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Association of Educational Achievement with Pulsatile Arterial Diameter Change of the Common Carotid Artery

The Atherosclerosis Risk in Communities (ARIC) Study, 1987–1992

Rebecca Din-Dzietham,[1] Duanping Liao,[2] Ana Diez-Roux,[3] F. Javier Nieto,[4] Catherine Paton,[1] George Howard,[5] Andrew Brown,[6] Mercedes Carnethon,[1] and Herman A. Tyroler[1]

Education is strongly inversely associated with common carotid artery intima-media thickness in the Atherosclerosis Risk in Communities (ARIC) Study. The authors extended the ARIC study of preclinical atherosclerosis by evaluating the cross-sectional association of education with common carotid artery elasticity. This study included 10,091 Black and White men and women aged 45–64 years who were free of clinical coronary heart disease and stroke/transient ischemic attack. Arterial elasticity was assessed by pulsatile arterial diameter change (PADC), derived from phase-locked echo-tracking. The smaller the PADC, the stiffer the artery. Education was categorized into grade school, high school without graduation, high school with graduation, vocational school, some college, and graduate/professional school. PADC was directly associated with educational attainment. The mean PADCs, adjusted for age, height, diastolic diameter, systolic blood pressure, pulse pressure (linear and squared), ethnicity, gender, and smoking status, in successively higher education strata were 402 (standard error (SE) 5), 403 (SE 4), 407 (SE 3), 413 (SE 4), 416 (SE 2), and 417 (SE 4) μm ($p = 0.007$). To the authors' knowledge, this is the first time such an association has been reported. If arterial dilation impairment precedes arterial wall thickening in the atherosclerotic process, as recent studies on endothelial dysfunction suggest, these results indicate that low socioeconomic status may be associated with early arterial pathophysiologic changes—an effect that appears to be mediated by established cardiovascular disease risk factors. *Am J Epidemiol* 2000;152:617–27.

carotid artery, common; education; elasticity

An inverse association between coronary heart disease mortality and socioeconomic status emerged in the United States approximately 30 years ago (1). Although there has subsequently been a marked decline in coronary heart disease mortality of more than 50 percent and a decline in cerebrovascular disease mortality of more than 66 percent, for the aggregate US population over the past quarter century these improvements have not been shared equally by all segments of the population. The decline in cardiovascular disease mortality has varied inversely with individuals' socioeconomic status (1, 2), as well as with the socioenvironmental characteristics of their places of residence (3, 4). This has resulted in strong, contemporary, inverse socioeconomic status gradients for both coronary heart disease mortality and morbidity (5). Recent investigations have detected equally strong inverse associations of socioeconomic status with preclinical atherosclerosis assessed in large population-based studies by noninvasive ultrasound measurements of the carotid arteries (6, 7).

Noninvasive ultrasound interrogation and measurement techniques have led to the identification and measurement of both the structural and functional components of atherosclerosis in large population-based studies and smaller clinical studies (8, 9). For example, B-mode ultrasound imaging techniques have been successfully developed to measure the thickness of the carotid arterial wall and the presence of plaque (10–12). Ultrasound echo-tracking of the carotid artery during consecutive cardiac cycles has led to the assessment of arterial function by the measurement of pulsatile arterial diameter change (PADC) (13). Measurement of arterial diameter change in relation to blood pressure parameters permits the calculation of various indices that putatively measure the elasticity of the vessel. Some of these measures consider the vessel as a hollow structure (compliance, distensibility); others evaluate the constituents of the

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; PADC, pulsatile arterial diameter change.

[1] Division of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC.
[2] Department of Health Evaluation Sciences, PSU Hershey Medical Center, Hershey, PA.
[3] Division of General Medicine, Columbia-Presbyterian Medical Center, New York, NY.
[4] Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD.
[5] Department of Public Health, Bowman Gray School of Medicine, Winston-Salem, NC.
[6] Division of Hypertension, University of Mississippi Medical Center, Jackson, MS.
Reprint requests to Dr. Herman A. Tyroler, UNC School of Public Health, Bank of America Center, Suite 306, 137 East Franklin Street, Chapel Hill, NC 27514 (e-mail: htyroler@aol.com).

arterial wall (elastic moduli) (14). Although there is controversy regarding the conceptual appropriateness of some of these indices and the methodological approaches employed in calculating them (15), these properties (or perhaps a single property) of the vessel are clearly related to age (16, 17). Degree of postmortem coronary atherosclerosis (18), hypercholesterolemia (19, 20), hyperglycemia, and diabetes mellitus (21) are directly related to decreased arterial elasticity, whereas the association with hypertension is controversial—decreased (22) or normal (23–25).

A previous Atherosclerosis Risk in Communities (ARIC) study, which found an inverse association of socioeconomic status with both prevalent coronary heart disease and preclinical atherosclerosis (measured as carotid artery intima-media wall thickness) (6), explored the roles of candidate lifestyle, biochemical, and physiologic variables as potential intervening factors on the pathways from socioeconomic status to atherosclerosis and its clinical sequellae. These factors fully explained the socioeconomic status association with preclinical atherosclerosis, but substantial residual association remained after adjustment for these factors for clinical coronary heart disease. Arterial stiffness as a precursor of clinically important atherosclerosis has been reviewed (26). The purpose of the present study was to extend this line of research to explore the relation of socioeconomic status to carotid artery stiffness in the ARIC population sample of individuals who were free of clinical coronary heart disease and cerebrovascular disease. This was done by determining whether there was an association of socioeconomic status with carotid artery diameter change during the cardiac cycle and, when such an association was detected, by ascertaining whether the established cardiovascular disease risk factors, which vary by socioeconomic status, explained the association.

MATERIALS AND METHODS

Study population

The ARIC Study is a longitudinal observational study designed to investigate the natural history and etiology of atherosclerosis and its clinical sequellae in community-based populations. The 15,792 participants in the cohort component of the ARIC Study were selected by probability sampling of eligible adults aged 45–64 years at enrollment. These persons were recruited to participate in a baseline examination (visit 1) at one of four locations, to obtain a sample of approximately 4,000 individuals per center: suburban Minneapolis, Minnesota; Forsyth County, North Carolina; Jackson, Mississippi; and Washington County, Maryland. The ethnic composition of the cohort reflected the demographic composition of the centers in Minneapolis and Washington County; African Americans were oversampled in Forsyth County and sampled exclusively in Jackson. Details on the sampling procedures used (27) and the response rates (28) for the baseline examination have been provided elsewhere. Once they were recruited and examined at visit 1, study participants were invited three more times to return for clinical assessments every 3 years. The participation rate at the second examination (visit 2) was 90.8 percent ($n = 14,348$).

When the data from visit 1 and visit 2 were pooled, 11,478 African Americans and European Americans had data permitting the calculation of elasticity of the left common carotid artery. For this study, the sample was further reduced through the following exclusions: 1) African-American examinees in Minnesota and Washington County ($n = 39$); 2) participants with aberrant data on blood pressure (i.e., systolic blood pressure <70 mmHg or pulse pressure ≤0 mmHg ($n = 6$)); 3) subjects with prevalent coronary heart disease ($n = 722$) or a history of neurologic symptoms consistent with stroke/transient ischemic attack ($n = 604$); and 4) participants with missing data on educational attainment ($n = 16$). The final study sample comprised 10,091 subjects, of which 2,404 were African Americans and 7,687 European Americans; 5,756 were female and 4,335 were male.

Participants included in this study had a more favorable profile than the total ARIC cohort with respect to the distribution of atherosclerosis risk factors (data not shown), as a result of the exclusion of subjects with symptomatic cardiovascular disease. They had higher educational achievement levels, were leaner, smoked less, and consumed less alcohol. They had slightly lower systolic and diastolic blood pressures, less atherosclerosis as measured by intima-media wall thickness of the carotid arteries, and lower levels of biologic cardiovascular disease risk factors, particularly for insulin, total cholesterol, and fibrinogen.

The clinical examinations

Details on the standardized ARIC procedures are provided elsewhere (27). In brief, participants were asked about their educational status during the prebaseline examination interview, during which they reported the highest level of schooling they had completed. The clinical examinations for visits 1 and 2 were conducted at the field centers in the four study communities. Each examination contained staff-administered interviews on demographic factors (age, gender), disease status (coronary heart disease, diabetes, hypertension, stroke, transient ischemic attack), and cardiovascular disease-related behavioral factors (current and former alcohol and cigarette consumption, current use of medications). Physical examinations (height, weight, waist and hip girth, sitting blood pressure) were performed, and fasting blood was drawn for clinical chemical analyses (glucose, insulin, high density lipoprotein cholesterol, low density lipoprotein cholesterol, total cholesterol, and triglycerides).

A noninvasive assessment of atherosclerosis was performed on participants at the baseline ARIC visit and subsequently at the follow-up visit approximately 3 years later. This protocol included B-mode ultrasound scanning of the thickness of the right and left carotid arteries, echo-tracking of arterial diameter in the left common carotid artery, and supine blood pressure measurements taken at 5-minute intervals. Because reliable echo-tracking data were not available until after the majority of participants had completed their baseline examination, in this paper we selected information from visit 2 (90 percent), and if it was not available, we used data from the baseline examination (10 per-

cent). Given the cross-sectional design of our study, the examination in which the covariates were measured was matched to that of the measurement of PADC.

Definition of study variables

The primary outcome measure of this study, pulsatile changes in the diameter of the left common carotid artery during the cardiac cycle, was obtained by echo-tracking methods during the B-mode ultrasound examination of the carotid arteries. The echoes, which correspond to the diametrically opposite media-adventitia interfaces, were identified on an oscilloscopic screen. Employing an arterial wall tracker (Autrec 4881-AWT (Autrec, Winston-Salem, North Carolina)) that used phase-locked loop techniques, centrally trained sonographers positioned electronic gates to track these two interfaces in order to precisely measure online the time interval between the arrival of these two echoes. Assuming a speed in the tissue of 1,540 m/second, the distance between these interfaces as a function of time during consecutive cardiac cycles was automatically calculated, digitized, and displayed on a strip-chart recording for immediate sonographer review (13). Repeat measures of PADC were obtained in a subset of participants at both the baseline and follow-up visits. Over this time, the mean difference in PADC between examination 1 and examination 2 was –6 μm (standard deviation 115), and the Pearson and Spearman correlation coefficients for these measurements were 0.66 and 0.66, respectively (unpublished ARIC data).

PADC was computed as the average difference between the systolic and diastolic adventitial diameters over five cardiac cycles. Supine blood pressure was measured automatically (with DINAMAP equipment (Critikon, Inc., Tampa, Florida)) from the right brachial artery at 5-minute intervals during the ultrasound examination and immediately before and after the PADC measurements were obtained (13). The smaller the PADC, the stiffer the common carotid artery.

Noninvasive ultrasonic B-mode imaging techniques were used to measure arterial wall intima-media thickness from three segments of both extracranial carotid arteries. All measurements were collected and read according to standardized protocols under stringent quality control. The scans were recorded on broadcast-quality videocassettes that were read centrally at the ARIC Ultrasound Reading Center in Winston-Salem, North Carolina (13). The intrasonographer correlation coefficient for maximal far wall thickness was 0.81, and the interobserver coefficient was 0.93 (33, 34). Intima-media thickness was defined in two ways: 1) as an overall grand mean intima-media thickness of the six carotid sites, indicative of the general atherosclerotic burden, and 2) as left common carotid artery far wall thickness, indicative of the local burden at the site of PADC measurement.

Self-reported educational achievement was ascertained during the home interview of the baseline examination, and was then collapsed into six levels: 1) grade school, 2) high school without graduation, 3) high school with graduation, 4) vocational school, 5) some college, and 6) graduate or professional school. The demographic factors included a composite variable containing ethnicity and center, to account for the sampling design and the high variability of arterial stiffness measurement across centers. This variable had five categories: African Americans in Jackson and Forsyth County and European Americans in Forsyth County, Minnesota, and Washington County. Age was used as a continuous variable. The behavioral factors included measures of lifetime cigarette and alcohol consumption. Smoking was defined in two ways: 1) as a categorical variable with three levels, never, former, and current smoking, and 2) as a continuous variable assessing lifetime cigarette use in pack-years. Self-reported alcohol consumption was converted into grams of alcohol per week for current drinkers.

The comorbidity variables included histories of coronary heart disease and stroke/transient ischemic attack, as exclusion criteria for creation of the study population, and diabetes and hypertension, for assessment of the effect of comorbid conditions on the associations between socioeconomic status and PADC. Information on prevalent coronary heart disease was derived from the electrocardiographic data or from a history of myocardial infarction, bypass surgery, or angioplasty (35). Prevalent stroke/transient ischemic attack was defined by a self-reported history of neurologic symptoms consistent with a diagnosis of these diseases (36). Non-insulin-dependent diabetes mellitus was defined as a blood glucose level ≥140 mg/dl and/or a history of diabetes or oral hypoglycemic medication use. Hypertension was defined as sitting systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication. Sitting blood pressure was measured three times on the right arm of the seated participant with a random-zero sphygmomanometer after a rest period of 5 minutes, before the ultrasound examination. The fifth phase of Korotkoff sounds was used to mark diastolic blood pressure. The mean of the last two measurements was used for blood pressure values (37).

Anthropometric characteristics included height, body mass index (weight (kg)/height $(m)^2$), and a measure of central obesity (waist:hip circumference ratio). Body mass index was derived from height measured at visit 1 and weight measured at the clinical examination from which the PADC was measured, with the subject in light clothing and no shoes (38). The waist:hip variable was the ratio of waist circumference, measured at the umbilicus, to hip girth, measured at the maximal gluteal protrusion.

For measurement of biologic factors, subjects were asked to fast for 12 hours prior to the clinical examination. Details have been reported elsewhere for blood collection (39, 40) and for centralized measurement of plasma cholesterol (41, 42), triglycerides (41, 43), high density lipoprotein cholesterol (41), calculated low density lipoprotein cholesterol (44), fibrinogen (45, 46), and glucose (47).

Statistical analyses

Summary statistics for variables that might explain the socioeconomic status-PADC associations were computed for the study population, stratified by educational level. Crude and multivariable regression analyses were then performed to assess the potential role of the traditional atherosclerosis-related demographic, behavioral, and bio-

medical factors in the relation of educational level with PADC. Tests of interaction of selected variables with education in their association with PADC were performed using the full model.

The association between PADC and education was evaluated by means of least-squares regression. Mean PADC (± standard error of the mean) by educational level was adjusted for age, height, diastolic diameter and sitting blood pressure, and linear and squared pulse pressure based on the operational definition of PADC in a previous study of the same population (13). The statistical significance for the association of PADC with education was assessed using the nominal value of $p < 0.05$. The contribution of covariates to the association between education and PADC was evaluated. These covariates were grouped on the basis of commonality of function into: 1) demographic factors—gender and ethnicity/center; 2) behavioral factors—alcohol consumption and cigarette smoking; 3) anthropometric factors—height, body mass index, and waist:hip ratio; 4) comorbidity factors—prevalent hypertension and diabetes; 5) biologic risk factors—glucose, insulin, high density lipoprotein and low density lipoprotein cholesterol, triglycerides, and fibrinogen; and 6) atherosclerosis factors—intima-media thickness. The choice of terms was based on theoretical plausibility, prior empirical findings, and their demonstrated association with both education and PADC in this study population. The explanatory effect of these classes of variables was measured by their influence on the pattern of association and the magnitude of the p value for trend upon successive addition of terms to the models.

All analyses were performed using SAS software, version 6.12 (SAS Institute, Cary, North Carolina).

RESULTS

Demographic attributes of the study population varied with educational level (table 1). Mean age decreased monotonically with increasing education. Ethnic disparities in educational achievement were marked. African Americans from Jackson comprised the largest portion of both the grade school and graduate/professional categories. The behavioral attributes of smoking and alcohol consumption also varied markedly with education. The proportion of current smokers and cumulative pack-years of smoking increased stepwise with decreasing education. In contrast, reported alcohol consumption (g/week) among the current drinkers was less in the lowest educational stratum (30 g/week) than in the highest (40 g/week).

Most of the major cardiovascular disease risk factors were inversely related to educational level (table 1). This was true for hypertension, diabetes, anthropometric measures, blood pressure, glucose, insulin, and fibrinogen. However, the direct and inverse associations of high density lipoprotein and low density lipoprotein cholesterol, respectively, with education were less remarkable.

The common carotid artery systolic and diastolic adventitial diameters and both measures of wall thickness (global intima-media thickness and left far wall thickness) monotonically decreased with increasing educational level (table 2). Crude PADC increased as educational level increased, varying by a magnitude of 24 μm between the extreme educational levels. The population distribution of PADC was slightly skewed but unimodal (data not shown).

Table 3 displays the individual point estimates of PADC for selected covariates, with adjustment for age, height, diastolic diameter, systolic blood pressure, and linear and squared pulse pressure. Persons with hypertension and persons with diabetes had smaller adjusted mean PADCs than their counterparts. The regression coefficients expressing mean differences in PADC per unit increment in each continuous covariate, adjusting for the same set of variables, were strongly statistically significant for each of the behavioral, anthropometric, hemodynamic, and biologic risk factors we found to be associated with educational level, with the exception of gender and fibrinogen. Left far wall intima-media thickness, indicative of the local atherosclerosis burden, pulse pressure, and cigarette consumption in pack-years were nonlinearly related to PADC. Based on current knowledge of atherosclerosis, the direction of association with PADC was as expected for all covariates except cigarette smoking; for smoking, PADC increased and then leveled off as cigarette pack-years increased.

In multiple regression analyses, education was associated with PADC (table 4). The positive, monotonic gradient for mean PADC associated with increasing educational level decreased from 21 μm (p for association < 0.0001) in the crude model to 15 μm (p for association = 0.007) in the model including age, height, diastolic diameter and blood pressure, linear and squared pulse pressure, gender, and ethnicity (model 2). This association was statistically explained by the obesity factors (model 5) and by study center (model 8) and was somewhat explained by biochemical factors. Age was the most potent confounder of the association of PADC with education. The presence of all factors in the model eliminated the statistical significance of the association between education and PADC, but the magnitude of the gradient was still 10 μm (model 9).

DISCUSSION

This study found that educational achievement, as a marker of socioeconomic status, was directly associated with arterial elasticity, measured as PADC of the common carotid artery, among persons who were free of clinically manifest coronary heart disease or stroke/transient ischemic attack. To our knowledge, this is the first time such an association has been reported.

There is renewed interest in studying large artery mechanical properties owing to a set of findings. First, large scale epidemiologic studies have shown that systolic blood pressure, a major correlate of arterial elasticity, is a stronger determinant than diastolic blood pressure for cardiovascular events such as left ventricular hypertrophy, stroke, carotid atherosclerosis, cardiac failure, and death (48–52). Second, disease of large vessels has been demonstrated to differ from disease of small vessels (53). Finally, recent data on patients with allograft coronary artery disease (54, 55) and patients who have undergone coronary angioplasty (56) suggest that impairment of arterial dilation may precede arterial wall thickening.

TABLE 1. Mean values and proportions for population characteristics, by educational level: Atherosclerosis Risk in Communities Study, 1987–1992

	Educational level											
	Grade school (*n* = 732 (7.3%))		High school without graduation (*n* = 1,223 (12.1%))		High school with graduation (*n* = 3,359 (33.3%))		Vocational school (*n* = 884 (8.8%))		Some college (*n* = 2,785 (27.6%))		Graduate/ professional school (*n* = 1,108 (11.0%))	
	Mean or %	SD*	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD
Demographic factors												
Age (years)	59.8	5.18	57.1	5.7	56.2	5.5	56.1	5.7	55.7	0.1	55.3	5.5
Ethnicity/center (%)												
Jackson, Mississippi (Blacks)	54.4		35.6		13.6		15.5		14.1		31.0	
Forsyth County, North Carolina (Blacks)	3.0		2.8		2.0		2.8		2.2		3.3	
Forsyth County, North Carolina (Whites)	13.3		18.1		23.4		25.0		27.2		23.8	
Minneapolis, Minnesota (Whites)	5.8		9.7		29.8		42.0		39.2		27.5	
Washington County, Maryland (Whites)	23.5		33.8		31.2		14.7		17.3		14.4	
Gender (% female)	50.1		60.9		64.9		51.5		54.1		45.2	
Behavioral factors												
Smoking status (%)												
Current smoker	29.9		28.0		22.8		21.5		19.2		13.4	
Former smoker	32.2		33.4		33.5		40.4		40.4		37.4	
Never smoker	37.9		38.6		43.7		38.1		40.4		49.2	
Cumulative smoking (pack-years)	16.9	22.8	16.1	21.4	13.9	19.5	13.4	17.8	13.3	18.3	8.9	16.0
Alcohol drinking (g/week)	29.9	103.4	26.5	80.5	34.5	91.1	41.5	101.2	41.0	81.5	40.4	71.2
Comorbidity factors												
Hypertension (%)	48.2		41.4		30.4		26.4		27.3		26.1	
Diabetes mellitus (%)	16.0		14.4		8.3		7.4		6.2		5.9	
Hemodynamic factors												
Diastolic blood pressure (mmHg)	73.3	10.5	72.7	11.0	71.6	9.8	72.0	9.6	72.0	10.2	72.3	9.7
Systolic blood pressure (mmHg)	126.6	19.4	123.2	19.5	119.9	17.8	120.3	16.6	119.0	17.4	117.9	17.0
Pulse pressure (mmHg)	53.3	15.2	50.5	14.3	48.3	13.3	48.3	12.4	47.0	12.7	45.6	12.7
Anthropometric characteristics												
Height (cm)	168.3	9.3	166.8	8.8	167.0	9.0	169.2	9.2	169.7	9.5	171.3	9.2
Body mass index (kg/m^2)†	28.4	5.5	28.2	5.1	27.2	4.9	27.2	4.6	26.9	4.6	27.0	4.4
Waist:hip ratio	0.943	0.065	0.935	0.073	0.914	0.082	0.916	0.081	0.909	0.084	0.909	0.082
Biologic risk factors												
Glucose (mg/dl)	121.6	58.3	119.0	52.4	110.6	39.8	107.4	27.4	107.4	31.7	107.1	28.7
Insulin (pmol/dl)	120.6	233.0	112.1	218.5	84.2	155.3	86.9	242.4	78.2	101.3	79.5	107.2
HDL* cholesterol (mg/dl)	50.3	17.0	48.8	16.0	51.1	17.0	49.9	16.2	51.0	17.1	51.8	17.2
LDL* cholesterol (mg/dl)	136.7	37.6	136.2	36.4	134.0	36.0	133.2	38.1	130.4	36.1	130.5	36.4
Triglycerides (mg/dl)	130.3	104.6	136.6	92.8	134.7	85.4	128.5	74.9	128.9	89.7	119.0	85.1
Total cholesterol (mg/dl)	212.4	40.1	211.9	39.7	211.9	38.1	208.8	40.9	207.0	38.8	205.9	38.4
Fibrinogen (mg/dl)	315.3	67.2	311.5	63.5	298.0	61.7	294.0	60.9	290.8	59.3	287.7	57.2

* SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein.
† Weight (kg)/height (m)^2.

Classical indices of arterial elasticity are ratios expressing the arterial strain (artery relative diameter change) in response to a given stress (blood pressure variations) (31, 32). Because of the nonlinear elastic and viscous nature of the artery wall constituents, arterial mechanical properties are strongly dependent on level of blood pressure, and therefore they vary throughout the cardiac cycle. The nonlinear characteristic of this dose-response curve has led investigators to find ways to account for blood pressure dependency. This has been achieved in several ways. The first approach expanded the study of vascular functional properties by exploring the microscopic properties of wall tissues and their structural arrangement. This approach, though the most accurate, has two disadvantages: 1) measurements are made experimentally, far from physiologic conditions, and 2) analyses of these measurements require the incorporation of a large number of parameters into the statistical models (57). Second, Gribbin et al. (58) took a mechanical approach, by blocking the arm where measurements were made in a cuff, in order to maintain a constant blood pressure. This approach was informative, but it is not practical for large scale epidemiologic studies. The third method is phenomenologic, whereby investigators derive an empirical, specific function that matches the experimental data. This approach has been widely used in clinical settings since Tardy et al.'s influential study (14). This method requires both arterial diameter and blood pressure pulsatile data. Once the best function is found, i.e., the one that yields the least residual mean square of the regression of diameter on blood pressure, classical ratio indices of elasticity are used

TABLE 2. Mean dimensions of the common carotid artery, by educational level: Atherosclerosis Risk in Communities Study, 1987–1992

	Educational level											
	Grade school (n = 732)		High school without graduation (n = 1,223)		High school with graduation (n = 3,359)		Vocational school (n = 884)		Some college (n = 2,785)		Graduate/ professional school (n = 1,108)	
	Mean	SD*	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Diastolic arterial diameter (μm)	7,935	805	7,808	847	7,598	890	7,627	868	7,603	896	7,585	874
Systolic arterial diameter (μm)	8,325	825	8,203	874	7,998	914	8,038	887	8,014	919	7,999	900
Pulsatile arterial diameter change (μm)	390	127	395	122	400	127	411	127	410	128	414	130
Intima-media thickness† (μm)	780	210	763	194	721	176	730	164	717	167	709	163
Left far wall thickness‡ (μm)	697	201	675	173	643	170	652	156	638	155	641	174
Heart rate (beats/minute)	66.6	10.6	66.8	10.6	66.6	10.0	65.7	9.5	65.9	9.9	64.2	9.4

* SD, standard deviation.
† An index of general atherosclerosis burden. Overall grand mean of six sites.
‡ An index of local burden.

wherein diameter is expressed as a function (the best) of pressure. This method has two advantages: 1) the diameter-pressure relation is modeled by nonlinear regression and 2) subgroups are compared at the same distending pressure. It is this method that first yielded the controversial result that large artery elasticity is not impaired in hypertensive persons compared with age-matched normotensive persons (23, 24). Finally, a variant of the previous method, which we term "analytical," consists of modeling the shape of the diameter-pressure association in the statistical analysis phase. This can be done either by using an index that is independent (data proven) of blood pressure, such as the arterial stiffness beta index (29, 30), or by statistically adjusting for blood pressure in such a way as to obtain a nonlinear association—e.g., blood pressure modeled as a quadratic term (13). The elasticity index that we used belongs to the latter: The absolute pulsatile adventitial diameter change is adjusted for pulse pressure modeled as a quadratic term (13). In the ARIC Study, the curve relating PADC to pulse pressure has a nonzero intercept (15). Thus, modeling strain as the outcome variable and stress as the predictor avoids the nonzero intercept assumption imposed by the use of ratio indices. However, one weakness of fitting a polynomial on a nonlinear association is the potential lack of fit at the extreme ranges of blood pressure. Nevertheless, the analytical approach is the only one that can be used when only one kind of pulsatile data is available.

Because the purpose of this investigation was to describe and quantify the relation of educational achievement level with carotid artery elasticity, it is useful to identify the causal pathways linking these two characteristics. We envision them as being at two distinct levels of organization: educational achievement as a surrogate, summary index of socioeconomic status and PADC as an index of carotid artery elasticity. Socioeconomic status reflects the command of societal resources which individuals can marshal. It encompasses material, financial, prestige, and knowledge dimensions, which singly or interactively influence health-relevant behaviors and physical, social, and psychological environmental exposures. The intervening links from the societal to the psychological to the arterial level constitute the established cardiovascular risk factors. The plausibility of this conceptualization was demonstrated in the finding of strong inverse associations of educational achievement with carotid artery intima-media thickness in the ARIC cohort—associations which were completely statistically accounted for by the established coronary heart disease risk factors (6). The associations were present among individuals who were free of clinical coronary heart disease, and the measure of wall thickness served as an indicator of preclinical atherosclerosis. It was postulated for the present study that intima-media thickness might predominantly reflect the atherotic component and that PADC might describe the sclerotic component of the pathologic complex of atherosclerosis.

The results of this study are consistent with the conceptual framework: They indicated that arterial elasticity of the common carotid artery was directly associated with education in this population, which was free of coronary heart disease and/or stroke/transient ischemic attack. This association was independent of age, height, artery size, and blood pressure and was further accounted for by ethnicity/center, obesity (body mass index, waist:hip ratio), biologic factors (glucose, insulin, lipids, fibrinogen), hypertension, and diabetes. Alcohol consumption did not contribute to this association at all, but covariates measured with error such as this one may bias estimates of their effects in either direction (59). Measures of elasticity varied markedly by study center, and statistical control for center site eliminated the overall statistical significance of the association of educational level with arterial elasticity. Data with which to assess the possibility of measurement (operator) differences across centers were not available. Furthermore, the strong association of educational level with study center raises the question of center-specific socioenvironmental influences on arterial elasticity for which statistical adjustment may be inappropriate in the context of the present investigation of socioeconomic status effects.

In this cross-sectional study, PADC was strongly and nonlinearly associated with left far wall carotid intima-media thickness, the index of local atherosclerosis burden, and was borderline and linearly associated with global carotid intima-media thickness. This finding may be explained by the site-

TABLE 3. Adjusted mean pulsatile arterial diameter change (PADC) in relation to categorical and continuous covariates (*n* = 8,428): Atherosclerosis Risk in Communities Study, 1987–1992

Covariates	PADC	Standard error	*p* value*
Mean adjusted PADC (μm) for each level of the categorical variable†			
Ethnicity/center			0.0001
Jackson, Mississippi (Blacks)	419	3	
Forsyth County, North Carolina (Blacks)	371	9	
Forsyth County, North Carolina (Whites)	398	3	
Minneapolis, Minnesota (Whites)	436	2	
Washington County, Maryland (Whites)	385	3	
Gender			0.18
Female	413	2	
Male	407	3	
Smoking status			0.0001
Current smoker	429	3	
Former smoker	408	2	
Never smoker	402	2	
Hypertension			0.0009
No	413	2	
Yes	404	3	
Diabetes mellitus			0.0003
No	412	1	
Yes	394	5	
Mean difference in PADC (μm) per unit increment in covariate†			
Linear association with PADC			
Age (years)	–6.1	0.2	0.0001
Height (cm)‡	1.8	0.2	0.0001
Body mass index (kg/m^2)§	–2.2	0.3	0.0001
Waist:hip ratio (0.01)	–1.7	0.2	0.0001
Systolic arterial diameter (mm)‡	35.9	1.6	0.0001
Diastolic arterial diameter (mm)	14.4	1.7	0.0001
Intima-media thickness (mm)	17.9	8.0	0.02
Diastolic blood pressure (mmHg)	–3.0	0.1	0.0001
Systolic blood pressure (mmHg)‡	–3.0	0.1	0.0001
Glucose (mg/dl)	–0.2	0.04	0.0001
Insulin (pmol/dl)	–0.07	0.01	0.0001
High density lipoprotein cholesterol (mg/dl)	0.3	0.08	0.0001
Low density lipoprotein cholesterol (mg/dl)	–0.2	0.02	0.06
Triglycerides (mg/dl)	–0.1	0.03	0.0001
Total cholesterol (mg/dl)	–0.1	0.03	0.0001
Fibrinogen (mg/dl)	–0.01	0.02	0.61
Alcohol drinking (g/week)	0.05	0.02	0.001
Quadratic association with PADC¶			
Left far wall thickness (mm)	166.3	28.1	0.0001
Left far wall thickness squared (mm^2)	–87.7	16.7	0.0001
Pulse pressure (mmHg)	6.0	0.5	0.0001
Pulse pressure squared (mmHg^2)	–0.030	0.004	0.0001
Cumulative smoking (pack-years)	0.9	0.1	0.0001
Cumulative smoking squared (pack-years^2)	–0.007	0.002	0.0002

* For categorical variables, *p* value for difference = 0; for continuous variables, *p* value for mean change = 0.

† Estimates were obtained from a multiple regression model, computed using PROC GLM in SAS. For the categorical variables, estimates were based on the least-squares means, and for the continuous variables, estimates were based on the type III, orthogonal sum of squares (i.e., with the variable listed as though it were entered last).

‡ Each estimate was adjusted for age (continuous variable), height (continuous variable), diastolic arterial diameter (continuous variable), linear and squared pulse pressure (continuous variable), and linear diastolic blood pressure (continuous variable). However, height was excluded from the model when the association of PADC with body mass index was evaluated; similarly, diastolic diameter was excluded for systolic diameter, and diastolic blood pressure for systolic blood pressure.

§ Weight (kg)/height (m)^2.

¶ Linear and quadratic terms were included in the model.

specificity of indices of arterial elasticity. The site-specificity results from the tubular and distributed nature of the arterial system, which leads to difference in absolute pressure along the arterial tree at the same point in time, and from the difference in the artery wall composition along this tree. As a consequence, both dimensions and pressure should ideally be measured at the same site (60). Brachial blood pressure correlates very well with intracarotid pressure, though it is higher

TABLE 4. Adjusted mean pulsatile arterial diameter change (PADC) in associative and explanatory regression modeling, by educational level: Atherosclerosis Risk in Communities Study, 1987–1992

Model	Covariates*	Educational level												Delta† mean PADC (μm)	*p* value for association‡
		Grade school (*n* = 579)		High school without graduation (*n* = 991)		High school with graduation (*n* = 2,831)		Vocational school (*n* = 768)		Some college (*n* = 2,355)		Graduate/ professional school (*n* = 939)			
		Mean	SE§	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
Crude	None	398	5	401	4	406	2	416	5	417	3	419	4	21	0.0001
Age-adjusted	Age	409	5	404	4	405	2	415	5	416	3	416	4	7	0.01
Model 1	Age, height, diastolic arterial diameter, diastolic blood pressure, pulse pressure, and pulse pressure squared	405	5	403	4	407	2	413	4	415	2	418	4	13	0.01
Model 2	Model 1 with ethnicity and gender	402	5	403	4	407	3	413	4	416	2	417	4	15	0.007
Model 3a	Model 2 with smoking	400	5	401	4	407	2	412	4	416	2	420	4	20	0.0003
Model 3b	Model 2 with alcohol consumption	402	5	403	4	407	2	412	4	416	2	418	4	16	0.008
Model 4	Model 2 with comorbidity risk factors	404	5	404	4	407	2	412	4	415	2	417	4	13	0.02
Model 6	Model 2 with biologic¶ risk factors	403	5	404	4	408	2	412	4	415	2	416	4	13	0.04
Model 7a	Model 2 with intima-media thickness	403	5	402	4	407	2	413	4	416	2	418	4	15	0.001
Model 7b	Model 2 with LFWT§ and LFWT^2	405	5	403	4	407	2	412	4	415	2	418	4	13	0.01
Model 5	Model 2 with obesity# risk factors	405	5	405	4	408	2	413	4	414	2	415	4	10	0.13
Model 8	Model 2 with study center	406	5	409	4	409	2	408	4	412	2	416	4	10	0.51
Model 9a	Model 2 with all risk factors, ethanol, and intima-media thickness	402	5	404	3	404	2	403	4	406	2	412	4	10	0.46
Model 9b	Model 2 with all risk factors, ethanol, and intima-media thickness	407	5	409	3	409	2	407	4	412	2	416	4	10	0.46

* Estimates were obtained from a multiple regression model, computed using PROC GLM in SAS. Estimates were based on the least-squares means with coefficients across classification effects proportional to observed margins. Age, height, diastolic diameter, diastolic blood pressure, pulse pressure, alcohol consumption, intima-media thickness, biologic factors, and obesity factors were included as continuous variables. Ethnicity, center, gender, smoking status, hypertension, and diabetes were included as categorical variables.

† Mean PADC (graduate/professional school) – mean PADC (grade school).

‡ *p* value for the overall association of adjusted PADC with education.

§ SE, standard error; LFWT, left far wall thickness.

¶ Biologic risk factors include glucose, insulin, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and fibrinogen.

Obesity risk factors include body mass index and waist:hip ratio.

as a result of the amplification phenomenon (60). Brachial peak systolic pressure has been reported to be higher than that in the aorta by 15–20 mmHg, and brachial pulse pressure has been reported to be higher than carotid pulse pressure by 10–15 percent (16). Another point to consider is the measurement of external rather than internal carotid arterial diameter in the ARIC Study. The external diameter is indeed subject to the compensatory enlargement; i.e., as the degree of atheroma (approximated by intima-media thickness) increases, the adventitial diameter increases up to a certain point where it starts to level off, resulting in a constant and then decreased internal diameter (61). Thus, the association between PADC and any risk factor should ideally be investigated with the data stratified by intima-media thickness.

All cardiovascular risk factors except smoking impacted on PADC in the expected direction. Participants who reported being current smokers had the largest PADCs. Similarly, PADC increased with pack-years of cigarette smoking in a nonlinear manner. This association was not statistically explained by blood pressure or by viscosity factors evaluated by fibrinogen and/or hematocrit measurement. Smoking increases blood viscosity, which has been reported to increase shear stress, which in turn stimulates nitric oxide production (62). Most of the literature reports a harmful effect of cigarette smoking on both arterial dilatation and thickening (63), though recent experimental or very small scale in vivo studies have reported endothelium-dependent dilatation of the carotid artery (64) and pulmonary circulation (65) and an increase of cerebral blood flow by acute smoking (66). Smokers had a positive, though not significant, distensibility coefficient in the SMART (Second Manifestations of Arterial Disease) Study (67). Smoking has also been found to be associated with greater interadventitial and internal diameters of the common carotid artery, a finding possibly related to elastin damage or production of functionally deficient elastin (68). The structural or functional decrease in elastin, however, cannot explain the increase in PADC among the smokers.

In conclusion, low educational achievement is associated with increased stiffness of the common carotid artery. If arterial dilation/elasticity impairment precedes arterial wall thickening in the atherosclerotic process, as recent studies on endothelial dysfunction suggest, these results indicate that low socioeconomic status may lead to early pathophysiologic changes of large arteries. This effect appears to be mediated by known risk factors such as obesity, lipids, glucose, fibrinogen, hypertension, diabetes, and carotid thickening—cardiovascular risk factors which are more prevalent among individuals of lower socioeconomic status. The findings of the ARIC Study suggest a continuous direct relation of increasing arterial elasticity with increasing education.

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