 35% black) community of Bogalusa, La. This panel design, based on repeated cross-sectional examinations conducted approximately every 3 to 4 years, resulted in serial observations from childhood to young adulthood and made it possible to measure the cumulative burden of risk factors since childhood. The participation rates of cross-sectional surveys ranged from 80% to 92% for children and 60% to 65% for young adults.

During the last 6 months of the 1995-1996 survey of young adults aged 20 to 38 years (n=1420), B-mode ultrasound examination of the carotid artery was introduced (n=516). Those who had carotid IMT measurements, 94.2% (n=486, aged 25-37 years, 71% white, 39% men) who were previously examined 3 or more times since childhood (69% examined ≥6 times) were selected for this study. The median follow-up period was 22.2 years (range, 14.0-23.3 years).

Written informed consent was obtained from parents or guardians in childhood and from the participants in adulthood. The protocol was approved by the institutional review board of the Tulane University Health Sciences Center.

Examinations
All examinations followed essentially the same protocols. Participants were instructed to fast for 12 hours before the screening, with compliance ascertained by interview on the morning of the examination. Height and weight were measured twice to within 0.1 cm and within 0.1 kg, respectively, and the mean values were used to calculate BMI as a measure of body fatness.

Replicate blood pressure measurements were obtained on the right arm of the participants in a relaxed sitting position. Arm measurements, length and circumference, were made during the examination to ensure proper cuff size. Systolic and diastolic blood pressure levels were analyzed as the first, fourth (in children), and fifth (in adults) Korotkoff phases by using mercury sphygmomanometers. Blood pressure levels were reported as the mean of 6 replicate readings, taken by each of 2 randomly assigned and trained observers. The trained observers were blinded to each other’s readings.

Serum Lipid and Lipoprotein Analyses
During 1973 to 1986, cholesterol and triglyceride levels were measured with a Technicon AutoAnalyzer II (Technicon Instrument Corp, Tarrytown, NY) according to the laboratory manual of the Lipid Research Clinics Program.21 Since 1987, these variables were determined by using an Abbott VP instrument (Abbott Laboratories, Abbott Park, Ill) by enzymatic procedures.22-23 Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program of the Centers for Disease Control and Prevention, which routinely monitors the accuracy of measurements of total cholesterol, triglyceride, and HDL-C concentrations. Measurements on Centers for Disease Control and Prevention-assigned quality control samples showed no consistent bias over time within or between surveys. Serum lipoprotein cholesterol was analyzed by using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures.24

Carotid Ultrasonography
Trained sonographers performed ultrasound examinations with a Toshiba Sonolayer SSH160A (Toshiba Medical, Tokyo, Japan), a 7.5-MHz linear array transducer, on participants in the supine position with the head slightly extended and turned to the opposite direction of the carotid artery being studied. Images were recorded at the common carotid, carotid bulb (bifurcation), and internal carotid arteries bilaterally according to previously developed protocols for the Atherosclerosis Risk in Communities Study.25 Images were recorded on S-VHS tapes and read by certified readers from the Division of Vascular Ultrasound Research (G.S.B., R.T.) by using a semiautomatic ultrasound image processing program developed by the California Institute of Technology Jet Propulsion Laboratory (Pasadena), according to strict protocols.26-28 The mean of the maximum carotid IMT readings of 3 right and 3 left far walls for common, bulb, and internal segments was used. The trained sonographers were blinded to risk factor data.

Statistical Analyses
Data analyses were performed by using SAS version 8 (SAS Institute Inc, Cary, NC). The area under the curve of serial measurements was used as a measure of cumulative risk burden from childhood to adulthood. To compute the area under the curve for each individual, quadratic growth curves of se-
rial measurements of cardiovascular risk factors from childhood to adulthood were established for each race and sex group by using a random-effects model with SAS Proc MIXED. This random-effects model allowed the intercept, linear, and nonlinear parameters to vary from individual to individual. The random coefficients represented the difference between fixed population parameters and the true values for individuals. The model allowed for repeated measurements and different numbers of unequally spaced observations across individuals.22 The most parsimonious growth curve model was considered. The higher-order terms of age were not included in the equation if they were not significant at the level of $P = .05$. Age was centered by subtracting 17.2, which was the mean value of age in the total sample. The area under the curve value was calculated by using an integral calculus formula based on the fixed and random effect parameters of the growth curve model during the follow-up period for each individual and divided by follow-up years.

Risk factors measured at the first and last examinations were used as childhood and adulthood values, respectively, and were standardized to $z$ scores specific for age, race, and sex. For area under the curve values, mean age was used for standardization. Pearson correlation coefficients were used to assess the relationship of carotid IMT to risk factors measured since childhood, with carotid IMT standardized to $z$ scores specific for age, race, and sex. To examine the risk factors measured since childhood as predictors of carotid IMT in young adults, carotid IMT $z$ scores were grouped into quartiles and logistic regression analysis was used with the upper quartile vs lower 3 quartiles as an outcome. General linear model was used to evaluate levels of carotid IMT among quartiles of the consistent predictors selected by logistic regression analyses.

RESULTS

Mean carotid IMT in young adults along with BMI, systolic blood pressure, LDL-C, HDL-C, and triglyceride levels measured from childhood to adulthood are shown in Table 1 by race and sex. As previously reported in this cohort and others,15,28,29 male vs female (0.757 mm vs 0.719 mm) and black vs white (0.760 mm vs 0.723 mm) participants had increased carotid IMT ($P < .001$ for both). The race-related and sex-related trends for other variables in Table 1 were in expected directions based on previous reports.20,30-33 With some exceptions, in particular age, race, and sex groups, black participants had higher systolic blood pressure and HDL-C level, and lower triglyceride and LDL-C levels than did white participants; men had higher systolic blood pressure, LDL-C level, and triglyceride level, and lower HDL-C level than women did; white men and black women had higher BMI than white women did; and black women had higher BMI than black men did.

Pearson correlation coefficients relating cardiovascular risk factors measured since childhood to carotid IMT in young adults are shown in Table 2. Childhood LDL-C level, BMI, and systolic blood pressure were correlated with carotid IMT in young adults, with LDL-C level showing the highest correlation. In adulthood, systolic blood pressure, LDL-C, BMI, HDL-C (inverse association), and triglyceride levels were all correlated with carotid IMT, with systolic blood pressure and LDL-C level showing the highest correlations. Risk factors measured as a cumulative burden from childhood to adulthood were all correlated with cardiovascular risk factors measured since childhood to carotid IMT.

### Table 1. Carotid IMT in Young Adults and Risk Factors Measured Since Childhood*

<table>
<thead>
<tr>
<th>Race</th>
<th>Sex</th>
<th>Carotid IMT (mm)</th>
<th>Body mass index</th>
<th>Systolic blood pressure</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Childhood</td>
<td>Adulthood</td>
<td>Childhood</td>
<td>Adulthood</td>
<td>Childhood</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>0.751 (0.087)</td>
<td>18.1 (3.5)</td>
<td>87.1 (26.0)</td>
<td>81.0 (10.0)</td>
<td>54.0 (17.6)</td>
<td>70.6 (37.3)</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>0.705 (0.089)</td>
<td>18.3 (3.7)</td>
<td>89.4 (26.0)</td>
<td>89.0 (10.0)</td>
<td>56.0 (17.6)</td>
<td>80.4 (46.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n = 212)</td>
<td>87.1 (26.0)</td>
<td>89.4 (26.0)</td>
<td>81.0 (10.0)</td>
<td>89.0 (10.0)</td>
<td>54.0 (17.6)</td>
<td>70.6 (37.3)</td>
<td></td>
</tr>
<tr>
<td>Women (n = 212)</td>
<td>89.4 (26.0)</td>
<td>81.0 (10.0)</td>
<td>89.0 (10.0)</td>
<td>54.0 (17.6)</td>
<td>70.6 (37.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SI conversion factors: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

**Bold** indicates statistically significant differences at $P < .05$.

©2003 American Medical Association. All rights reserved.
Table 3 shows results of multivariable logistic regression analyses of risk factors measured since childhood for carotid IMT in the upper quartile vs lower 3 quartiles. Childhood LDL-C level and BMI were significant risk factors for having increased carotid IMT in adulthood. In adulthood, LDL-C level, HDL-C level, and systolic blood pressure were significant risk factors. With respect to cumulative cardiovascular burdens since childhood, LDL-C and HDL-C (inversely) levels were significant risk factors. Thus, LDL-C level was the most consistent risk factor in all 3 models. A significant increasing trend in carotid IMT across LDL-C level quartiles measured since childhood further illustrates the consistency of this association (FIGURE). The mean value of carotid IMT for those participants who were in the top quartile of LDL-C level in childhood was 0.761 mm (95% CI, 0.743-0.780 mm) compared with 0.724 mm (95% CI, 0.715-0.734 mm) for those in the lower 3 quartiles ($P<.001$).

**COMMENT**

We found that carotid IMT in asymptomatic healthy young adults is associated with traditional cardiovascular risk factors measured since childhood. The LDL-C level and BMI in childhood; LDL-C, HDL-C, and systolic blood pressure in adulthood; and cumulative burden of LDL-C and HDL-C levels since childhood were in-
dependent risk factors for having increased carotid IMT in young adulthood. Among the risk factors we examined, LDL-C level in childhood, adulthood, or as a cumulative burden was the most consistent and independent predictor of carotid IMT in young adults. These observations from a community-based cohort suggest that elevated LDL-C level and BMI are important risk factors early in life and may be predictive of eventual CAD risk.

A single measurement of LDL-C level and BMI in childhood was associated with carotid IMT in young adults. Another comparable study, the Muscatine Study, did not measure LDL-C and HDL-C levels in childhood. However, childhood total cholesterol levels and BMI (in women only) were the only risk factors independently associated with carotid IMT in that study cohort of participants aged 33 to 42 years. Overall, these findings are consistent with autopsy studies that show an association of total cholesterol and LDL-C levels with the extent and severity of atherosclerosis in infants, children, and adolescents. Furthermore, histologic investigations have shown macrophage infiltration into coronary vessels even in early infancy. The development of foam cells resulting from the uptake of modified LDL by monocyte-macrophages is considered an indicator of early atherosclerosis. Excess body fat in childhood may potentiate early atherosclerosis through its adverse effect on atherogenic mediators, such as hyperinsulinemia/insulin resistance, proinflammatory cytokines, and the renin-angiotensin system.

With respect to concurrent (cross-sectional) association between risk factors and carotid IMT in young adulthood, systolic blood pressure, LDL-C, and HDL-C have emerged as significant risk factors for carotid IMT. In the Muscatine Study, although concurrent LDL-C level was an independent predictor of carotid IMT in both men and women aged 33 to 42 years, diastolic blood pressure showed an independent association only in women. In the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study, the deleterious effect of excess blood pressure on coronary atherosclerosis was observed only after 19 years of age. No such age differential was noted regarding lipoprotein variables in PDAY or other autopsy studies.

Although hypertension and dyslipidemia have been established as independent risk factors for increases in carotid IMT, hypertension-mediated changes in carotid IMT do not generally lead to atherosclerosis in the absence of dyslipidemia.

Surprisingly, the cumulative burden of risk factors since childhood did not enhance the predictive value when compared with those measured either during childhood or adulthood, although cumulative burden of risk factors vs concurrently measured risk factors in the older Framingham cohort were more predictive regarding carotid stenosis. In the Muscatine cohort, the total cholesterol load measured over time from childhood to adulthood did not predict carotid IMT in adulthood. Although no childhood data on LDL-C and HDL-C levels were available in that study, the cumulative burden of LDL-C and HDL-C levels in men only, aged from 20 to 34 years to 33 to 42 years, was found to be a significant risk factor. Also, the risk factor load or burden from childhood did not improve the predictive value compared with adult risk factors.

The causality of the observed association between LDL-C level measured in childhood and carotid IMT in young adulthood could not be established by this observational study. Tracking of LDL-C over time may play a role in this regard. Earlier findings from the Bogalusa Heart Study cohort indicated that among childhood lipoprotein variables LDL-C level was the most predictive of adult dyslipidemia, with a prevalence more among those individuals who had higher BMI in childhood. Furthermore, both the PDAY study and the Bogalusa Heart Study have shown that atherosclerosis begins in childhood and its extent and severity are associated with cardiovascular risk factors, in particular LDL-C level.

The PDAY research group pointed out that it may not be possible to conduct a controlled clinical trial to test whether lowering LDL-C level from childhood or adolescence will delay the onset of CAD in midlife. However, the Johns Hopkins Precursors Study has demonstrated the predictability of serum cholesterol level measured early in adult life at a median age of 22 years for developing CAD up to 42 years later.

In our study, the mean value of adulthood carotid IMT for those participants who were in top quartile of LDL-C level in childhood was 0.761 mm compared with 0.724 mm for those in the lower 3 quartiles. Although the observed difference in carotid IMT is relatively small in this young-adult age group, the trend is consistent with earlier studies in middle-aged (aged 45-64 years) and older adults (aged 65-86 years) showing an association between increases in LDL-C level over time or aggregation of risk factors including hypercholesterolemia and accelerated progression of carotid IMT. Those individuals who were in top quartile vs lower 3 quartiles of LDL-C level in childhood might be at an increased risk for developing clinical CAD.

In conclusion, LDL-C level measured either in childhood, adulthood, or as a cumulative burden since childhood is a consistent predictor of carotid IMT in young adults who are still too young to experience coronary events. The fact that body fatness, as measured by BMI, is also a significant childhood predictor in this regard points to the potential usefulness of LDL-C level along with BMI, both modifiable and interrelated risk factors, in CAD risk assessment and intervention in childhood. The single measurement of LDL-C level in childhood is predictive of adult changes in IMT of carotid vessels and by inference in coronary arteries.

**Author Contributions:** Study concept and design: Li, Chen, Srivivasan, Urbina, Berenson. Acquisition of data: Chen, Srivivasan, Bond, Tang, Urbina, Berenson. Analysis and interpretation of data: Li, Berenson. Drafting of the manuscript: Li, Berenson.

©2003 American Medical Association. All rights reserved.
CHILDHOOD LDL-C AND ADULT VASCULAR CHANGES

Critical revision of the manuscript for important intellectual content: Chen, Srinivasan, Bond, Tang, Urbina.

Statistical expertise: Li, Chen.

Obtained funding: Chen, Srinivasan, Berenson.

Administrative, technical, or material support: Bond, Urbina, Berenson.

Study supervision: Berenson.

Funding/Support: This study was supported by grants HL-38844 from the National Heart, Lung, and Blood Institute; AG-16592 from the National Institute on Aging; HD-043820 from the National Institute of Child Health and Human Development; and 01062618 from the American Heart Association.

Acknowledgment: The Bogalusa Heart Study is a joint effort of many investigators and staff members whose contribution is gratefully acknowledged. We especially thank the Bogalusa, La, school system and most importantly, the children and young adults who have participated in this study for many years.

REFERENCES


assessed from computerized pharmacy registries. Use of benzodiazepines was observed in more than a quarter of the participants. During follow-up, use of benzodiazepines was not related to all-cause mortality. Similar to prior studies, however, we found an increase of mortality related to fracture in individuals who used benzodiazepines. The small number of deaths from fractures may explain the absence of statistical significance.

The use of benzodiazepines is common in individuals aged 85 years or older, although benzodiazepines are indicated only for a limited number of psychiatric disorders. In practice, clinicians should weigh the risks and benefits of benzodiazepine use. However, we did not find an increased risk of mortality related to benzodiazepine use.

David J. Vinkers, MD, MA
Jacobijn Gussekloo, MD, PhD
Department of General Internal Medicine
Roos C. van der Mast, MD, PhD
Frans G. Zitman, MD, PhD
Department of Psychiatry
Rudi G. J. Westendorp, MD, PhD
Department of General Internal Medicine
Leiden University Medical Center
Leiden, the Netherlands

Acknowledgment: This study was funded by unrestricted grants from the Netherlands Organisation of Scientific Research (ZonMw) and the Ministry of Health, Welfare, and Sports.