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Risk Factors for Progression of Common Carotid Atherosclerosis: The Atherosclerosis Risk in Communities Study, 1987–1998

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Intima-media thickness of the common carotid arteries is a marker of atherosclerosis and has been shown to be associated with prevalent and incident coronary heart disease and with coronary heart disease risk factors. The authors examined the association of baseline risk factors or change in risk factors with change in intima-media thickness over follow-up (1987–1998) in the Atherosclerosis Risk in Communities (ARIC) population-based cohort (baseline: age 45–64 years, n = 15,792). Subjects were members of households sampled in four areas of the United States. Either not adjusting for baseline intima-media thickness or doing so with correction for its measurement error resulted in statistically significant associations of change in intima-media thickness with baseline diabetes, current smoking, high density lipoprotein cholesterol, pulse pressure, white blood cell count, and fibrinogen. The associations were of a similar order of magnitude as anticipated from the authors' cross-sectional findings. Statistically significant associations were found between change in intima-media thickness and change in low density lipoprotein cholesterol and triglycerides and with onset of diabetes and hypertension. In summary, established risk factors for coronary heart disease are associated with the rate of change of subclinical atherosclerosis. *Am J Epidemiol* 2002;155:38–47.

atherosclerosis; carotid arteries; cohort studies; risk factors

Intima-media thickness (IMT) of the carotid arteries, as measured by B-mode ultrasound, is a marker of atherosclerosis as assessed pathologically (1–3) and serves as a marker of generalized atherosclerosis, having been shown to be positively associated with prevalent (4) and incident (5–8) coronary heart disease and with incident stroke (8, 9). Carotid IMT is associated with risk factors for atherosclerotic disease (10–25), and lipid-lowering therapy slows progression of carotid IMT (26–31). Although opinions are mixed concerning whether carotid IMT is a good marker for coronary atherosclerosis (27, 32–36), trials showing that lowering lipid levels slows IMT progression concomitantly have reported reduced progression of coronary atherosclerosis (26, 27) or fewer cardiovascular events (28–31) in the active treatment group. In a population study of middle-aged adults, we examined the relation between change in carotid IMT over 9 years of follow-up (1987–1998) and baseline risk factors or change in those risk factors.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; HDL, high density lipoprotein; IMT, intima-media thickness; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; LDL, low density lipoprotein; Lp(a), lipoprotein(a).

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MATERIALS AND METHODS

Cohort examination

At baseline, the Atherosclerosis Risk in Communities (ARIC) Study population consisted of household members aged 45–64 years sampled in selected Minneapolis suburbs of Minnesota; Forsyth County, North Carolina; Washington County, Maryland; and Jackson, Mississippi (the latter sample from Black residents only). Details of the sampling procedures have been described elsewhere (37, 38). The 15,792 participants underwent a baseline examination in 1987–1989 and follow-up examinations in 1990–1992, 1993–1995, and 1996–1998. The response rate for the baseline sample was 60 percent. Of those subjects still alive at the time of the scheduled follow-up visits, response rates were 93, 86, and 81 percent, respectively.

Carotid ultrasound measurements for the ARIC Study were based on the technique validated by Pignoli et al. (1). The scanning protocol was common to the four field centers (39, 40), and a Biosound 2000II-SA ultrasound system and standardized central reading were used (41, 42). Sonographers were centrally trained and certified and were recertified annually to assure standardization across the ARIC Study centers. Far-wall IMT was estimated for 1-cm lengths of the carotid bifurcation and the internal and common carotid arteries (right and left) as the mean of as many 1-mm-apart intima-to-media distances as were available. Maximum likelihood techniques for linear models, with the SAS PROC MIXED procedure (43), were used to adjust for carotid site-specific reader differences and temporal trends in the measurement process over each 3-year examination cycle.

Participants were asked to fast for 12 hours before the clinical examination. Details have already been reported for blood collection (44, 45) and for centralized measurement of plasma lipoproteins (46–49), lipoprotein(a) (Lp(a)) (50), fibrinogen (51–54), and glucose (55). Counts of white blood cells were made by using Coulter counters in local hospital laboratories. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dl, a nonfasting level of ≥200 mg/dl, a self-reported physician diagnosis, or pharmacologic treatment.

Methods have been described previously for determining body mass index (kg/m^2) (56) and systolic and diastolic blood pressures (57). Pulse pressure was defined as the difference between systolic blood pressure and diastolic blood pressure. Hypertension was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg or self-reported use of antihypertensive medications. Participants were defined from interview as current, former, or never smokers.

Reliability coefficients are available from repeat measurements 1–2 weeks apart for low density lipoprotein (LDL) cholesterol (0.91), high density lipoprotein (HDL) cholesterol (0.94), triglycerides (0.85), Lp(a) (0.95) (58), and fibrinogen (0.72) (59). We did not have a direct reliability estimate for body mass index, but since those for weight and height are 0.99, we used an estimate of 0.95. Unpublished results from 190 ARIC participants who made repeat visits 1–2 weeks apart during the second follow-up examination period gave reliability coefficients of 0.75 for systolic blood pressure, 0.62 for diastolic blood pressure, and 0.66 for pulse pressure.

For measurements at ARIC follow-up examinations, the same protocols as those implemented for the baseline examination were used. After 1 year of the second follow-up examination, the ultrasound scanning and reading equipment was replaced. There were too few overlap samples on the same persons to enable reliable, direct comparison of old and new equipment, so statistical modeling of information from all ARIC participants scanned was used to detect equipment differences. Sex- and race-specific differences were found between the old and new equipment regarding common carotid IMT and also between examinations; however, after adjustment for age, sex, race, and body mass index, these differences did not vary by level of IMT and were subtracted from each participant's IMT measurement to remove this source of variation. Because differences between the old and new equipment varied by IMT level for the internal carotid artery and bifurcation, these sites were not included in this analysis.

All ARIC Study participants were invited to undergo an ultrasound scan at baseline and at the first follow-up examination; subjects at the Jackson and the Forsyth County centers were also invited at the second follow-up. At the Minnesota and the Washington County centers, a randomly chosen half of the participants was invited to have the scan at the second follow-up, and the remaining half was invited at the third follow-up. At the third follow-up in Jackson and in Forsyth County, all participants who had not had a second follow-up scan were to be scanned, as were all Blacks at the Forsyth County center and a randomly chosen half of other participants.

Statistical methods

Age- and field-center-adjusted cross-sectional relations between baseline common carotid IMT and baseline risk factors were obtained from linear regression by using the SAS PROC MIXED procedure (43). The association between change in IMT and baseline risk factors or changes in risk factors was modeled with side-specific differences between follow-up and baseline IMT measurements as a function of side-specific baseline IMT and either baseline risk factors or change in risk factors. The dependent change variable was multivariate, with as many as three follow-up examinations for two sides each, although we included in the analysis all participants for whom at least one value of the six possible was not missing. The independent variables for the analysis of baseline risk factors were baseline age, field center indicators, baseline side-specific IMT, and baseline risk factor, which were all multiplied by time since the baseline visit. To analyze change in risk-factor levels, time-dependent risk-factor change variables were added to the baseline model (including the baseline level of the risk factor being considered). (Follow-up measurements of fibrinogen, Lp(a), and white blood cells were not available for such analysis.) Results from all models were side specific, but this paper presents only those results averaged over the two sides, with appropriate standard errors. All models were race and sex specific.

Estimates for determining the reliability of the IMT measurements were available from 278 pairs of scans performed up to a year apart during the second follow-up examination. The estimated correlation between scans performed at different visits by different sonographers, read by different readers, was 0.56 for mean right common carotid IMT and 0.55 for the left. This coefficient is also interpretable as 1 minus the measurement variance divided by the total variance. The between-side measurement covariance divided by total covariance was –0.12. This latter ratio and the correlations between repeat scans were used in model fitting to correct for measurement error in baseline IMT. An analysis of 39 repeat scans performed 7–10 days apart during the ARIC baseline examination (60) yielded a similar correlation of 0.53 for measurement of the left and right sides combined.

All analyses were corrected for measurement error in baseline IMT and continuous risk factors except white blood cell count, assuming random intraindividual plus measurement process variation in these variables. A regression calibration method (61) was used to correct for multivariate measurement error. First, we transformed the dependent IMT change variables to make their measurement errors uncorrelated with that of baseline IMT. After we transformed observed values of independent variables measured with error to estimated true values (expected values, conditional on the observed values of all other variables in the model, i.e., conditional Stein estimators (62)), models were fit with the SAS PROC MIXED procedure (43). (Note that transformation of the dependent change variables reduces to simply calculating change in IMT from the transformed observed values of baseline IMT.) Measurement error in determining baseline IMT was assumed to be statistically independent of that obtained by using other independent variables and from using IMT in later examinations. In this paper, "measurement error" is used to encompass all short-term within-person variability of a factor; thus, for IMT, this measurement error was derived mainly from variability in the measurement process, whereas for plasma lipoproteins or blood pressure, there was also a large component of within-person biologic variability.

This paper presents point estimates of sex-race-specific associations with two-sided p values. For a summary test over all race/sex categories of the age-/center-adjusted associations, we computed a weighted average of the category-specific predicted differences, with "weights" equal to the proportions of the entire sample in the four race/sex strata. The resulting test statistic, this weighted average divided by its standard error, is approximately standard normal under the null hypothesis of no association.

RESULTS

We excluded non-Whites in Minneapolis and in Washington County as well as participants in Forsyth County who were neither Black nor White (altogether 103 persons). In addition, 3,045 persons without a baseline measurement of common carotid IMT on at least one side plus, for one follow-up visit, IMT data for the same side as the available baseline data were excluded, leaving 12,644 persons (table 1). For 70 percent of the participants, data for both sides were available. For 54 percent of Blacks and 69 percent of Whites, common carotid artery data were available for at least three examinations. Of those persons who participated in at least three examinations, the figures were 74 and 79 percent, respectively.

Table 2 gives baseline means and proportions to describe the ARIC Study population. Baseline mean common carotid IMT, averaged over the left and right sides, was 629, 688, 587, and 655 μm for Black women, Black men, White women, and White men, respectively. The average annual change in mean common carotid IMT was 8.4, 7.4, 9.1, and 8.6 μm, respectively; within each group, the mean ±2 standard deviation intervals of annual change were approximately –60 to 80 μm/year. For comparison, the cross-sectional average 1-year age difference in baseline mean common carotid IMT, adjusted for most of the variables shown in table 3, was 7.3, 10.0, 7.0, and 8.0 μm, respectively.

At baseline, the cross-sectional associations (table 3) between common carotid IMT and the risk factors, corrected for measurement error in the risk factors measured on a continuous scale, were strong, consistent, and in the directions expected.

The "univariate" associations (table 4) between baseline risk factors and change in IMT, adjusted for baseline IMT, age, and field center only, were consistent in direction (positive) across the four race-sex groups for diabetes, current smoking, systolic blood pressure, pulse pressure, and white blood cell count and overall statistically significant, except for systolic blood pressure. The association for Lp(a) was consistently negative, contrary to expectation, but not quite statistically significant. The associations for fibrinogen, HDL cholesterol, and triglycerides were consistently in the expected direction for Whites and overall were statistically significant for the first two factors, in the range of 0.6–2.9 μm/year for the given difference in risk-factor level. Other risk factors showed less consistency and no statistical significance. Associations were generally smaller for Blacks, with statistically significant race differences for women regarding HDL cholesterol, white blood cell count, and fibrinogen and no statistically significant race difference for men. Sex differences by race were statistically significant only for Blacks for fibrinogen. There were 56 tests of race or sex differences, with 2.8 expected to be statistically significant "by chance" in the absence of any differences; we found four such "significant" differences.

TABLE 1. Availability of data (no.) on common carotid intima-media thickness for race-gender subgroups, visit 1–4 change analysis, Atherosclerosis Risk in Communities Study, 1987–1998

Status	Black women	Black men	White women	White men	Total
Baseline participants	2,609	1,602	6,050	5,428	15,689
Eligible* for inclusion	1,868	1,128	5,149	4,499	12,644
Both sides eligible*	1,267	857	3,636	3,104	8,864
No missing common carotid data at any of the four examinations	180	143	280	214	817

* Subjects who had a baseline (visit 1) measurement of intima-media thickness and at least one follow-up measurement on the same side.

TABLE 2. Percentage or mean (standard deviation) of baseline potential risk factors, Atherosclerosis Risk in Communities Study, 1987–1998

Risk factor	Black women (n = 1,868)	Black men (n = 1,128)	White women (n = 5,149)	White men (n = 4,499)
Hypertension	54	52	25	27
Use of antihypertensive medication	43	32	18	19
Diabetes	18	16	7	9
Current smoker	24	37	24	24
Former smoker	18	33	25	48
Right common carotid artery IMT* (μm)	637 (169)	689 (185)	585 (142)	641 (185)
Left common carotid artery IMT (μm)	620 (161)	687 (195)	590 (148)	668 (181)
HDL* cholesterol (mg/dl)	58.6 (17.8)	50.5 (16.6)	58.1 (17.2)	43.1 (12.4)
LDL* cholesterol (mg/dl)	137.2 (42.7)	138.1 (42.3)	135.3 (39.6)	140.1 (35.2)
Triglycerides (mg/dl)	104.3 (62.3)	112.5 (66.3)	125.4 (82.8)	144.8 (94.6)
Lipoprotein(a) (μg/dl)	171.3 (130.0)	146.8 (112.9)	86.9 (98.0)	74.7 (87.5)
Body mass index (kg/m^2)	30.0 (6.1)	27.3 (4.5)	26.2 (5.1)	27.2 (3.8)
Systolic blood pressure (mmHg)	126.4 (20.3)	128.8 (20.3)	116.6 (17.5)	119.9 (16.0)
Diastolic blood pressure (mmHg)	77.7 (11.3)	82.3 (12.2)	69.7 (9.7)	73.4 (9.9)
Pulse pressure (mmHg)	48.7 (15.8)	46.6 (14.4)	46.9 (13.2)	46.5 (12.0)
White blood cell count (1,000/mm^3)	5.6 (2.0)	5.5 (1.9)	6.1 (1.8)	6.4 (1.9)
Fibrinogen (mg/dl)	323.9 (69.6)	302.0 (65.8)	297.5 (59.7)	292.4 (61.8)

* IMT, intima-media thickness; HDL, high density lipoprotein; LDL, low density lipoprotein.

To model the joint effects of the risk factors (table 5) to avoid problems introduced by multicolinearity between independent variables, 1) systolic blood pressure, diastolic blood pressure, and pulse pressure were not included because of their redundancy with hypertension; and 2) triglycerides were not included because of their close association with HDL cholesterol. The overall statistically significant univariate associations shown in table 4 persisted in this multivariable analysis for diabetes and current smoking, and Lp(a) became statistically significant; however, the magnitude of the associations between change in IMT and risk factors was somewhat smaller in this analysis of joint effects.

Among the univariate associations between change in IMT and change in individual risk factors (table 6), with adjustment for age, field center, baseline IMT, and baseline level of the risk factor, change in triglycerides was positively associated in all four race-sex groups, was overall statistically significant, and was stronger for Blacks than for Whites. For incident diabetics compared with those participants who remained nondiabetic, mean annual IMT increases were generally consistent and statistically significantly larger by 3–5 μm/year. For incident hypertensives compared with those who remained nonhypertensive, IMT increases were generally consistent and statistically significantly larger by 3–10 μm/year. For men, a 1 standard deviation higher mean annual increase in HDL cholesterol was associated with an approximately 1.6-μm smaller mean annual IMT change ($p = 0.02$ for Whites and $p = 0.09$ for Blacks). For women, no significant association was found with change in HDL cholesterol. Recently quitting smoking was associated with a statistically significant decrease in IMT compared with remaining a smoker, but for White women only.

DISCUSSION

Main findings

In our findings and in earlier publications (16–20, 63–66), the ARIC Study has shown that carotid IMT is related cross-sectionally to hypertension (or blood pressure), diabetes, smoking, body mass index, and white blood cell count and to plasma HDL cholesterol, LDL cholesterol, Lp(a), and fibrinogen levels. When table 4 is compared with table 3, change in common carotid IMT seems to be related less strongly than is baseline IMT to these baseline risk factors, but this perception is misleading. Baseline IMT is the sum of IMT at birth plus change accumulated over 45–65 years; thus, for example, if the difference between diabetics and nondiabetics predicted in this study (table 4) for White men is projected over just 20 years to 20×2.94 μm = 58.8 μm, the size of the difference is similar to the cross-sectional difference of 44.7 μm (table 3). We do not mean to imply that our results over 9 years of follow-up can be directly extrapolated to 20 years but that this time factor must be considered when orders of magnitude between the cross-sectional and longitudinal findings are compared. Alternatively considered, cross-sectionally, the difference between diabetic and nondiabetic White men is 6.8 percent (44.7/655) of the mean IMT. Longitudinally, the diabetic/nondiabetic

TABLE 3. Predicted difference* in baseline mean common carotid artery wall thickness (μm) for a given difference† in baseline risk factors, Atherosclerosis Risk in Communities Study, 1987–1998

Risk factor	Black women		Black men		White women		White men	
	Difference	*p* value	Difference	*p* value	Difference	*p* value	Difference	*p* value
Hypertension (yes vs. no)	42.3	<0.01	37.3	<0.01	38.3	<0.01	37.5	<0.01
Diabetes (yes vs. no)	65.7	<0.01	54.1	<0.01	49.2	<0.01	44.7	<0.01
Current smoker vs. never smoked	12.7	0.11	19.2	0.09	15.3	<0.01	44.8	<0.01
Former smoker vs. never smoked	14.3	0.10	32.5	0.01	4.5	0.27	32.4	<0.01
Body mass index‡ (5.37 kg/m^2)	12.2	<0.01	35.2	<0.01	16.0	<0.01	26.3	<0.01
HDL§ cholesterol‡ (17.1 mg/dl)	−21.9	<0.01	−7.5	0.14	−14.6	<0.01	−18.4	<0.01
LDL§ cholesterol‡ (39.4 mg/dl)	16.7	<0.01	18.7	<0.01	16.9	<0.01	21.7	<0.01
Triglycerides‡ (90.5 mg/dl)	15.9	0.01	−1.3	0.86	15.4	<0.01	11.5	<0.01
Lipoprotein(a)‡ (107.7 μg/dl)	6.0	0.04	6.7	0.16	4.5	0.02	3.7	0.21
Systolic blood pressure‡,¶ (19.0 mmHg)	37.5	<0.01	26.1	<0.01	30.9	<0.01	35.8	<0.01
Diastolic blood pressure‡,¶ (11.3 mmHg)	12.6	0.03	18.2	0.02	11.3	<0.01	7.5	0.10
Pulse pressure‡,¶ (13.9 mmHg)	47.3	<0.01	31.1	<0.01	42.1	<0.01	51.6	<0.01
White blood cell count (2,009/mm^3)	9.0	0.01	6.9	0.17	9.6	<0.01	14.0	<0.01
Fibrinogen‡ (65.5 mg/dl)	13.5	<0.01	7.2	0.28	12.1	<0.01	18.4	<0.01

* Adjusted for age and field center.
† Values in parentheses are standard deviations for continuous variables.
‡ Corrected for measurement error in this analyte.
§ HDL, high density lipoprotein; LDL, low density lipoprotein.
¶ Also adjusted for use of antihypertensive medication.

TABLE 4. "Univariate" effects* of risk factors measured at baseline on mean annual change in intima-media thickness (μm) during follow-up, for a given difference† in a specific risk factor, Atherosclerosis Risk in Communities Study, 1987–1998

Risk factor	Black women		Black men		White women		White men		Overall	
	Difference	*p* value	Difference	*p* value	Difference	*p* value	Difference	*p* value	Difference	*p* value‡
Hypertension (yes vs. no)	−0.05	0.96	−0.40	0.76	0.53	0.39	0.13	0.87	0.22	0.60
Diabetes (yes vs. no)	1.47	0.27	0.20	0.91	1.69	0.12	2.94	0.02	1.97	<0.01
Current smoker vs. never smoked	0.79	0.47	1.58	0.30	2.33	<0.01	1.72	0.07	1.82	<0.01
Former smoker vs. never smoked	0.58	0.63	−0.76	0.63	1.09	0.08	−0.04	0.96	0.45	0.31
Body mass index§ (5.37 kg/m^2)	0.07	0.86	−0.26	0.76	0.27	0.38	0.80	0.13	0.38	0.12
HDL¶ cholesterol§ (17.1 mg/dl)	0.17	0.72	0.14	0.84	−0.99	<0.01	−0.63	0.21	−0.59	0.01
LDL¶ cholesterol§ (39.4 mg/dl)	−0.36	0.46	−0.01	0.98	0.20	0.49	0.55	0.20	0.22	0.29
Triglycerides§ (90.5 mg/dl)	−0.42	0.59	0.68	0.52	0.81	0.03	0.27	0.51	0.43	0.10
Lipoprotein(a)§ (107.7 μg/dl)	−0.23	0.57	−0.15	0.81	−0.62	0.04	−0.23	0.59	−0.38	0.07
Systolic blood pressure§,# (19.0 mmHg)	0.20	0.77	1.05	0.24	0.27	0.54	0.37	0.55	0.36	0.24
Diastolic blood pressure§,# (11.3 mmHg)	−0.23	0.77	0.69	0.52	−0.50	0.36	−0.44	0.52	−0.33	0.36
Pulse pressure§,# (13.9 mmHg)	0.46	0.56	1.22	0.27	0.83	0.13	0.92	0.22	0.84	0.03
White blood cell count (2,009/mm^3)	0.05	0.91	0.28	0.68	1.19	<0.01	0.64	0.08	0.75	<0.01
Fibrinogen§ (65.5 mg/dl)	−1.10	0.08	1.61	0.07	0.63	0.11	1.10	0.03	0.63	0.02

* Predicted differences were estimated by using a site-specific repeated-measures model; adjusted for age, field center, and baseline intima-media thickness and corrected for measurement error.
† Values in parentheses are standard deviations for continuous variables.
‡ Test of the association across all groups.
§ Corrected for measurement error in this analyte.
¶ HDL, high density lipoprotein; LDL, low density lipoprotein.
# Also adjusted for use of antihypertensive medication.

TABLE 5. "Multivariable" effects* of risk factors measured at baseline on mean annual change in intima-media thickness (mm) during follow-up, for a given difference† in a specific risk factor in the presence of other risk factors shown in the table, Atherosclerosis Risk in Communities Study, 1987–1998

Risk factor	Black women		Black men		White women		White men		Overall	
	Difference	*p* value	Difference	*p* value	Difference	*p* value	Difference	*p* value	Difference	*p* value‡
Hypertension (yes vs. no)	0.65	0.51	−0.18	0.89	0.35	0.58	0.01	0.99	0.23	0.60
Diabetes (yes vs. no)	2.13	0.13	0.51	0.79	0.92	0.42	2.89	0.02	1.76	0.01
Current smoker vs. never smoked	1.22	0.31	0.68	0.70	1.21	0.09	0.53	0.63	0.92	0.09
Former smoker vs. never smoked	1.03	0.41	0.22	0.89	1.20	0.05	−0.22	0.78	0.58	0.19
Body mass index§ (5.37 kg/m^2)	0.17	0.72	−0.59	0.54	0.08	0.81	0.40	0.50	0.15	0.59
HDL¶ cholesterol§ (17.1 mg/dl)	0.03	0.96	0.35	0.65	−0.80	0.01	−0.07	0.90	−0.31	0.22
LDL¶ cholesterol§ (39.4 mg/dl)	−0.23	0.67	0.32	0.66	−0.07	0.84	0.68	0.12	0.21	0.36
Lipoprotein(a)§ (107.7 μg/dl)	0.06	0.90	−0.36	0.59	−0.67	0.03	−0.39	0.39	−0.43	0.05
White blood cell count (2,009/mm^3)	0.08	0.88	−0.22	0.77	0.78	0.02	0.18	0.68	0.38	0.11
Fibrinogen§ (65.5 mg/dl)	−1.05	0.17	2.05	0.05	0.00	0.99	0.69	0.26	0.28	0.39

* Predicted differences were estimated by using a site-specific repeated-measures model; adjusted for all risk factors shown in the table, age, field center, and baseline intima-media thickness and corrected for measurement error.
† Values in parentheses are standard deviations for continuous variables.
‡ Test of the association across all groups.
§ Corrected for measurement error in this analyte.
¶ HDL, high density lipoprotein; LDL, low density lipoprotein.

difference is 34.2 percent (2.94/8.6) of the mean annual change in IMT.

Another distinction between cross-sectional and longitudinal analysis of IMT is precision. Even if baseline IMT is not included as an independent variable in the regression model, so that bias related to measurement error is not an issue, the within-person variance of the dependent variable is twice as large for IMT change as for baseline IMT and is a much larger percentage of the mean of the dependent variable. This difference in variances is reflected in the *t*-test statistics for the estimated beta coefficients for risk factors, which are expected to be much larger for the cross-sectional analysis than for the change analysis.

In spite of expecting less precision in the analysis of change, we demonstrated a statistically significant overall association between IMT progression in the common carotid artery and baseline risk-factor levels for diabetes, current smoking, HDL cholesterol, pulse pressure, white blood cell count, and fibrinogen. Each of these associations was in the same direction as the cross-sectional associations observed at the baseline examination and was consistent with the putative atherogenic effect of the risk factor.

TABLE 6. "Univariate" effects* of the change in risk factors over the follow-up period† on mean annual change in intima-media thickness (μm) over the follow-up period, for a given difference‡ in change in a specific risk factor, Atherosclerosis Risk in Communities Study, 1987–1998

Risk factor	Black women		Black men		White women		White men		Overall	
	Difference	*p* value	Difference	*p* value	Difference	*p* value	Difference	*p* value	Difference	*p* value§
HDL¶ cholesterol# (3.42 mg/dl per year)	0.06	0.92	−1.68	0.09	0.35	0.36	−1.57	0.02	−0.56	0.08
LDL¶ cholesterol# (10.4 mg/dl per year)	−0.01	0.99	1.76	0.15	0.50	0.27	0.99	0.16	0.71	0.04
Triglycerides# (24.8 mg/dl per year)	2.13	0.08	2.13	0.13	0.64	0.21	0.64	0.29	0.99	0.01
Incident diabetes vs. remaining nondiabetic**,††	4.76	0.07	5.24	0.16	3.95	<0.01	3.43	0.01	4.00	<0.01
Incident hypertension vs. remaining normotensive**,††	2.78	0.25	10.34	<0.01	3.92	<0.01	2.97	0.01	3.99	<0.01
Quitting smoking vs. remaining a smoker**,‡‡	1.89	0.61	4.10	0.39	−3.50	<0.01	−1.40	0.30	−1.28	0.17

* Predicted differences were estimated by using a site-specific repeated-measures model; adjusted for age, field center, and baseline intima-media thickness and corrected for measurement error.
† Change from baseline.
‡ Values in parentheses are standard deviations of mean annual change.
§ Test of the association across all groups.
¶ HDL, high density lipoprotein; LDL, low density lipoprotein.
# Corrected for measurement error in this analyte.
** For changed status by first follow-up visit.
†† Assuming once diabetic or hypertensive, always so.
‡‡ Excluding persons with a change in smoking status other than current smoker to quitter.

However, we failed to detect any statistically significant association between IMT progression and baseline values of hypertension, former smoking, body mass index, LDL cholesterol, or systolic or diastolic blood pressure.

Our findings on the associations between IMT change and *changes* in risk factors over the same period were somewhat stronger than the associations with baseline risk factors. Increases in LDL cholesterol and triglyceride levels were positively associated with IMT increases in both sexes, except for LDL cholesterol for Black women, and increases in HDL cholesterol were negatively associated with IMT increases in men. New onset of diabetes and hypertension was also positively associated with an IMT increase. Associations with change in smoking habits were more complex, possibly because of confounding by reason for quitting smoking.

Partially because of limited precision when measuring IMT change, associations examined in this study were generally less statistically significant compared with our cross-sectional analyses reported in table 3, but differences in the results of these analytical approaches may have clinical relevance. Those factors that emerge as most important in the IMT change analysis may represent the current determinants of atherosclerosis progression rather than those long-persisting factors that affect such progression over a lifetime. Diabetes stands out in the current analysis ($p < 0.01$ in tables 5 and 6) perhaps because, for most diabetic patients in the ARIC Study, their disease is of adult onset and may have had a substantial influence on atherogenesis relatively recently in the participant's life. In lipid-lowering trials, changes in LDL cholesterol are known to affect coronary heart disease incidence rather quickly, and they clearly affected progression of carotid IMT in our study (table 6). Finally, the rather strong associations of IMT change with white blood cell count and fibrinogen (table 4) may indicate that inflammation is an effective, relatively current atherogenic stimulus.

Adjustment for measurement error in independent variables

When the association between change in an outcome variable and baseline levels of other factors is estimated, there is frequently a dispute about whether to adjust for the baseline level of the outcome variable. If baseline IMT is associated with both change in IMT and the baseline risk factor, then baseline IMT is a potential confounder of the IMT change/risk-factor association. Indeed, for linear models such as those presented here, it can be shown that the difference between risk-factor coefficients, adjusting versus not adjusting for baseline IMT, is the product of two terms: 1) the coefficient of the risk factor in a cross-sectional model of baseline IMT and 2) the coefficient of baseline IMT in the model of IMT change as a function of the risk factor and baseline IMT. Thus, if no cross-sectional relation exists between a risk factor and baseline IMT, or no relation exists between baseline IMT and change in IMT, then there is no need for or impact on adjusting for baseline IMT when studying the relation between change in IMT and the risk factor.

In the ARIC Study, the cross-sectional risk-factor coefficient was generally large (table 3), but the effect of baseline IMT on IMT change was in the range of –0.02 to 0.02/year^{-1} over different races, sexes, risk factors, and sides, with a mean of –0.003/year^{-1} over these groups. Since this effect was so small, generally there was no great need to adjust for baseline IMT. However, if one did adjust for baseline IMT, a huge bias would result from not correcting for measurement error. As an example, for White women, the difference in IMT change for those with versus without baseline diabetes was 1.69 μm/year ($p = 0.12$) when adjusting for baseline IMT and correcting for measurement error (table 4), 1.85 μm/year ($p = 0.11$) when not adjusting for baseline IMT, and 5.02 μm/year ($p < 0.01$) when adjusting for baseline IMT but not correcting for measurement error.

Correction for measurement error in our models obviously depends on the amount of measurement error assumed in the correction methods. Our estimates of 0.55–0.56 for correlation between repeat measurements (adjusted for reader effect and drift) during the third ARIC examination were quite precise (length of 95 percent confidence intervals, <0.017), but it is still an assumption that these estimates apply to all ARIC examinations from 1987 to 1996. There is some support for this finding, in that our estimate of 0.53 for reliability during the first examination on measurements *not* adjusted for reader effect and drift was nearly identical to the estimate of 0.51 from the third examination on similarly unadjusted data. The high precision of our estimate for the size of the measurement error also implies that our not accounting for variability of the error estimate in the error correction procedure had little effect.

Comparison with previous studies

Comparison with similar studies of IMT progression is difficult; most such studies were clinical trials (26–30, 67–73) with high-risk persons, and several of the published observational studies (74–78) did adjust for baseline IMT but did not correct for measurement error, exactly the situation that we have demonstrated produces large bias. Ultrasound methodology varied in these studies, but measurement error was sizable in each (60). Only one known published observational study of IMT did not adjust for baseline IMT. In an early paper reporting on a subgroup of 100 men aged 42–60 years in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) (79) who had a repeat ultrasound examination after 2 years, six IMT measurements on the far walls of the common carotid arteries at the sites of greatest IMT were averaged. The mean annual increase in IMT was 60 μm, 6–10 times as large as that observed in the ARIC Study. HDL cholesterol, hypertension, blood pressure, and body mass index did not enter their multivariable regression model for IMT change, while age, LDL cholesterol, number of years of cigarette smoking, leukocyte count, and platelet aggregability did. The associations in the KIHD were 20–30 times larger than those in the ARIC Study, but it is not clear why they were so much larger. The reasons might be related to higher rates of cardiovascular disease in Finland or the fact that IMT was mea-

sured at the point of maximum IMT, whereas the ARIC Study measurements were means over a 1-cm segment.

Our estimates of progression, in the 6.5–10.1 μm/year range, are comparable to the estimate in another observational study (80) of 5.2 μm/year over 10 years for the common carotid artery or to a cross-sectional difference of 8.5–11.5 μm/year in ARIC baseline data by year of age (81). They are also at the low end of progression of 6–50 μm/year observed in placebo groups of trials (28, 29, 67, 69–71). Over 10 years, the KIHD estimate of a mean annual change of 60 μm would result in a change of 600 μm, close to mean IMT itself and so perhaps not tenable.

In a methodology paper (82), Cardiovascular Health Study statisticians presented an example similar to the change models considered here, except that they were restricted to two time points; did not account for time between measurements; considered IMT univariately; and did not adjust for measurement error in risk factors. Their reliability coefficient for the common carotid artery was 0.67. When they adjusted for baseline IMT *and* corrected for measurement error, the results were quite similar to those with no adjustment for baseline IMT; however, when they adjusted for baseline IMT and did *not* correct for measurement error, the results were greatly different. Although we used a different approach to adjust for measurement error in baseline IMT and also adjusted for measurement error in risk factors, our findings share with the Cardiovascular Health Study the property that risk-factor associations, after control for baseline IMT, were substantially attenuated after adjustment for measurement error, and the associations approximated those observed with no adjustment for baseline IMT. Nevertheless, our results differed from those reported in the Cardiovascular Health Study in that we were able to detect several statistically significant associations between change in IMT and baseline risk factors or risk factor changes, even after correcting for measurement errors.

Summary

We found common carotid IMT to progress at 6.5–10.1 μm/year, similar to findings from other studies. When we either did not adjust for baseline IMT at all or, if we did so, also corrected for measurement error, we found many of the expected associations between baseline (or change in) risk factors and change in IMT. With one exception, these associations were in the expected directions and were of a similar order of magnitude as those anticipated from our cross-sectional findings. IMT level reflects lifetime risk-factor exposure, and changes over 3–9 years were relatively small. This factor and the relatively higher variance of the dependent variable "change in IMT" as compared with the variance of "cross-sectional IMT" led to less precision in our estimates of the size of associations, but this finding should not be interpreted to mean that risk factors for coronary heart disease are not important in relation to a change in IMT. Clinical trial data show that lowering cholesterol levels, raising HDL cholesterol levels, controlling hypertension, and quitting smoking can lower the rate of atherosclerosis progression (26–30) or incident coronary heart disease (28–31). Yet, our data do indicate the importance of advances in procedures or technology to increase the precision of measuring IMT change.

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