

Association of Coronary Heart Disease Incidence with Carotid Arterial Wall Thickness and Major Risk Factors: The Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993

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Few studies have determined whether greater carotid artery intima-media thickness (IMT) in asymptomatic individuals is associated prospectively with increased risk of coronary heart disease (CHD). In the Atherosclerosis Risk in Communities Study, carotid IMT, an index of generalized atherosclerosis, was defined as the mean of IMT measurements at six sites of the carotid arteries using B-mode ultrasound. The authors assessed its relation to CHD incidence over 4–7 years of follow-up (1987–1993) in four US communities (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland) from samples of 7,289 women and 5,552 men aged 45–64 years who were free of clinical CHD at baseline. There were 96 incident events for women and 194 for men. In sex-specific Cox proportional hazards models adjusted only for age, race, and center, the hazard rate ratio comparing extreme mean IMT (≥ 1 mm) to not extreme (< 1 mm) was 5.07 for women (95% confidence interval 3.08–8.36) and 1.85 for men (95% confidence interval 1.28–2.69). The relation was graded (monotonic), and models with cubic splines indicated significant nonlinearity. The strength of the association was reduced by including major CHD risk factors, but remained elevated at higher IMT. Up to 1 mm mean IMT, women had lower adjusted annual event rates than did men, but above 1 mm their event rate was closer to that of men. Thus, mean carotid IMT is a noninvasive predictor of future CHD incidence. *Am J Epidemiol* 1997;146:483–94.

carotid arteries; coronary disease; incidence; risk factors; ultrasonography

Smoking, hypertension, diabetes, fibrinogen, and low density lipoprotein cholesterol (LDL cholesterol) are widely accepted coronary heart disease (CHD) risk factors. These risk factors are also associated with preclinical atherosclerosis, generally measured as the intima-media thickness (IMT) of carotid arteries by B-mode ultrasound (1–16). Although researchers accept that IMT serves as a marker of generalized atherosclerosis and association of IMT with prevalent

CHD has been documented (17), only one population study has addressed the association of IMT with incident CHD (18, 19). We examined this relation over 4–7 years of follow-up (1987–1993) in a population study of middle-aged adults. We hypothesized a positive association between mean IMT and CHD incidence, which would be attenuated but still positive after controlling for known CHD risk factors. Further, we hypothesized that the mean IMT relative risk would be constant over the range of baseline mean IMT.

MATERIALS AND METHODS

Cohort examination

The Atherosclerosis Risk in Communities (ARIC) Study population consists of members of samples of households aged 45–64 years in selected Minneapolis suburbs, 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 (20, 21).

The ultrasound measurements of the ARIC Study are based on the technique validated by Pignoli et al.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; ECG, electrocardiogram; HDL cholesterol, high density lipoprotein cholesterol; HRR, hazard rate ratio; IMT, intima-media thickness; LDL cholesterol, low density lipoprotein cholesterol.

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(22), using a scanning protocol common to the four field centers (23, 24), and standardized central reading of scans (25, 26). Analyses are based on mean IMT of the far wall for 1-cm lengths of the carotid bifurcation and the internal carotid and common carotid, right and left. Maximum likelihood techniques for linear models were used to adjust for site-specific reader differences and downward measurement drifts in mean IMT over the baseline visit. Since only 13 percent of the sample had a mean IMT at all six carotid sites, the means at the missing sites were imputed from sex- and race-specific multivariate linear models of mean IMT as a function of age, body mass index, and arterial depth, fit by maximal likelihood methods using BMDP 5V (27). On average, 2.3 sites per person were imputed. The means at the six sites were combined in an unweighted average to produce an overall mean IMT or averaged over left and right sides at each of the bifurcation, internal carotid, or common carotid. Estimates of correlations between scans at different visits 7–10 days apart, performed by different sonographers and read by different readers, were 0.77, 0.73, and 0.70 for mean far wall IMT at the bifurcation, internal carotid, and common carotid, respectively (28). For categorical analysis of mean IMT, both sex-specific percentiles and overall absolute cutpoints were used. The cutpoints 0.6, 0.7, 0.8, and 1.0 mm were chosen a priori for simplicity, starting with 0.6 mm because there were few incident CHD events below that level and stopping with 1.0 mm because there were few persons in the sample (6 percent) above that level.

Participants were asked to fast for 12 hours before the clinical examination. Details have been reported for blood collection (29, 30) and for centralized measurement of plasma total cholesterol (31, 32), triglycerides (31, 33), high density lipoprotein cholesterol (HDL cholesterol) (31), calculated LDL cholesterol (34), fibrinogen (35–38), and glucose (39). Estimates of intraindividual variability in blood measurements have been reported (40–42). Prevalent diabetes mellitus was defined as a fasting glucose level of 140 mg/dl or more, a nonfasting level of 200 mg/dl or more, self-reported physician diagnosis of diabetes, or pharmacologic treatment for diabetes.

Methods have been reported for ascertainment of body mass index (kg/m^2) (43), systolic and diastolic blood pressures (44), and a sport activity index (45). Prevalent hypertension was defined as systolic pressure of 140 mmHg or more, diastolic pressure of 90 mmHg or more, or self-reported use of antihypertensive medications. Participants were defined as current, ex-, or never smokers, and pack-years of cigarettes smoked and current ethanol consumption (g/week) were estimated from interview. Prevalent CHD at

baseline was defined, for exclusion, as a self-reported history of a physician-diagnosed heart attack, evidence of a prior myocardial infarction by electrocardiogram (ECG) (46) or self-report of cardiovascular surgery or coronary angioplasty. Angina pectoris by the Rose questionnaire (47) was used for exclusion of 500 persons in one ancillary analysis.

Ascertainment of incident events

CHD incidence in the ARIC Study was ascertained by contacting participants annually, by identifying hospitalizations and deaths during the previous year, and by surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential cardiovascular events (20, 48, 49).

Trained abstractors obtained hospital charts, recorded presenting symptoms and cardiac enzymes, and photocopied up to three ECGs for each person. The ECGs were coded using Minnesota Code (46, 50) at the University of Minnesota. Out-of-hospital deaths were investigated by means of death certificates and, in most cases, by an interview with one or more next-of-kin (98 percent) and a questionnaire filled out by the patient's physician (85 percent). Coroner reports or autopsy reports, when available, were obtained. Details on quality assurance for ascertainment and classification of events have been presented (48, 49).

A CHD incident event was defined as a validated definite or probable hospitalized myocardial infarction, a definite CHD death, or an unrecognized myocardial infarction (definition 1). The criteria for definite or probable hospitalized myocardial infarction were based on combinations of chest pain symptoms, ECG changes, and cardiac enzyme levels (48, 49). The criteria for definite fatal CHD were based on chest pain symptoms, underlying cause of death from the death certificate, and other associated hospital information or medical history (48, 49). A Morbidity and Mortality Classification Committee reviewed potential clinical events and determined the final diagnosis. Unrecognized incident myocardial infarction was determined by the ARIC Study visit 2 follow-up examination ECG (a major Q wave or a minor Q wave with ischemic ST-T changes or an myocardial infarction by computerized NOVACODE criteria (51), confirmed by a side-by-side visual comparison of baseline and follow-up ECGs).

A second definition for incident CHD events was also considered, which included all events by definition 1, plus CHD-related revascularizations (*International Classification of Diseases*, Ninth Revision, hospital discharge code 36.0, 36.1, or 36.2). All results

presented are based on definition 1 except as otherwise noted.

Data analysis

Sex-specific proportions or mean baseline values of mean IMT and risk factors were compared for those who developed CHD versus those who did not, adjusted for age, center, and race by analysis of covariance (or similar method for proportions, using logistic regression (52)). Sex-specific, adjusted CHD incidence rates, by level of the categorical risk factor variables, were computed from Poisson regression (52, 53).

For participants with a clinical CHD event, follow-up was between baseline clinic visit and date of the first CHD event. The date of unrecognized myocardial infarction was assigned as the midpoint between baseline and visit 2. For participants with no event, follow-up continued until date of death or until December 31, 1993, or for the 39 participants lost to follow-up, until the date of last contact.

Cox proportional hazards models were used to estimate the ratios of hazard rates of incident CHD between different levels of a baseline risk factor or mean IMT, adjusting for potential confounding factors, under the assumption that those ratios were constant over the period of the follow-up, given fixed values of other variables in the model (54). The assumption of proportional hazards was checked by testing differences between hazard rate ratios (HRR) estimated for each of three periods of follow-up (first year, next 2 years, and afterwards).

HRRs were first estimated from a model for each risk factor or mean IMT alone, adjusting only for age, race, and ARIC Study field center. Variables were entered as linear in the log (hazard) scale, as a restricted piecewise cubic spline (55), or as a categorized variable. The spline models were used to explore nonlinearity in the relations, allowing a cubic relation in each of several subintervals of the continuous factor's range, but requiring that there be linearity at the beginning and end of the range and that the pieces join smoothly. The subintervals for mean IMT were defined by the 50th, 66.7th, 85th, and 95th sex-specific percentiles (0.65, 0.70, 0.80, and 0.96 for women and 0.73, 0.80, 0.92, and 1.13 for men).

Next, risk factors were modeled simultaneously, and then mean IMT was added to the model. Interactions of sex with mean IMT and all risk factors were evaluated. Consideration of other interactions in the proportional hazard models was limited to those between mean IMT and each of the other risk factors, one at a time. Race interactions were not considered because of the small number of CHD events among blacks.

Finally, the effect on model estimates of random measurement variation in mean IMT (56) was considered by refitting the Cox models after replacing observed mean IMT with a Stein estimate of true mean IMT (57), but conditional on predicted mean IMT from sex-specific linear regression of mean IMT on race, center, and age.

RESULTS

The ARIC Study cohort consists of 15,792 persons. For this analysis, we excluded the nonwhites in Minneapolis and Washington County and participants in Forsyth County who were neither black nor white (103 persons total). An additional 769 were excluded for prevalent CHD, 343 others for unknown status regarding prevalent CHD, 980 for missing mean arterial wall thickness, and, finally, 756 for missing information on LDL cholesterol, pack-years of cigarettes, body mass index, fibrinogen, sports index, hypertension, or diabetes status. This left 7,289 women and 5,552 men for this analysis. There were 290 incident CHD events (96 women, 194 men), by definition 1. Of these, 231 had a hospitalized myocardial infarction, 44 had other fatal CHD, and 15 had unrecognized myocardial infarction. The number of incident events by definition 2 were 117 for women and 275 for men. Median follow-up time was 5.2 years, and every person had nonzero follow-up time.

Except for ethanol intake and diastolic pressure in men, CHD cases had higher ($p < 0.01$) baseline mean CHD risk levels and mean IMT, overall and at each site, than did noncases (table 1). The prevalences of hypertension, hyperlipidemia, and current smoking were also statistically significantly higher for incident cases than for noncases (table 2). The prevalence of overall mean IMT of 1 mm or more was much higher for those with incident CHD versus those without ($p < 0.0001$) and was especially pronounced for women.

Adjusted CHD incidence rates were higher ($p < 0.05$) for higher levels of the major risk factors and of IMT (table 3). There was a clear increase in the CHD event rate as mean IMT increased across categories, with the increase more pronounced for women. In the lowest mean IMT categories up through [0.8, 1.0), women had clearly and statistically significantly ($p < 0.05$) lower adjusted CHD incidence rates than did men, but above 1 mm mean IMT, the incidence rate for women nearly reached the level of men, with both being above 10 per 1,000 person-years. Stratification on none of the other variables listed equalized the estimated incidence rates for men and women as mean IMT did.

TABLE 1. Age-, field center-, and race-adjusted means and 95% confidence intervals for CHD† risk factors and carotid IMT‡, by sex and incident CHD status, the ARIC‡ Study, 1987–1993

Risk factors	Women				Men			
	No CHD event (n = 7,193)		CHD event (n = 96)		No CHD event (n = 5,358)		CHD event (n = 194)	
	Mean	95% confidence interval	Mean*	95% confidence interval	Mean	95% confidence interval	Mean*	95% confidence interval
Age (years)	53.7	53.6–53.8	57.0	55.9–58.2	54.3	54.2–54.5	56.3	55.5–57.1
Cholesterol (mmol/liter)	5.62	5.59–5.64	6.05	5.84–6.26	5.43	5.40–5.45	5.70	5.55–5.84
LDL cholesterol‡ (mmol/liter)	3.50	3.48–3.53	3.95	3.76–4.15	3.58	3.55–3.60	3.87	3.73–4.01
HDL cholesterol‡ (mmol/liter)	1.51	1.50–1.52	1.29	1.21–1.37	1.18	1.17–1.19	1.05	0.99–1.11
Systolic blood pressure (mmHg)	119.5	119.1–119.9	132.8	129.3–136.2	122.0	121.5–122.4	126.2**	123.7–128.6
Diastolic blood pressure (mmHg)	71.7	71.4–71.9	75.1**	73.0–77.1	75.7	75.4–76.0	77.2†	75.7–78.6
Cigarette pack-years	10.3	9.8–10.7	23.1	19.1–27.1	21.4	20.9–22.0	29.2	26.4–32.0
Ethanol intake (g/week)	21.2	19.1–23.3	18.6†	0.5–36.6	70.8	68.3–73.2	71.4†	58.6–84.2
Carotid IMT (mm)								
Mean	0.68	0.68–0.68	0.83	0.79–0.86	0.76	0.76–0.77	0.84	0.82–0.86
Bifurcation	0.78	0.78–0.79	0.97	0.93–1.02	0.89	0.88–0.90	1.01	0.98–1.04
Internal	0.66	0.65–0.66	0.80	0.75–0.84	0.74	0.73–0.74	0.82	0.79–0.85
Common	0.60	0.60–0.60	0.71	0.68–0.73	0.66	0.65–0.66	0.69	0.68–0.71

* *p* values are for the difference of a given risk factor between those with and those without a CHD event: *p* ≤ 0.0001 unless otherwise indicated.

** 0.0001 < *p* < 0.01.

† *p* ≥ 0.05.

‡ CHD, coronary heart disease; IMT, intima-media thickness; ARIC, Atherosclerosis Risk in Communities; LDL cholesterol, low density lipoprotein cholesterol; HDL cholesterol, high density lipoprotein cholesterol.

Table 4 provides the age-, field center-, and race-adjusted hazard rate ratios from Cox proportional hazard models, including each major risk factor and mean IMT one at a time. For LDL cholesterol, whether one compared high with low tertile, high risk (≥160 mg/dl) with non-high risk, or differences of 1 mmol/liter LDL cholesterol, the relation was strong, positive, and statistically significant. Findings were similar for low versus high HDL cholesterol. The associations for current versus never smoking, pack-years of cigarettes, and hypertension versus nonhypertension were also pronounced. When mean IMT of 1 mm or more was compared with mean IMT of less than 1 mm, the HRR was very large for women (HRR = 5.07, 95 percent confidence interval 3.08–8.36) and elevated for men (HRR = 1.85, 95 percent confidence interval 1.28–2.69). The HRRs between high and low tertiles were also large: 6.69 for women and 2.88 for men. Categorizing mean IMT into subintervals of absolute level indicated a monotonic (graded) relation with incident disease. The HRR for a 0.19 mm (one stan-

dard deviation) increment of mean IMT, as assessed from a Cox model with linear mean IMT, was significantly elevated for the overall mean IMT and for each specific site. Using definition 2 for “CHD event” produced results similar to those in table 4, so the remainder of the discussion is focused on definition 1. Exclusion of persons with positive or missing Rose angina at baseline also resulted in only minor differences, so this exclusion was not made for the results reported here.

HRRs adjusted for multiple risk variables (table 5, model 1) were generally lower than those in table 4, with the largest reduction, proportionally, for HDL cholesterol for women, from 1.78 to 1.25. All factors remained related to incident CHD, although the addition of diabetes decreased the HRR for linear HDL cholesterol HRR somewhat, so that the confidence interval for women contained unity.

Since the major risk factors exert their effect at least partially through atherogenesis or atherosclerosis progression, we investigated whether mean IMT was still related to CHD incidence after controlling for the

TABLE 2. Age-, field center-, and race-adjusted proportions and 95% confidence intervals for risk factors, by sex and incident CHD[†] status, the ARIC[‡] Study, 1987–1993

Risk factors	Women				Men			
	No CHD event		CHD event		No CHD event		CHD event	
	Proportions	95% confidence interval	Proportions*	95% confidence interval	Proportions	95% confidence interval	Proportions*	95% confidence interval
LDL cholesterol [¶] ≥ 160 mg/dl (≥4.14 mmol/liter)	0.23	0.22–0.25	0.39†	0.29–0.49	0.27	0.26–0.29	0.39†	0.32–0.46
HDL cholesterol [¶] ≤ 35 mg/dl (≤0.905 mmol/liter)	0.05	0.04–0.06	0.21	0.14–0.32	0.22	0.20–0.24	0.39	0.31–0.48
Hypertension	0.33	0.31–0.34	0.65	0.55–0.73	0.31	0.29–0.32	0.47	0.40–0.54
Smoker	0.23	0.22–0.25	0.52	0.42–0.61	0.28	0.26–0.30	0.44	0.38–0.51
Ex-smoker	0.23	0.22–0.25	0.17†	0.10–0.26	0.42	0.39–0.44	0.34†	0.27–0.42
IMT [¶] (mm)								
≥1	0.03	0.03–0.04	0.17	0.11–0.25	0.07	0.07–0.08	0.14‡	0.10–0.20
[0.8, 1.0)	0.10	0.09–0.11	0.16§	0.11–0.25	0.22	0.21–0.24	0.35	0.29–0.43
[0.7, 0.8)	0.19	0.18–0.20	0.28§	0.21–0.39	0.28	0.27–0.30	0.27†	0.21–0.34
[0.6, 0.7)	0.40	0.39–0.42	0.32†	0.23–0.44	0.29	0.27–0.31	0.18‡	0.13–0.25
<0.6	0.28	0.27–0.29	0.07‡	0.03–0.16	0.13	0.12–0.14	0.06‡	0.03–0.11
>95% percentile#	0.05	0.05–0.06	0.22	0.15–0.33	0.04	0.03–0.05	0.08‡	0.05–0.13
3rd tertile**	0.33	0.31–0.34	0.64	0.54–0.75	0.31	0.29–0.32	0.50	0.43–0.57
2nd tertile	0.36	0.35–0.37	0.28†	0.20–0.39	0.35	0.34–0.37	0.32†	0.26–0.39
1st tertile	0.32	0.31–0.38	0.09‡	0.04–0.18	0.34	0.33–0.35	0.19‡	0.14–0.26

* *p* values are for the difference of a given risk factor between those with and those without a CHD event: *p* ≤ 0.0001 unless otherwise indicated.

† *p* ≥ 0.05.

‡ 0.0001 < *p* < 0.01.

§ 0.01 ≤ *p* < 0.05.

¶ CHD, coronary heart disease; ARIC, Atherosclerosis Risk in Communities; LDL cholesterol, low density lipoprotein cholesterol; HDL cholesterol, high density lipoprotein cholesterol; IMT, intima-media thickness.

IMT 95th percentiles: 0.97 mm for women and 1.13 mm for men.

** IMT 2nd and 3rd tertiles [0.61, 0.70) mm for women and [0.67, 0.80) mm for men.

other risk factors (table 5, model 2). The strength of the mean IMT association was reduced by including these variables, but remained statistically significantly elevated. After further adjustment (table 6) for baseline fibrinogen level, body mass index, ethanol intake, and sport activity index, the HRRs for the extreme mean IMT categories were much reduced from those in table 4, although they still remained high. The HRR for mean IMT was smallest at the internal carotid.

There were no major violations of the proportional hazards assumptions for mean IMT or other risk factors, except with hypertension for men. The HRRs for hypertensive versus nonhypertensive men were significantly (*p* = 0.04) smaller in years 2–3 (HRR = 1.5) and after year 3 (HRR = 1.9) than in the first year (HRR = 4.2), when the variables in table 5 were controlled (not shown).

Plots from proportional hazard models with splined mean IMT were overlaid with plots from models with linear mean IMT (figure 1), adjusting only for age,

race, and center. We plotted the HRR comparing the hazard at each mean IMT with the hazard at 0.60 mm. The range for the graphs (but not for the fitted models) was limited to 0.6–1.2 mm. The HRRs were plotted on a log scale, in which the plot for the “linear” model is indeed linear. The nonlinearity for the splined model was statistically significant for both men and women (*p* = 0.002 for men and *p* = 0.04 for women), with the hazard increasing faster at lower levels of mean IMT. Similar trends were observed in the categorical analysis in table 4, except for the extreme HRR for women with mean IMT above 1.0 mm.

The splined plots (not shown) for LDL cholesterol for both sexes and for HDL cholesterol for men did not differ notably or statistically significantly from the linear plots. However, for women, the decrease in hazard with greater HDL cholesterol was steeper at lower levels of HDL cholesterol. For men and women, the hazards of smoking increased faster at lower levels of smoking.

TABLE 3. Sample size; number of events; age-, field center-, and race-adjusted CHD* incidence rates (per 1,000 person-years) with 95% confidence intervals, by sex and risk factor level, the ARIC* Study, 1987–1993

Risk factors	Women				Men			
	Sample size	Events	Rate	95% confidence interval	Sample size	Events	Rate	95% confidence interval
LDL cholesterol* \geq 160 mg/dl (\geq 4.14 mmol/liter)								
Yes	1,771	43	3.8	2.7–5.3	1,495	74	9.7	7.7–12.4
No	5,518	53	1.9	1.4–2.5	4,057	120	6.0	4.9–7.2
HDL cholesterol* \leq 35 mg/dl (\leq 0.905 mmol/liter)								
Yes	386	19	9.2	5.7–14.7	1,260	72	12.3	9.6–15.6
No	6,903	77	2.0	1.5–2.6	4,292	122	5.5	4.5–6.7
Hypertension								
Yes	2,386	69	4.9	3.7–6.6	1,756	100	11.0	8.8–13.7
No	4,903	27	1.1	0.8–1.7	3,796	94	5.1	4.2–6.3
Smoking status								
Current	1,799	50	5.3	3.9–7.1	1,520	82	11.5	9.2–14.4
Former	1,606	14	1.6	0.9–2.7	2,390	73	5.8	4.5–7.4
Never	3,884	32	1.3	0.9–1.9	1,642	39	4.7	3.4–6.5
Diabetes								
Yes	614	35	9.2	6.2–13.6	433	32	13.8	9.6–19.8
No	6,675	61	1.8	1.3–2.3	5,119	162	6.4	5.4–7.6
IMT* (mm)								
\geq 1.0	299	21	11.7	7.2–18.8	531	36	12.9	9.1–18.3
[0.8, 1.0)	821	19	3.8	2.3–6.2	1,277	70	10.7	8.4–13.8
[0.7, 0.8)	1,402	27	3.4	2.3–5.1	1,474	47	6.5	4.9–8.7
[0.6, 0.7)	2,497	23	1.8	1.2–2.7	1,528	31	4.4	3.1–6.2
$<$ 0.6	2,270	6	0.6	0.3–1.4	742	10	3.0	1.6–5.7
\geq 95% percentile†	365	23	9.4	5.9–14.9	278	22	13.8	8.8–21.5
$<$ 95% percentile	6,924	73	2.0	1.5–2.6	3,274	172	6.7	5.7–7.8
3rd tertile‡	2,428	66	4.5	3.4–6.1	1,849	106	11.1	8.9–13.7
2nd tertile	2,434	23	1.8	1.2–2.8	1,855	56	6.2	4.8–8.1
1st tertile	2,427	7	0.7	0.3–1.4	1,848	32	3.8	2.7–5.4

* CHD, coronary heart disease; ARIC, Atherosclerosis Risk in Communities; LDL cholesterol, low density lipoprotein cholesterol; HDL cholesterol, high density lipoprotein cholesterol; IMT, intima-media thickness.

† IMT 95th percentiles: 0.97 mm for women and 1.13 mm for men.

‡ IMT 2nd and 3rd tertiles: [0.61, 0.70) mm for women and [0.67, 0.80) mm for men.

The differences in table 4 between men and women in the size of the association between mean IMT and CHD incidence were statistically significant ($p \leq 0.014$) for the continuous mean IMT measure, overall and at the bifurcation and common carotid, and also for the category 1 mm or more versus less than 1 mm or versus less than 0.6 mm. None of the interactions of linear mean IMT with the other variables considered in table 4 (with center and race not considered) were statistically significant at the 0.05 level.

Cox models with a linear mean IMT term were adjusted for measurement error in mean IMT, assuming reliability coefficients for mean IMT of either 0.7 or 0.8 (28). For women, the HRR for an increment of

0.19 in mean IMT changed from 1.69 (table 4) to 2.11 and 1.92, respectively, for $r = 0.7$ or 0.8 . For men, the HRR of 1.36 shown in table 4 rose to 1.55 and 1.47, respectively.

DISCUSSION

Mean carotid IMT is a valid marker of early carotid atherosclerosis assessed from pathology (22, 58, 59) and is associated with risk factors for atherosclerotic disease (1–16). Furthermore, lipid-lowering therapy slows carotid IMT progression (60–64). Opinions of whether carotid IMT is a good marker for coronary atherosclerosis are mixed (61, 65–69). The trials

TABLE 4. Age-, field center-, and race-adjusted hazard rate ratios from one-risk-factor Cox models with 95% confidence intervals for various risk factors or IMT* comparison groups, the ARIC* Study, 1987–1993

Risk factors	Women		Men	
	HRR*	95% confidence interval	HRR	95% confidence interval
LDL cholesterol* (increment = 1 mmol/liter†)	1.42	1.21–1.67	1.33	1.16–1.52
≥160 mg/dl (yes vs. no)	2.01	1.34–3.03	1.63	1.22–2.18
3rd vs. 1st tertile	2.54	1.45–4.43	1.95	1.34–2.85
2nd vs. 1st tertile‡	1.63	0.89–2.99	1.34	0.88–2.00
HDL cholesterol* (decrement = 0.4 mmol/liter†)	1.78	1.41–2.26	1.75	1.42–2.16
≤35 mg/dl (yes vs. no)	4.65	2.80–7.72	2.24	1.66–3.01
1st vs. 3rd tertile§	3.34	2.03–5.48	2.73	1.65–4.50
2nd vs. 3rd tertile	1.59	0.96–2.65	1.27	0.73–2.20
	4.28	2.68–6.85	2.13	1.58–2.85
Hypertension (yes vs. no)	1.24	1.17–1.31	1.11	1.06–1.16
Cigarette pack-years (increment = 10)	4.41	2.77–7.04	2.19	1.52–3.15
High vs. none	1.59	0.92–2.74	0.96	0.61–1.50
Low vs. none¶				
Smoking	4.01	2.56–6.27	2.42	1.64–3.55
Current vs. never	1.22	0.65–2.28	1.22	0.82–1.80
Former vs. never				
IMT (increment = 0.19 mm†)				
Mean	1.69	1.50–1.90	1.36	1.23–1.51
Bifurcation	1.40	1.29–1.53	1.23	1.15–1.31
Internal	1.28	1.18–1.39	1.15	1.08–1.23
Common	1.92	1.66–2.22	1.32	1.13–1.54
IMT > 1 mm (yes vs. no)	5.07	3.08–8.36	1.85	1.28–2.69
≥1.0 vs. IMT < 0.6 mm	18.93	7.40–48.40	4.22	2.06–8.67
[0.8, 1.0] vs. IMT < 0.6 mm	6.13	2.38–15.77	3.52	1.79–6.89
[0.7, 0.8] vs. IMT < 0.6 mm	5.47	2.23–13.44	2.14	1.08–4.26
[0.6, 0.7] vs. IMT < 0.6 mm	2.91	1.18–7.20	1.43	0.70–2.92
3rd vs. 1st tertile	6.69	3.01–14.89	2.88	1.91–4.34
2nd vs. 1st tertile#	2.70	1.15–6.34	1.62	1.05–2.51

* IMT, intima-media thickness; ARIC, Atherosclerosis Risk in Communities; HRR, hazard rate ratios; LDL cholesterol, low density lipoprotein cholesterol; HDL cholesterol, high density lipoprotein cholesterol.

† One mmol/liter difference in LDL cholesterol, 0.4 mmol/liter difference in HDL cholesterol, and 0.19 mmol/liter difference in IMT are very close to the standard deviation in the ARIC Study for these variables.

‡ LDL cholesterol (2nd and 3rd tertiles): [3.08, 3.90] mmol/liter.

§ HDL cholesterol (2nd and 3rd tertiles): [1.12, 1.47] mmol/liter.

¶ Pack-year used median for smokers to define low and high: 24.

IMT (2nd and 3rd tertiles): [0.61, 0.70] mm for women and [0.67, 0.80] mm for men.

showing that lipid lowering slows IMT progression concomitantly observed less progression of coronary atherosclerosis (60, 61) or fewer major cardiovascular events (62–64) in the active treatment group.

Whether greater carotid IMT is associated with CHD incidence is of interest for several reasons. As a quantitative indicator of the burden of atherosclerosis, IMT can be expected to be associated positively with incident CHD, a relation that requires the type of validation provided by our results. Both the only study prior to this one that reported an association between IMT and incident CHD (18, 19) and the clinical trials

of atherosclerosis regression (60–65) have relied on maximum carotid IMT. The use of an average IMT adds new information as well as credence to the usefulness of a wider range of IMT measures as indicators of generalized atherosclerosis. Because B-mode ultrasound is noninvasive, low risk, reliable (28), and valid (22, 58–59), its use in research applications is of considerable interest if supported by predictive validity as presented here, permitting the study of atherosclerosis in vivo during its subclinical phase. Our outcomes are salient to several ongoing and planned studies of the causes and natural history of atherosclerosis.

TABLE 5. Adjusted hazard rate ratios from multivariate Cox models for a given difference in risk factor level, with 95% confidence intervals, the ARIC* Study, 1987–1993

Risk factors	Model 1†				Model 2‡			
	Women		Men		Women		Men	
	HRR*	95% confidence interval	HRR	95% confidence interval	HRR	95% confidence interval	HRR	95% confidence interval
LDL cholesterol* (1 mmol/liter)§	1.31	1.10–1.55	1.34	1.17–1.54	1.25	1.04–1.49	1.31	1.14–1.51
HDL cholesterol* (0.4 mmol/liter decrement)§	1.25	0.99–1.58	1.60	1.29–1.98	1.20	0.95–1.51	1.57	1.27–1.94
Hypertension (yes vs. no)	3.51	2.17–5.67	2.05	1.52–2.76	3.14	1.94–5.10	1.93	1.43–2.60
Smoking status								
Current vs. never	4.21	2.67–6.62	2.50	1.70–3.68	3.64	2.30–5.76	2.27	1.53–3.35
Former vs. never	1.33	0.71–2.50	1.23	0.83–1.82	1.20	0.64–2.27	1.17	0.79–1.73
IMT* (0.19 mm)§					1.42	1.24–1.64	1.18	1.06–1.32

* ARIC, Atherosclerosis Risk in Communities; HRR, hazard rate ratio; LDL cholesterol, low density lipoprotein cholesterol; HDL cholesterol, high density lipoprotein cholesterol; IMT, intima-media thickness.

† Adjusted for age, race, center, diabetes, and other variables in the table, except IMT.

‡ Adjusted for age, race, center, diabetes, and other variables in the table.

§ One mmol/liter difference in LDL cholesterol, 0.4 mmol/liter difference in HDL cholesterol, and 0.19 mmol/liter difference in IMT are close to the standard deviations in the ARIC Study for these variables.

TABLE 6. Hazard rate ratios by type of IMT* variables, adjusted for baseline age, race, center, LDL cholesterol*, HDL cholesterol*, body mass index, sports activity, cigarette-years, hypertension, diabetes, ethanol, and fibrinogen, the ARIC* Study, 1987–1993

IMT variable	Women		Men	
	HRR*	95% confidence interval	HRR	95% confidence interval
Increment = 0.19 mm				
Mean	1.38	1.21–1.58	1.17	1.04–1.31
Bifurcation	1.27	1.15–1.40	1.13	1.05–1.22
Internal	1.15	1.04–1.26	1.06	0.98–1.14
Common	1.46	1.22–1.74	1.08	0.91–1.27
≥1.0 mm (yes vs. no)	2.62	1.55–4.46	1.20	0.81–1.77
≥1.0 mm vs. IMT < 0.6 mm	7.40	2.83–19.38	2.15	1.02–4.54
[0.8, 1.0] vs. IMT < 0.6 mm	3.35	1.29–8.68	2.44	1.23–4.84
[0.7, 0.8] vs. IMT < 0.6 mm	3.56	1.44–8.76	1.56	0.78–3.15
[0.6, 0.7] vs. IMT < 0.6 mm	2.53	1.02–6.26	1.21	0.59–2.47
≥95th percentile† vs. less	2.42	1.45–4.04	1.36	0.84–2.18
3rd vs. 1st tertile‡	3.76	1.68–8.43	2.02	1.32–3.09
2nd vs. 1st tertile	2.34	0.99–5.48	1.34	0.86–2.10

* IMT, intima-media thickness; LDL cholesterol, low density lipoprotein cholesterol; HDL cholesterol, high density lipoprotein cholesterol; ARIC, Atherosclerosis Risk in Communities; HRR, hazard rate ratio.

† IMT 95th percentiles: 0.97 mm for women; 1.13 mm for men.

‡ IMT 2nd and 3rd tertiles: [0.61, 0.70] mm for women; [0.67, 0.80] mm for men.

rosis in populations across a wide range of age and to studies of the efficacy of interventions to alter its course. Because our research protocol for B-mode ultrasound is standardized and includes neither Doppler capabilities nor the identification of focal areas of disease, our findings probably underestimate the predictive ability of applications of B-mode ultrasound for clinical outcomes.

Few population studies have investigated carotid IMT as an independent predictor of incident CHD. The Cardiovascular Health Study (70) included IMT

as a component of an index of subclinical disease in a prospective study, but no separate results for IMT have been published. A subsample of 1,257 men from the Kuopio Ischemic Heart Disease Risk Factor Study (19) was followed for 1–36 months, with 36 CHD events during follow-up; the HRR for a 0.19-mm difference in IMT assessed as the maximal IMT of the common carotid arteries was 1.22 ($p < 0.001$). This is very similar to our estimate in table 4 for the mean IMT for the common carotid. It was also reported that the HRR remained statistically significant ($p < 0.01$)

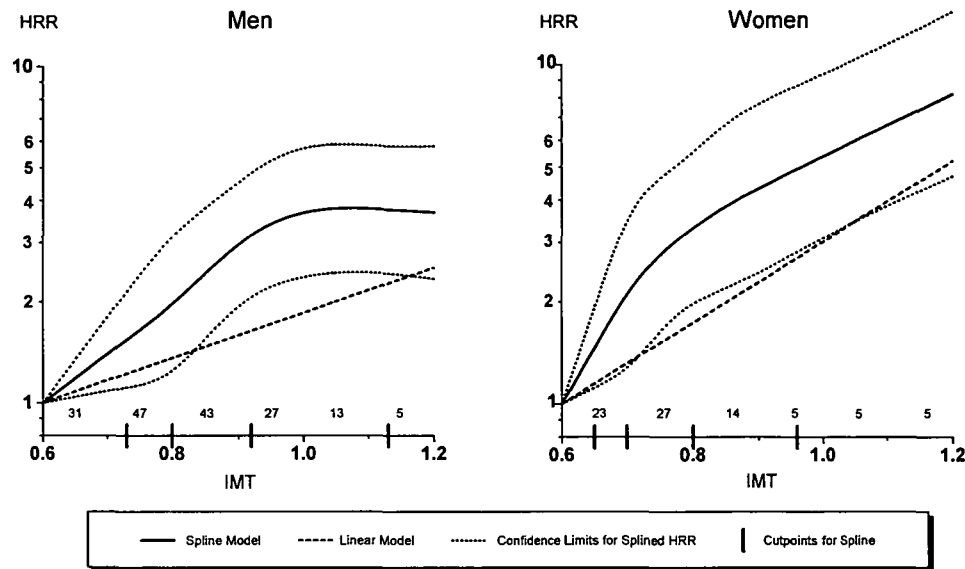


FIGURE 1. Gender-specific hazard rate ratio (HRR) relative to intima-media thickness (IMT) = 0.6 mm for splined and linear IMT, with the number of events listed per 0.1 mm subinterval, from proportional hazards models adjusted for age, center, and race, 1987–1993.

after adjustment for age, cigarette pack-years, systolic pressure, HDL cholesterol, and the HDL cholesterol/LDL cholesterol ratio.

The relation between mean IMT and incident CHD persisted after adjustment for other CHD risk factors, many of which play a causal role in atherogenesis, with persons whose mean IMT was above 1 mm having several times the incident CHD hazard of those whose mean IMT was below 0.60 mm. For both men and women, the hazard appeared to increase faster at lower levels of mean IMT. This may be because the absence of atherosclerosis is unusual in this age group (71, 72), so that low mean IMT in the carotid arteries is probably predictive of no atherosclerosis in the coronary arteries. However, when atherosclerosis is prominent in the carotid arteries, its extent may be less associated with the extent of atherosclerosis elsewhere, possibly due to the focal, patchy nature of the disease.

The associations of CHD incidence with LDL cholesterol, HDL cholesterol, smoking, and hypertension are well documented for both men and women. However, it is useful to compare the relative importance of major CHD risk factors between men and women. This was done recently in the Finnmark Study (73), a population-based study of more than 11,000 persons aged 35–52 years at baseline, with 495 first myocardial infarctions for men and 103 for women. In age-adjusted, one-risk factor Cox models, it was found that men and women had similar HRRs for total cholesterol and HDL cholesterol and systolic pressure, but that women had 1.7 times the “daily smoking” HRR as men (3.3 vs. 1.9). Our findings for LDL cholesterol

(instead of total cholesterol) and HDL cholesterol were similar to those of the Finnmark Study when these risk factors were linear terms in the model, but in the ARIC Study, an HDL cholesterol level of 35 mg/dl or less (vs. an HDL cholesterol level of more than 35 mg/dl) had an HRR of 4.65 for women and 2.24 for men ($p = 0.01$ for the difference). The HRRs for current versus never smoking were 4.01 for women and 2.42 for men (ratio of 1.7, $p = 0.09$), again similar to those in the Finnmark Study. The ARIC Study found HRRs for hypertension of 4.28 for women versus 2.13 for men ($p = 0.01$). Similar comparisons can be made for absolute risk levels (table 3). For hypertension, LDL cholesterol, and smoking, the differences in CHD incidence rates between men and women were about the same or slightly greater at high-risk as at low-risk levels. The sex differences in incidence rates were intermediate for diabetics and those with an HDL cholesterol level of 35 mg/dl or less. Women had lower estimated absolute levels of CHD risk than did men at lower levels of mean IMT, but at mean IMT levels above 1 mm, absolute risk levels were similar for men and women, although our power to detect incidence rate ratios under two between men and women was small.

There are some limitations to this study. A single mean IMT assessment was used, and correction for the measurement’s lack of reliability indicated considerable attenuation of HRRs if the measurement error is ignored. Furthermore, considerable ultrasound data were missing, necessitating exclusion of some participants and imputation for most others. However, extensive analyses in the ARIC Study suggest that the

mean IMT data are missing at random; for example, missingness at one site is not strongly related to wall thickness at other sites, conditional on the variables used in the imputation process. This justifies the use of the maximum likelihood techniques in the imputation procedure (74). It would be invalid to compute overall mean IMT by averaging only observed sites out of the six, since the sites have different population means. In addition, to exclude a person entirely because of data missing for at least one site would be inefficient as well as potentially introduce a selection bias. One alternative to the imputation procedure would be to average over the observed sites, but weighting in order to bring site-specific population means all to the same value, here the mean over all six sites in the imputed data to keep the scale of the present analysis. This was done, and table 5, model 2, was refit, changing the IMT HRR from 1.42 (95 percent confidence interval 1.24–1.64) to 1.29 (95 percent confidence interval 1.16–1.42) for women and from 1.18 (95 percent confidence interval 1.06–1.32) to 1.13 (95 percent confidence interval 1.03–1.25) for men. The confidence intervals with the alternative IMT definition were narrower but still excluded unity. Although the results were similar and the alternative approach has some appeal, we believe that our approach through imputation is preferable for estimating a directly interpretable parameter, the mean of mean IMT over the six sites measured in the ARIC Study. Another alternative would be to restrict analysis to the observed data at the common carotid. Only 4 percent of the persons in this study are missing data at both left and right common carotids, and an analysis using the mean of the number of observed sites available (one or two) yielded results for the common carotid that were virtually identical to the results in table 4 for the common carotid, using imputed data.

Another limitation to this study is the low response rate among African Americans, which tended to bias the results of the analysis toward a somewhat healthier subgroup of the population, the responders (21), if indeed the associations considered here are different for responders and nonresponders. Another possible limit to the generalizability of the results is that the four ARIC Study communities were not a random or representative sample of the US population, although again there is no evidence that the associations between incident CHD and either risk factors or IMT should show geographic variation within the United States. Loss to follow-up, another potential source of bias, should have minimal effect on our results, since only 39 of more than 12,000 persons were not followed until incident event, death, or the end of the study period.

Finally, there is always a potential problem of confounding related to variables not considered, although many factors often considered in analysis of CHD likely have their effect partially *through* atherosclerosis. Examples of such confounders would be socioeconomic or dietary factors and even many of the additional covariates for which we have adjusted in table 6. The effect of these variables on the IMT/CHD association was not the primary interest of this paper and goes beyond the usual practice of adjusting for confounders.

The ARIC Study has obtained well-standardized measurements in a population-based study of 15,792 persons across four communities. The associations of IMT with known CHD risk factors have been previously firmly established (1–16), as has the association between IMT and CHD in a cross-sectional mode (17, 75). This analysis establishes the association of carotid IMT with CHD prospectively.

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