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Short- and Long-Term Prediction of Clinical and Subclinical Atherosclerosis by Traditional Risk Factors

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ABSTRACT. This study compares the cross-sectional and longitudinal associations of cardiovascular risk factors with clinical coronary heart disease (CHD) and with subclinical carotid atherosclerosis measured by ultrasound. The study population were 1410 participants in the Atherosclerotic Risk in Community (ARIC) Study (1987–1989) who also participated in a 1974 community health survey. Smoking in 1974 was associated with increased CHD prevalence in 1987–1989 (adjusted prevalence ratio = 2.2), whereas the corresponding cross-sectional association was practically absent. For hypercholesterolemia and hypertension, the longitudinal associations with CHD were also stronger than the cross-sectional associations. In contrast, the strength of the longitudinal and cross-sectional associations with carotid atherosclerosis was generally similar. These results underscore the advantages of using subclinical measures of atherosclerosis in cross-sectional studies. In addition, they suggest that the presence of smoking, hypertension, or hypercholesterolemia in mid-adulthood may have some persisting effects on the development of atherosclerotic disease in later life. J CLIN EPIDEMIOL 52;6:559–567, 1999. © 1999 Elsevier Science Inc.

KEY WORDS. Atherosclerosis, bias (epidemiology), coronary disease, hypertension, cholesterol, smoking

INTRODUCTION

Cohort studies have clearly established that hypercholesterolemia, cigarette smoking, and hypertension are independent risk factors for clinical manifestations of atherosclerosis [1,2]. There have been recent cross-sectional studies reporting the association between risk factors and concurrent measurements of subclinical atherosclerosis [3–6], but evidence regarding the longitudinal association between these risk factors and subclinical atherosclerosis is limited [7,8]. The cross-sectional and longitudinal associations between risk factors and clinical coronary heart disease (CHD) have been compared [9,10], and a recent study compared the cross-sectional and "time-integrated" measurements of these risk factors in relation to carotid stenosis in older adults [8]. To our knowledge, there are no studies comparing such associations in middle-aged adults.

Using longitudinal information based on the linkage of two population-based surveys conducted in Washington County, Maryland, in 1974 and in 1987–1989, we investigated and compared the longitudinal and the cross-sectional associations of traditional risk factors with both clinical (self-reported history of CHD) and subclinical atherosclerosis [carotid intimal-medial thickness (IMT) or carotid plaque]. In addition, we also examined the associations between certain predictors and changes in risk factor status between the surveys.

METHODS

Study Population

For the present study, a subset of participants from the Washington County baseline cohort of the Atherosclerosis Risk in Communities (ARIC) Study (1987–1989) [11] were identified as participants in a 1974 county-wide survey that collected information on cigarette smoking, blood pressure, and serum cholesterol [12,13] (see Figure 1).

The ARIC Study is a prospective investigation of the natural history and determinants of clinical and subclinical atherosclerosis. As described in detail elsewhere [11], approximately 15,800 participants from four U.S. communities were first examined between 1987 and 1989. A total of 4020 participants were recruited in Washington County, Maryland. Of these, 3694 (94% of those alive) returned 3 years later for their second examination, conducted between 1990 and 1992 (Figure 1).

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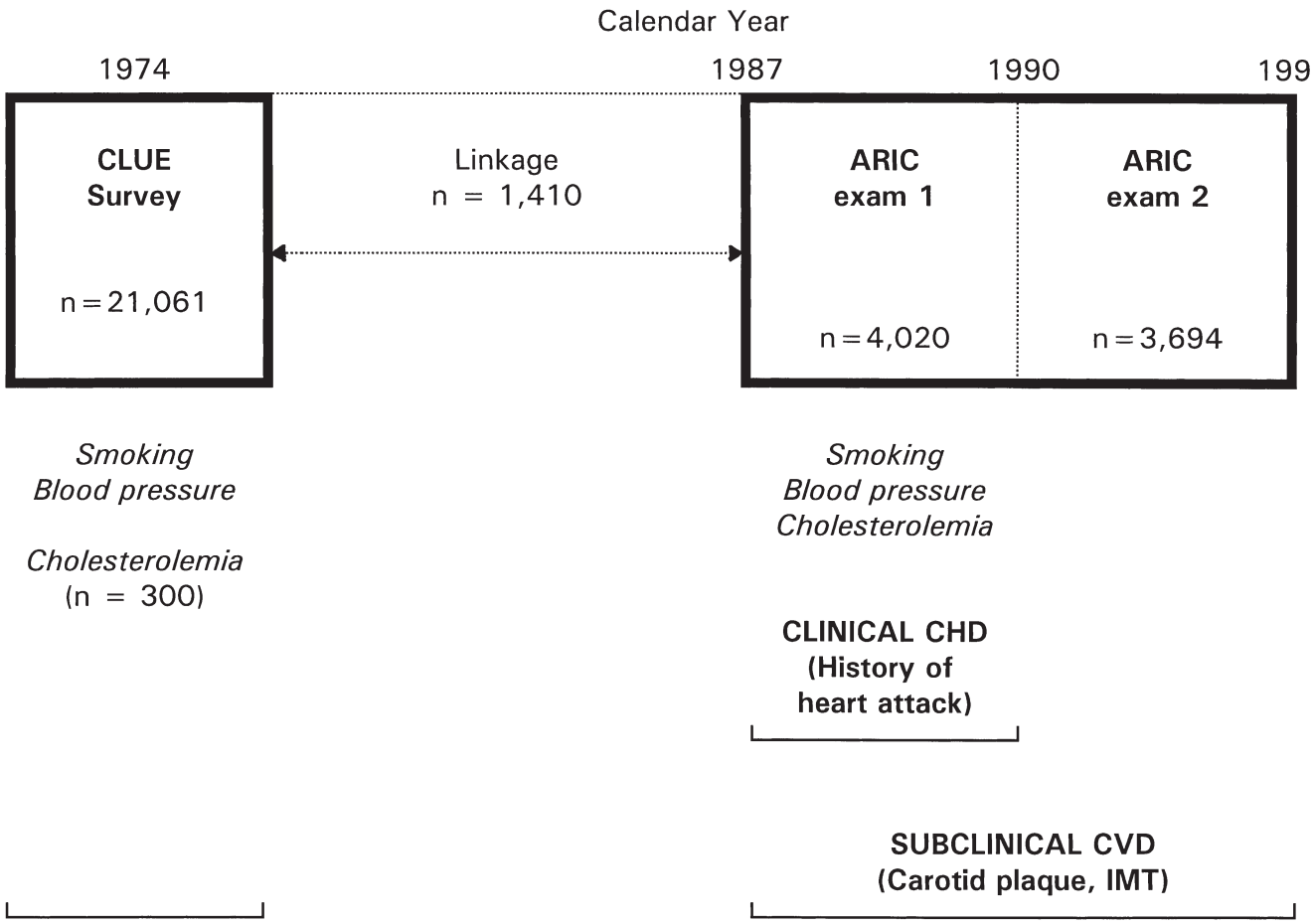

FIGURE 1. Study design: linkage between a countywide campaign to collect blood for a serum bank, conducted by the Johns Hopkins University Training Center for Public Health Research (CLUE) and Atherosclerosis Risk in Communities (ARIC) surveys and time and sources of information on risk factors (in italics) and outcomes (in bold). *Abbreviations*: CHD, coronary heart disease; CVD, cardiovascular disease; IMT, carotid intimal medial thickness

Additional information came from a county-wide campaign to collect blood for a serum bank, conducted by the Johns Hopkins University Training Center for Public Health Research in 1974 [14,15]. The campaign was nicknamed "operation CLUE" (for "Give us a clue to cancer"). A total of 21,061 adult residents of Washington County participated in this survey that included donating 15 mL of blood. These individuals were interviewed and examined in large trailers parked along the streets and roads of Washington County.

On the basis of exact matches on both birth date and name (first and last, or maiden name among females), the two datasets were linked. Exact matches (i.e., not allowing for name misspellings) were required in order to maximize the specificity of the matching criteria. Given the relatively small size of the population frame (the total population of Washington County is about 120,000), the occurrence of false matches based on exact name and birth date is unlikely. A total of 1410 individuals were identified among participants in both the 1974 campaign and ARIC's baseline examination (Figure 1). Some of the results presented here are based on this full cohort sample of 1410 participants in CLUE-ARIC (the results on smoking and hypertension). The results related to hypercholesterolemia, are based on a subset of 300 individuals among these 1410 persons (case-control sample) who were included in a previous cohort-based case-control study that involved thawing the 1974 serum samples to determine viral antibody levels [13]. These included 150 individuals with elevated carotid IMT as determined by B-mode ultrasound (see later) as well as 150 age- and gender-matched controls with low carotid IMT.

Examination Procedures

Information on cigarette smoking, educational level, weight at age 25 years, marital status, and medication use was obtained by interview at the CLUE and the ARIC surveys. For the CLUE (1974) survey, the time of the day for each

individual's examination was variable; participants were not fasting. On the other hand, blood pressure measurements, anthropometry, and venipuncture at the ARIC examination (1987–1989) were carried out in the morning after subjects had fasted for 12 hours. Anthropometric measurements in ARIC were done with subjects wearing a scrub suit and no shoes. Body mass index (BMI) was calculated as weight(kg)/height(m)^2.

The blood pressure measurement procedures differed in the 1974 (CLUE) and in the 1987–1989 (ARIC) examinations [12]. Briefly, in the 1974 CLUE survey, a nurse took three sitting blood pressure measurements with a standard mercury sphygmomanometer after the participant had been resting for several minutes; the lowest value of the three measurements was recorded. In the 1987–1989 ARIC examination, technicians used a random-zero sphygmomanometer to take three sitting blood pressure measurements after 5 minutes of rest; the average of the second and third measurements was recorded. Total cholesterol was measured by enzymatic methods [16] in both surveys. A cholesterol determination at the time of the 1974 survey was only available in the subset of 300 participants comprising the case-control sample (as already described).

Definition of Risk Factors and Outcomes

Among the main CVD risk factors, diabetes was not considered in the present report because the information was not available at the time of the CLUE survey. Hypertension at either the CLUE or the ARIC examinations was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or use of antihypertensive medication. Hypercholesterolemia in the CLUE survey (before the wide availability of lipid-lowering medications) was simply defined as serum cholesterol $\geq$ 240 mg/dL, whereas in ARIC it was defined as either cholesterol $\geq$ 240 mg/dL or use of lipid-lowering medication. Educational level and marital status at the time of CLUE, as well as an indicator of adult weight change (based on self-reported weight at age 25 years and measured weight at the time of ARIC), were investigated as possible predictors of risk-factor status change.

Clinical CHD was assessed at ARIC visit 1 based on a self-reported physician-diagnosed heart attack, or history of coronary procedures. Presence of subclinical atherosclerotic disease was based on B-mode ultrasound examination of the carotid arteries by trained sonographers following a standardized protocol [11,17]. Measurements of the IMT of the far wall of the carotid arteries were taken at the common, bifurcation, and internal carotids in both sides of the neck. The ultrasound images were recorded on videotapes and sent to the central ARIC Ultrasound Reading Center at Bowman Gray School of Medicine, Winston-Salem, North Carolina, where trained personnel read them. Estimates of correlation between scans conducted 7–10 days apart in the same individual, by different sonographers, and read by different readers, ranged from 0.70 to 0.77 for the different carotid sites [18]. The average IMT (expressed in millimeters) of all measurements of the carotid far wall at all sites at both ARIC examinations was used as a marker of carotid atherosclerosis. The reason to average IMT measurement over both examinations was to maximize reliability.

In addition, the presence of carotid plaque at any of the examined sites in either examination was qualitatively assessed by the ultrasound reader, based on the presence of a lesion accompanied by acoustic shadowing at any of the examined sites [19]. A lesion was recorded if two of the following conditions were met: (a) wall shape: protrusion into the lumen, loss of alignment with adjacent arterial boundary, or roughness of the arterial boundary; (b) wall texture: brighter echoes than adjacent boundaries; or (c) wall thickness: IMT exceeding 1.5 mm. Acoustic shadowing was defined as the reduction in amplitude of echoes caused by intervening structures with high attenuation and is indicative of mineral deposit within the plaque. Intrareader and interreader agreement for the presence of plaque in any of the six artery segments (kappa statistic) were 0.76 and 0.56, respectively [19], both in the range of good agreement beyond chance [20].

Statistical Analysis

Analysis of binary outcomes (change in risk-factor status, prevalent clinical disease, carotid plaque) was carried out using multiple logistic regression. Adjusted prevalence and prevalence ratios (PR) were obtained from the logistic regression prediction equation for each exposure category and the average covariate values. Analysis of continuous outcomes (baseline IMT) was conducted using multiple linear regression models. For analyses of subclinical outcomes, participants with history of heart attacks at the ARIC examination were excluded; the reason for this exclusion is to assess the net association between risk factors and subclinical atherosclerosis, avoiding the biases due to changes in health behaviors or treatments subsequent to clinical events. Because data on 1974 cholesterol levels were available only for a subset of participants (n = 300), the 1974 and the 1987–1989 associations with hypercholesterolemia could only be compared in this subset. Statistical analyses were carried out using Statistical Analysis System (SAS) software (SAS Institute, Cary, NC).

RESULTS

Of the 1410 participants, 559 (40%) were male. At the time of the CLUE survey (1974), the median age of this cohort was 41 years (range, 29–51 years); at the first ARIC examination, the median age was 55 years (range, 45–64 years). Table 1 shows the distribution and mean values of selected variables for the study population at the two differ-

ent time periods. The proportion of cigarette smokers decreased, whereas the proportion of participants with hypercholesterolemia and the mean serum cholesterol levels increased between the two time periods. Among individuals with cholesterol measurements available at both times (including a high proportion of "atherosclerosis cases"; see Methods), the average increase in serum cholesterol was 11.4 mg/dL. The apparent decrease in prevalence of hypertension and mean arterial blood pressure is most likely an artifact resulting from the different equipment and procedures of blood pressure measurements in the 1974 and 1987–1989 surveys (see Methods).

At the time of the ARIC examination (1987–1989), ~5% of participants reported a history of a physician diagnosed heart attack or coronary surgery, and about 15% had evidence of carotid plaque. Table 1 also shows the mean BMI and mean carotid IMT at the ARIC examination.

The association between the presence of each of the main risk factors in 1974 and the presence of the same risk factor in the ARIC examination was very strong for each of the risk factors considered (Table 2). The proportion of participants affected in 1974 still exposed to the risk factor in 1987–1989 was ~60% for all three risk factors. In contrast, the prevalence in the latter examination was much lower among those without the risk factor in 1974, particularly for smoking. Pearson correlation coefficients between 1974 and 1987–1989 measurements were 0.52 for serum cholesterol, 0.41 for systolic blood pressure, and 0.34 for diastolic blood pressure.

Table 3 shows the associations of selected baseline characteristics and weight loss with new acquisition or persistence of the three main risk factors. Both acquisition and persistence of the smoking habit were associated with adult weight loss. Smoking persistence was also significantly less likely in males than in females. Persistent hypertension was significantly associated with older age in 1974. Adult weight gain was significantly related to both hypertension acquisition and persistence. The results for hypercholesterolemia are not shown in Table 3 because the numbers were too small. Only 48 of 242 individuals newly developed hypercholesterolemia between 1974 and 1987–1989, and the only statistically significant predictor was adult weight gain

TABLE 1. Characteristics of the cohort: Washington County participants in CLUE (1974) and ARIC (1987–1989)

	1974		1987–89	
	Number	**%**	**Number**	**%**
Cigarette smoking	419/1408	29.8	284/1410	20.1
Hypercholesterolemia[a]	57/299	19.1	409/1408	29.0[b]
Hypertension[c]	564/1409	40.0	483/1402	34.5
Education < high school	334/1306	25.6	370/1408	26.3
History of heart attack[d]	—	—	73/1376	5.3
Carotid plaque[e,f]				
All	—	—	127/864	14.7
Excluding positive history of heart attack or stroke	—	—	107/818	13.1
	Number	**Mean**	**Number**	**Mean**
Serum cholesterol (mg/dL)	299	207.1	1408	218.3
Systolic blood pressure (mmHg)	1409	130.8	1410	119.0
Diastolic blood pressure (mmHg)	1409	83.3	1409	71.2
Body mass index (kg/m^2)	—	—	1409	27.9
Baseline IMT (mm)[f,g]				
All	—	—	1252	0.744
Excluding positive history of heart attack or stroke	—	—	1153	0.736

[a]Hypercholesterolemia: total serum cholesterol ≥240 mg/dl or lipid lowering treatment.

[b]When only the participants with cholesterol measured in 1974 were included (case-control sample), the proportion of hypercholesterolemic participants in 1987–1989 was 84/299 (28.1%).

[c]Hypertension: blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic or antihypertensive treatment.

[d]Self-reported heart attack confirmed by a physician, or coronary surgery.

[e]Defined by the presence of both plaque and shadow at visits 1 (1987–1989) or 2 (1990–1992) ultrasound examinations.

[f]The small numbers in the denominator are due to missing ultrasound information at either examination.

[g]Mean intima-media wall thickness on all ultrasound measurements of the carotid arteries taken during visits 1 (1987–1989) and 2 (1990–1992).

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CLUE, a countywide campaign to collect blood for a serum bank, conducted by the Johns Hopkins University Training Center for Public Health Research; IMT, carotid intimal-medial thickness.

TABLE 2. Cigarette smoking, hypertension, and hypercholesterolemia status in 1974 and 1987–1989

	Total number	Same risk factor absent in 1987–1989	Same risk factor present in 1987–1989		
		Number	Number	Percent	Ratio[a]
Full cohort (n = 1410)					
Current cigarette smoking					
Absent in 1974	989	963	26	2.6	
Present in 1974	419	161	258	61.6	23.7
Hypertension[b]					
Absent in 1974	840	679	161	19.2	
Present in 1974	561	249	322	57.4	3.0
Case-control subset (n = 300)[c]					
Hypercholesterolemia[b]					
Absent in 1974	242	194	48	19.8	
Present in 1974	57	21	36	63.2	3.2

[a]Prevalence of the risk factor in 1987–1989 in those with the risk factor in 1974 divided by prevalence of risk factor in 1987–1989 among those without the risk factor in 1974; all three ratios differ significantly from one ($P < 0.0001$).

[b]Hypertension and hypercholesterolemia defined as in the footnote to Table 1.

[c]The results for smoking and hypertension using the case-control subset were similar as those shown in the table for the full cohort: prevalence ratios 37.0 and 3.1, respectively, both $P < 0.0001$.

(age-gender–adjusted prevalence ratio = 2.4, 95% confidence interval [CI] 1.4–4.1). Of the 57 individuals with hypercholesterolemia at baseline in the case-control subset (Table 2), this condition persisted in 36 by 1987–1989, but none of the risk factors analyzed in Table 3 was significantly associated with its persistence (not shown).

The longitudinal and cross-sectional associations of smoking and hypertension with both clinical and subclinical atherosclerosis are compared in Table 4. For smoking, the highest prevalence of clinical manifestations of atherosclerosis (history of heart attack or coronary surgery) was observed among participants reporting smoking only in

TABLE 3. Age- and gender-adjusted prevalence ratios[a] of new or persistent main cardiovascular risk factor at the ARIC visit (1987–1989) according to baseline characteristics (1974) adult weight change

	Smoking		Hypertension[b]	
	Newly developed[c] (26/989)	Persistent[d] (258/419)	Newly developed[c] (161/840)	Persistent[d] (322/561)
Age ≥40 yrs[a]	0.5	0.9	1.3	1.4[e]
Male gender[a]	1.5	0.8[e]	0.8	0.9
Married	0.9	0.9	2.0	1.3
Education <HS	0.7	1.1	1.0	1.1
Adult weight loss[f]	3.1[e]	1.3[e]	0.6	0.9
Adult weight gain[f]	0.6	0.9	1.5[e]	1.2[e]

[a]Prevalence ratios for age and gender are each adjusted for each other; all other risk factors shown are adjusted for age and gender. The reference category are all other individuals, e.g., for age, those <40 years.

[b]Hypertension: blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic or antihypertensive treatment.

[c]Risk factor present in the ARIC examination (1987–1989) among those free of the risk factor at the time of a countywide campaign to collect blood for a serum bank, conducted by the Johns Hopkins University Training Center for Public Health Research (CLUE) (1974). Overall numbers shown in parentheses.

[d]Risk factor present in the ARIC exam (1987–1989) among those with the risk factor at the time of CLUE (1974). Overall numbers shown in parentheses.

[e]The 95% confidence interval for the prevalence ratio did not include 1.0.

[f]Based on weight change according to self-reported weight at age 25 and measured weight at the Atherosclerosis Risk in Communities (ARIC) examination: weight loss represent a negative increment; weight gain is defined as an increment of 20 kg or more; the reference category for these dummy variables is weight gain between 0 and 19.9 kg.

TABLE 4. Age- and gender-adjusted prevalence of clinical and subclinical cardiovascular disease, and mean carotid IMT in 1987–1992 according to the presence of smoking and hypertension in 1974 and/or in 1987–1989, full cohort sample (n = 1410)

		Clinical atherosclerosis[a] (1987–89)		Subclinical atherosclerosis (1987–1992)			
				Carotid plaque/shadow[b]		Carotid IMT[c]	
		Adjusted prevalence %	Adjusted prevalence ratio (95% CI)	Adjusted prevalence %	Adjusted prevalence ratio (95% CI)	Adjusted mean (mm)	Adjusted percent difference
Current cigarette smoking							
Not present in 1974 or 1987–89		2.9		8.8		0.719	
Only present in 1974		8.3*		11.5		0.757*	
Only present in 1987–89		[d]		14.2		0.696	
Present in 1974 and 1987–89		5.0		22.6*		0.793*	
Present in 1974[e]	No	2.8		9.0		0.719	
(Longitudinal)	Yes	6.3	2.2 (1.4–3.6)	18.7	2.1 (1.5–3.0)	0.780	8.5*
Present in 1987–90[e]	No	3.7		9.2		0.724	
(Cross-sectional)	Yes	4.4	1.2 (0.7–2.1)	22.0	2.4 (1.7–3.4)	0.783	8.1*
Hypertension[f]							
Not present in 1974 or 1987–89		2.1		7.2		0.714	
Only present in 1974		6.0*		17.6*		0.755*	
Only present in 1987–89		4.3		11.7		0.731	
Present in 1974 and 1987–89		5.3*		16.1*		0.772*	
Present in 1974[e]	No	2.6		8.5		0.717	
(Longitudinal)	Yes	5.7	2.2 (1.3–3.5)	16.8	2.0 (1.4–2.8)	0.764	6.5*
Present in 1987–90[e]	No	3.1		9.8		0.725	
(Cross-sectional)	Yes	4.8	1.5 (0.9–2.5)	14.7	1.5 (1.0–2.1)	0.758	4.6*

[a]Self-reported physician diagnosis of a heart attack or coronary surgery.
[b]Defined by the presence of both plaque and shadow in visits 1 (1987–1989) or 2 (1990–1992) ultrasound examinations, among participants without an ARIC history of heart attach, coronary surgery, or stroke.
[c]Grand mean of all measurements at all sites in visits 1 (1987–1989) and 2 (1990–1992) ultrasound examinations, among participants without an ARIC history of heart attack, coronary surgery, or stroke.
[d]Adjusted prevalence not calculable due to the small number of smokers only in 1987–1989 (nonconvergence of logistic model).
[e]Regardless of the presence of the risk factor in the other examination.
[f]Hypertenstion: blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic or antihypertensive treatment.
*$P < 0.05$ compared with the category "Not present" or "No."
Abbreviation: CI, confidence interval; IMT, intimal-medial thickness.

1974. Moreover, while a strong longitudinal association of smoking with clinical CHD was evident (PR = 2.2), the cross-sectional association (using only the smoking status in 1987–1989) was nearly absent (PR = 1.2). In contrast, for subclinical disease, there was little difference in the strength of the longitudinal and cross-sectional associations, with the highest prevalence of carotid plaque and the highest mean IMT among subjects reporting smoking at both examination periods.

For hypertension, the results were similar to those of smoking, in that a weak cross-sectional association with clinical disease was observed (PR = 1.5, nonstatistically significant). For subclinical outcomes, the longitudinal associations with hypertension were somewhat stronger than the cross-sectional ones (Table 4).

Table 5 shows the data regarding the association between hypercholesterolemia and cardiovascular disease (CVD) outcomes among the 300 participants on whom cholesterol levels were determined at both examination periods (the case-control sample). As for smoking, the highest prevalence of clinical disease in this case was observed among participants with hypercholesterolemia only in 1974, and the cross-sectional association with clinical disease was absent. In contrast, the strength of the association with subclinical outcomes was similar in the cross-sectional and in the longitudinal analyses.

DISCUSSION

To our knowledge, this is the first epidemiologic study comparing the long-term and the concurrent associations of the three main CVD risk factors (cigarette smoking, hypertension, and hypercholesterolemia) with both clinical and subclinical atherosclerosis. This study extends similar analyses conducted more than 30 years ago by Friedman *et al.* [9] comparing the cross-sectional and longitudinal associations between hypertension and hypercholesterolemia with clinical CHD in the Framingham cohort, as well as a subsequent report from the Evans County study [10]. The present study replicates the Framingham and Evans County study find-

TABLE 5. Age- and gender-adjusted prevalence of clinical and subclinical cardiovascular disease and mean carotid IMT in 1987–1992 according to the presence of hypercholesterolemia in 1974 and/or in 1987–1989, case-control sample (n = 300)

		Clinical atherosclerosis[a] (1987–89)		Subclinical atherosclerosis (1987–1992)			
				Carotid plaque/shadow[b]		Carotid IMT[c]	
		Adjusted prevalence %	Adjusted prevalence ratio (95% CI)	Adjusted prevalence %	Adjusted prevalence ratio (95% CI)	Adjusted mean (mm)	Adjusted percent difference
Hypercholesterolemia[d]							
Not present in 1974 or 1987–89		5.0		19.3		0.765	
Only present in 1974		18.1*		40.5*		0.980*	
Only present in 1987–89		7.4		37.4*		0.869*	
Present in 1974 and 1987–89		5.2		34.6		0.952*	
Present in 1974[e]	No	5.7		23.0		0.785	
(Longitudinal)	Yes	9.4	1.6 (0.7–4.0)	36.7	1.6 (1.0–2.7)	0.961	22.4*
Present in 1987–1990[e]	No	6.4		21.6		0.783	
(Cross-sectional)	Yes	6.5	1.0 (0.4–2.5)	36.2	1.7 (1.0–2.7)	0.903	15.3*

[a]Self-reported physician diagnosis of a heart attack or coronary surgery.
[b]Defined by the presence of both plaque and shadow in visits 1 (1987–1989) or 2 (1990–1992) ultrasound examinations, among participants without an ARIC history of heart attack, coronary surgery, or stroke.
[c]Grand mean of all measurements at all sites in visits 1 (1987–1989) and 2 (1990–1992) ultrasound examinations, among participants without an ARIC history of heart attack, coronary surgery, or stroke.
[d]Hypercholesterolemia: total serum cholesterol ≥240 mg/dL or lipid lowering treatment.
[e]Regardless of the presence of the risk factor in the other examination.
*$P < 0.05$ compared with the category "Not present" or "No."
Abbreviation: CI, confidence interval; IMT, intimal-medial thickness.

ings, adding cigarette smoking and comparing clinical and subclinical outcomes.

One of the principle findings of this study is that the presence of any of these traditional risk factors in 1974 is strongly associated with both clinical and subclinical atherosclerosis in the ARIC examination in 1987–1989. Moreover, for clinical atherosclerotic disease (heart attack or coronary surgery) associations with earlier assessment of risk factors were stronger than associations seen cross sectionally in 1987–1989. The practically absent cross-sectional association between current cigarette smoking or hypercholesterolemia and prevalent CHD (Tables 4 and 5) could in part stem from "prevalence-incidence bias" [21], for example, decreased survival post-CHD in those with, compared to those without, the risk factor. Alternatively, this observation may result from temporal bias ("reverse causality") due to changes in lifestyle after clinical manifestations of coronary disease. The latter would be consistent with the literature reporting changes in lifestyle habits (e.g., quitting smoking and reducing intake of dietary fat) in heart attack survivors [22,23]. Such changes will affect studies in which the effect of these risk factor is assessed cross sectionally.

Another intriguing finding is that presence of the risk factor in 1974 only, was more strongly associated with clinical atherosclerosis than when the risk factor was present in both periods. It is possible that those who had the risk factor in 1974 and made successful effort to change their status before 1987 were at particularly high risk to begin with, for example, because of clustering of other risk factors and/or comorbidity, and that that is why they made the effort. It is also possible that this apparent stronger effect of the 1974 risk-factor status compared with its persistence might stem from survival bias. Given that the present study was restricted to participants in both the 1974 and 1987–1989 surveys, all the dropouts (including deaths) that occurred in the interim period are excluded; thus, it is theoretically possible that the subset of participants with persistent risk factors at both times may include a larger proportion of individual with particular resistance to these risk factors (e.g., lesser susceptibility stemming from genetic makeup or lack of other contributing environmental risk factors). The possibility of survival bias is more theoretical than real in this case, however, because given the young age of the participants at the inception of this cohort (median 41 years), only a small number (we estimate less than 2%) will be expected to die between the surveys in this study. Furthermore, as both longitudinal and cross-sectional analyses presented here are restricted to survivors, we think it is unlikely that this survival bias would differentially affect both types of analyses, thus affecting the "internal" validity of these comparisons.

The results for hypercholesterolemia should be interpreted with caution, given the peculiar nature of the subset of participants used for these analyses (atherosclerosis cases and controls). In fact, when the same cross-sectional analysis was replicated in the entire ARIC cohort with nonmissing relevant information (n = 15,338) or in the entire CLUE-ARIC cohort (n = 1410), the corresponding age-gender–adjusted prevalence ratio of clinical CHD in rela-

tion to hypercholesterolemia was 1.6 in both cases. Nonetheless, it is noteworthy that the discrepant longitudinal vis-à-vis cross-sectional results obtained in our case-control sample (Table 5) correspond almost exactly with the findings of Friedman *et al.* [9] in the Framingham study, in which the longitudinal association of baseline cholesterol levels with incident clinical CHD contrasted with the practically absent cross-sectional association. Furthermore, for hypertension, both our study and the earlier report from Framingham [9] show that the cross-sectional association, while slightly weaker than the longitudinal one, was still present.

In contrast with the clinical outcomes, the cross-sectional associations between risk factors and subclinical outcomes (presence of plaque or average carotid IMT in those without clinical CHD) were generally almost as strong as those observed in the corresponding longitudinal analyses (Tables 4 and 5). This pattern underscores the advantages of using subclinical measures of atherosclerosis compared with clinical outcomes when assessing cross-sectional associations [3,24,25]. The subclinical character of the outcome reduces the likelihood of disease-related prior changes in the individual's behavior or changes due to treatment that greatly limit the interpretation of associations observed in cross-sectional studies using clinical outcomes.

That the subclinical associations tended to be stronger when the factor was present only in 1974 than when it was present only concurrently with the ultrasound measurement (Tables 4 and 5) suggests that an assessment of the risk factor 15 years earlier may be more representative of its long-term cumulative effects. It is hard to measure the cumulative exposure to hypertension or hypercholesterolemia. However, data related to smoking in this cohort is compatible with this hypothesis. Mean lifetime cumulative smoking (estimated by smoking history at the time of the ARIC examination) was 33 pack-years in those who were current smokers only in 1974 and only 23 pack-years for 1987–1989–only smokers. In addition, the presence of the risk factor only in the latter examination, unless it is an error, means recent onset and, consequently, less time for it to exert its harmful effects given the long latency process characterizing atherosclerosis. On the other hand, those who had the risk factor in 1974 but did not have it in 1987–1989 may include relatively large numbers of persons who quit smoking (or who had their high blood pressure or high cholesterol controlled shortly before 1987–1989). Indeed, for smoking, among individuals who reported in 1987–1989 that they had quit, of those who reported smoking in 1974, 30% had quit within 3 or less years prior to the ARIC examination, compared to 6% of those who were not smokers in 1974.

Regardless of the preceding discussion, an important inference from these results relates to the long-term importance of these risk factors. As evidenced by the stratified analyses (Tables 4 and 5), those who were smoking, or hypertensive, or hypercholesterolemic in early adulthood, maintain substantial elevated risk of atherosclerosis (clinical or subclinical) about 15 years later, even if they were no longer exposed to the risk factor at the latter time. This conclusion is also consistent with data from other prospective studies documenting the important long-term effects of these risk factors [8,26–28].

As secondary objectives of the present study, we also documented strong tracking of risk factors in the 15-year period between the two surveys (Table 2). Moreover, we examined the predictors of acquisition and/or persistence of risk factors in the interim period between the surveys (Table 3). Perhaps the most striking findings of these analyses were the relation between weight loss in adulthood and acquisition/persistence of smoking; conversely, acquisition or persistence of hypertension was associated with adult weight gain.

One of the main limitations of this study is the lack of information on the presence of CHD or level of atherosclerosis at the earlier survey (1974). This prevents us from drawing firm conclusions regarding temporal associations. However, given the relatively young age of this cohort in 1974 (range 29–51 years) and the evolving character of atherosclerosis, it appears reasonable to assume a temporal relationship between the presence of the risk factor in 1974 and atherosclerosis measurements in 1987–1989.

Another potential limitation is that ultrasound measurements of the carotid arteries are not necessarily a direct measure of atherosclerosis per se. These measurements, however, have been validated with in vitro observations [17]. In addition, ultrasound assessment of the carotid arteries has been shown to correlate with both prevalent and incident CHD [19,29–31].

This study shows that cardiovascular risk factors track throughout adulthood and have longstanding atherogenic effects. These results confirm the critical importance of targeting young adults in order to prevent the consequences of atherosclerosis later in life.

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