The Association Between Lipid Levels and the Risks of Incident Myocardial Infarction, Stroke, and Total Mortality: The Cardiovascular Health Study

Bruce M. Psaty, MD, PhD, Melissa Anderson, MS,† Richard A. Kronmal, PhD,† Russell P. Tracy, PhD,‡ Trevor Orchard, MD,§ Linda P. Fried, MD, MPH,‖ Thomas Lumley, PhD,† John Robbins, MD,¶ Greg Burke, MD, MS,# Anne B. Newman, MD,§ and Curt D. Furberg, MD, PhD#*

OBJECTIVES: To assess the association between lipid levels and cardiovascular events in older adults.

DESIGN: A prospective population-based study.

SETTING: Four field centers in U.S. communities.

PARTICIPANTS: A total of 5,201 adults aged 65 and older living in U.S. communities, plus a recruitment of 687 African Americans 3 years later.

MEASUREMENTS: Fasting lipid measures included low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides.

RESULTS: At baseline, 1,954 men and 2,931 women were at risk for an incident myocardial infarction (MI) or stroke. During an average 7.5-year follow-up, 436 subjects had a coronary event, 332 had an ischemic stroke, 104 a hemorrhagic stroke, and 1,096 died. After adjustment, lipid measures were not major predictors of the outcomes of MI, ischemic stroke, hemorrhagic stroke, and total mortality. For total cholesterol and LDL-C, the associations with MI and ischemic stroke were only marginally significant. HDL-C was inversely associated with MI risk (hazard ratio = 0.85 per standard deviation of 15.7 mg/dL, 95% confidence interval = 0.76–0.96). For the outcome of ischemic stroke, high levels of HDL-C were associated with a decreased risk in men but not women. Lipid measures were generally only weakly associated with the risks of hemorrhagic stroke or total mortality.

CONCLUSION: In this population-based study of older adults, most lipid measures were weakly associated with cardiovascular events. The association between low HDL-C and increased MI risk was nonetheless strong and consistent. **J Am Geriatr Soc 52:1639–1647, 2004.**

Key words: myocardial infarction; stroke; total mortality; cholesterol; lipids; older adults

Although the association between lipid levels and cardiovascular risk is strong and graded in middle-aged adults,[1,2] the relationship is weaker and more controversial in older adults.[3] In several studies of older adults, coronary heart disease (CHD) is directly associated with total cholesterol[4,5] and inversely associated with high-density lipoprotein cholesterol (HDL-C).[6] Recent reports from the Framingham Study have focused on risk prediction models,[7] which include low-density lipoprotein cholesterol (LDL-C) or total cholesterol and HDL-C for men and women younger than 75. Nonetheless, the strength of the association defined in terms of relative risk tends to decline with age.[8,9] For cerebrovascular disease, the type of stroke appears to be important. In the Multiple Risk Factor Intervention Trial, total cholesterol was found to be directly associated with ischemic-stroke mortality and inversely associated with hemorrhagic-stroke mortality.[10] One study reported an association between high HDL-C levels and a reduced risk of ischemic stroke.[11] In several studies of total mortality in older adults,[12,13] cholesterol level was found to be inversely associated with all-cause mortality.

Recommendations for screening and treatment of elevated cholesterol levels in older adults have relied heavily on extrapolations from clinical trial data from middle-aged

From the *Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, †Department of Biostatistics, University of Washington, Seattle, Washington; ‡Departments of Biochemistry and Pathology, University of Vermont, Colchester, Vermont; §Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania; ‖Department of Medicine, Johns Hopkins University, Baltimore, Maryland; ¶Department of Medicine, University of California at Davis, Sacramento, California; and #Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

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Address correspondence to Bruce M. Psaty, MD, PhD, Cardiovascular Health Research Unit, 1730 Minor Avenue, Suite 1360, Seattle, WA 98101. E-mail: psaty@u.washington.edu

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persons or from those with established CHD.[14] Although the secondary prevention trials evaluating hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) have included large numbers of older adults,[15–17] the clinical trial evidence that statin therapy may prevent a first CHD event in older adults is more limited.[18–20] Data from epidemiological association studies have also been derived largely from middle-aged persons and men,[1,2] although pooling of a large number of diverse observational studies in older adults demonstrated a modestly increased risk.[3]

The Cardiovascular Health Study (CHS) is a large, multicenter, population-based cohort study of risk factors for cardiovascular disease (CVD) and stroke in men and women aged 65 and older.[21] CHS data were used to assess the association between total cholesterol, LDL-C, HDL-C, and triglycerides and the risks of myocardial infarction (MI), stroke, and total mortality.

METHODS

Setting

In June 1990, four field centers completed the recruitment of 5,201 participants. In June 1993, an additional 687 African Americans were recruited using similar methods. Each community sample was obtained from random samples of the Medicare eligibility lists, and those eligible to participate included all persons who were living in the household of each individual sampled from the Health Care Finance Agency (now called Centers for Medicare and Medicaid Services) lists who were aged 65 and older, were noninstitutionalized, expected to remain in the area for 3 years, gave informed consent, and did not require a proxy respondent. Of those contacted and eligible, 57.3% were enrolled. The CHS design and recruitment experiences are described in detail elsewhere.[21,22]

Baseline Examination

The baseline examination on 5,201 older adults consisted of a home interview and a clinic examination in 1989–90. An additional 687 African Americans were evaluated using the same methods in 1992–93. Participants answered standard questionnaires assessing a variety of risk factors, including smoking, physical activity, and medical history of cardiovascular conditions and procedures.[21] Self-reported medical conditions such as MI, angina pectoris, and stroke were validated.[23] Medications were assessed using an inventory at the home interview.[24]

Participants were asked to come to the clinic examination after an 8- to 12-hour overnight fast. All examinations were scheduled in the morning. Standardized measures included seated blood pressure, ankle-arm systolic blood-pressure index, weight, height, fasting blood samples for glucose, total cholesterol, HDL-C, and triglycerides, standardized according to the Centers for Disease Control and Prevention as previously described.[21,25] LDL-C was calculated according to the Friedewald equation.[26] C-reactive protein (CRP) was measured using a high-sensitivity assay. Laboratory drift in total cholesterol levels was detected in CHS between the baseline measure in 1989–90 for the original cohort and 1992–93 for the minority cohort; the drift was verified by comparing the baseline measures to Able-Kendall measurements on a subset of the cohort. To correct for this drift, 3.25 was subtracted from the original cohort measures, and 6.97 was added to the new cohort measures of total cholesterol. Because LDL-C levels were calculated from the total cholesterol, they were adjusted as well.

Carotid sonography was performed using the Toshiba SSA-270 A sonographic units (Toshiba America Medical Systems, Tustin, CA). The ultrasound reading center recorded and read a single longitudinal lateral view with measurements taken at the distal 10 mm of the far wall of the right and left common carotid arteries and three views with measurements centered on the site of maximum wall thickening of the proximal right and left internal carotid arteries.[27] The maximal intimal-medial thickness (IMT) was the average of the discrete maximum separately for the common and internal carotids.

Subjects were excluded from these analyses if they had had an MI, stroke, or congestive heart failure before entry into CHS[23] or if they had had missing data at baseline on key variables, including lipid measures, diabetes mellitus, carotid ultrasound, blood pressure, or smoking status.

Follow-Up and Classification of Events

Participants were contacted every 6 months; the contacts alternated between a telephone interview and a clinic examination. At each contact, participants were asked about cardiovascular events and all hospitalizations. Discharge summaries and diagnoses were obtained for all hospitalizations. For all potential incident cardiovascular events, additional information, including chest-pain history, cardiac enzymes, and serial electrocardiograms for potential MI events and onset of symptoms, duration of deficits, and findings on computed tomography or magnetic resonance imaging examinations for potential stroke events, was collected. The CHS Cardiovascular Events Committee and the CHS Stroke Committee reviewed and classified all potential MI and stroke events, respectively. The algorithms for classifying MI[28] and stroke[29] have been published. MI in this analysis included definite and probable hospitalized nonfatal MI and fatal MI. Stroke included fatal and nonfatal stroke; results are presented separately for the subtypes of ischemic and hemorrhagic stroke.

For analyses of MI or stroke, event times were computed as the time to the first event. Subjects could have an incident MI and an incident stroke during follow-up, and these subjects were included as events in both analyses. For subjects without an MI or stroke, censoring times were calculated according to the last date of follow-up or the date of death. For analyses of total mortality, event times were times to death, and censoring times were the dates of last follow-up.

Definition of Variables and Methods of Statistical Analysis

Although participants with a validated prebaseline MI or stroke were excluded, some had a history of CHD, defined as a history at baseline of angina pectoris, coronary angioplasty, or coronary artery by-pass surgery. Clinical CVD was defined as a history at baseline of CHD, carotid endarterectomy, or peripheral vascular disease surgery.

Diabetes mellitus was defined as a fasting glucose of 126 mg/dL or greater[30] or the use of insulin or oral hypoglycemic agents. Treated hypertension at baseline was defined, regardless of blood pressure level, as report of a history of high blood pressure and use medications that are usually used to treat hypertension.

With two minor exceptions, the current Adult Treatment Panel III (ATP III) guidelines were used to define categories of lipid levels (given here in mg/dL).[14] The total cholesterol categories were less than 160, 160 to 199, 200 to 239, and 240 or greater; the LDL-C categories were less than 100, 100 to 129, 130 to 159, 160 to 189, and 190 or greater; the HDL-C categories were less than 40, 40 to 59, and 60 or greater; and the triglyceride categories were less than 150, 150 to 199, 200 to 399, and 400 or greater. Cholesterol levels less than 200 were divided into two groups, and the boundary between the last two triglyceride categories differs from the ATP III recommendation of 500 or greater. Subjects with triglycerides greater 400 do not have values of calculated LDL-C.[26]

In models that used continuous lipid measures, each measure was divided by its standard deviation to facilitate comparisons between total cholesterol, LDL-C, HDL-C, and triglycerides. Based on previous work[31] and sensitivity analyses, Cox models were adjusted for major risk factors, including age, sex, current smoking, diabetes mellitus, systolic blood pressure, and clinical CVD. In sensitivity analyses, centered linear-plus-quadratic terms were used to screen lipid levels for deviations from linear associations between lipid levels and the risk of MI, stroke, and total mortality. Significant deviations from the linear model were further explored. For each endpoint, sensitivity analyses included potential two-way interactions with age, sex, diabetes mellitus, race, CRP level, carotid IMT, and clinical CVD. In additional sensitivity analyses, subjects on lipid-lowering therapy were excluded from the analyses.

SPSS for Windows was used for data analysis (Version 10, SPSS Inc., Chicago, IL). Techniques included analysis of variance for continuous variables, chi-square tests for categorical variables, and Cox proportional hazards models for multivariate analysis.[32] All *P*-values represent two-sided tests. These analyses were based on the updated CHS database, which incorporates minor corrections through April 20, 2001.

RESULTS

Ineligible for this analysis were 351 men and 212 women who, at baseline, had a history of MI; 109 men and 93 women who had had a previous stroke; and 49 men and 87 women who had had congestive heart failure. Another 32 men and 70 women were excluded because of missing data on lipids (n = 49), carotid ultrasound (n = 21), diabetes mellitus status (n = 17), blood pressure (n = 9), or smoking status (n = 6). Of 5,888 participants in CHS, 1,954 men and 2,931 women who were at risk of a first MI or stroke were included in this analysis and followed for an average of 7.5 years.

Lipid levels for men and women were significantly different,[33] so sex-specific results are presented for the baseline risk factors in subjects according to ATP III categories of total cholesterol. In women (Table 1), cholesterol level was associated with common and internal carotid IMT but not weight or physical activity. In men (Table 1), cholesterol was associated with height and diastolic blood pressure but not with weight or either measure of carotid IMT. At baseline, lipid-lowering therapy was uncommon in CHS[34] and even in ATP II diet- or drug-eligible subjects increased only modestly during follow-up.[35]

Tables 2 and 3 show the crude incidence rates for the four endpoints according to various ATP III lipid categories in women and men. The data include the number of subjects (N), events (n), person-years (PY), and the rates of events per 1,000 PY. In Table 4, data on men and women were combined. Each model represents the association between one of the four continuous lipid measures and one of the four outcomes. The hazard ratios (HRs) represent a change in risk for each standard deviation of change in the lipid measure. Of the 16 models adjusted for age, sex, diabetes mellitus, smoking, systolic blood pressure, and clinical CVD, the most pronounced HR was 0.85 for the association between HDL-C and MI risk (95% confidence interval (CI) = 0.76–0.96). This association was similar in men (HR = 0.82, 95% CI = 0.69–0.98) and women (HR = 0.85, 95% CI = 0.72–1.00; $P = .04$). Although there was no statistical evidence of an interaction ($P = .10$), the HDL-C–MI association was more pronounced in subjects younger than 75 (HR = 0.75, 95% CI = 0.64–0.88) than in subjects aged 75 and older (HR = 0.95, 95% CI = 0.80–1.13). Other lipid associations were generally marginal with ischemic stroke, weak with hemorrhagic stroke, and total mortality (Table 4).

For the association between ischemic stroke and HDL-C, the quadratic term contributed significantly to the model. The inverse association between ischemic stroke and HDL-C was less pronounced in women than men (Tables 2 and 3). In additional analyses using quintiles of HDL-C levels, the ischemic stroke rates in women were 2.6, 9.3, 7.9, 10.2, and 7.1 per 1,000 person years, respectively. For women, the HDL-C–ischemic stroke HR was 1.00 (95% CI = 0.87–1.16); for men, it was 0.74 (95% CI = 0.58–0.94). These sex-specific HRs differed significantly ($P = .03$). A systematic assessment of 80 potential interactions of the 16 associations between four lipid measures and four outcomes in groups defined by age, sex, race, diabetes mellitus, and clinical CVD identified only four others that were statistically significant at the .05 level. For ischemic stroke, for instance, the association with total cholesterol was slightly stronger in subjects aged 75 and older (HR = 1.23, 95% CI = 1.06–1.44) than in subjects aged 65 to 74 (HR = 1.03, 95% CI = 0.89–1.20; *P* for difference in HRs = .03).

Table 5 summarizes the findings for more complex models that included two lipid measures. For the adjusted MI risk, the addition of total cholesterol to the model with HDL-C alone improved the fit. The findings for the adjusted model with LDL-C and HDL-C were similar, although LDL-C did not significantly improve the model with HDL-C alone. For the outcomes of ischemic stroke, hemorrhagic stroke, and death, no other two-lipid model represented a significant improvement over the weak associations for the single-lipid model.

In additional analyses comparing the associations for early versus late events for all outcomes, the associations

Table 1. Characteristics of Participants by Levels of Total Cholesterol

Characteristic	Total Cholesterol Category							
	Women				Men			
	<200 (n = 865)	200–239 (n = 1,208)	≥240 (n = 858)	Total (N = 2,931)	<200 (n = 1,040)	200–239 (n = 703)	≥240 (n = 211)	Total (N = 1,954)
Age, mean ± SD	72.5 ± 5.6	72.3 ± 5.2	72.0 ± 5.2	72.3 ± 5.3	73.3 ± 5.8	72.9 ± 5.7	72.2 ± 4.9	73.0 ± 5.7*
Weight, pounds, mean ± SD	150.1 ± 34.4	148.4 ± 30.2	149.8 ± 28.6	149.3 ± 31.1	174.5 ± 27.8	175.5 ± 26.8	176.7 ± 27.8	175.1 ± 27.4
Height, cm, mean ± SD	159.3 ± 6.4	158.8 ± 6.2	158.7 ± 6.1	158.9 ± 6.2	173.7 ± 6.5	172.8 ± 6.5	172.4 ± 6.6	173.2 ± 6.5*
Body mass index, kg/m^2, mean ± SD	26.8 ± 5.7	26.7 ± 5.1	26.9 ± 4.8	26.8 ± 5.2	26.2 ± 3.7	26.6 ± 3.6	26.9 ± 3.6	26.4 ± 3.7*
Physical activity, kcal/wk, mean ± SD	1,687 ± 2,045	1,587 ± 1,900	1,613 ± 2,013	1,624 ± 1,977	1,991 ± 2,160	1,984 ± 2,166	2,052 ± 2,223	1,995 ± 2,168
Systolic blood pressure, mmHg, mean ± SD	136.2 ± 21.3	136.0 ± 21.8	137.2 ± 21.8	136.4 ± 21.7	135.3 ± 21.5	137.2 ± 20.2	136.3 ± 21.2	136.1 ± 21.0
Diastolic blood pressure, mmHg, mean ± SD	69.5 ± 11.3	70.0 ± 11.0	70.2 ± 11.0	69.9 ± 11.1	71.9 ± 11.3	73.3 ± 11.5	74.0 ± 10.1	72.6 ± 11.3*
Pulse pressure, mean ± SD	66.7 ± 18.5	65.9 ± 19.2	67.0 ± 18.7	66.4 ± 18.8	63.4 ± 18.4	64.0 ± 17.0	62.3 ± 17.4	63.5 ± 17.8
Total cholesterol, mg/dL, mean ± SD	178.2 ± 18.2	219.7 ± 11.3	267.0 ± 23.6	221.3 ± 38.4†	172.8 ± 20.2	218.2 ± 10.9	262.7 ± 23.5	198.8 ± 35.4†
High-density lipoprotein cholesterol, mg/dL, mean ± SD	57.0 ± 14.6	60.5 ± 15.7	61.0 ± 17.2	59.6 ± 15.9†	46.5 ± 11.9	50.1 ± 13.4	51.3 ± 13.3	48.3 ± 12.8†
Low-density lipoprotein cholesterol, mg/dL, mean ± SD	97.3 ± 19.9	132.9 ± 17.3	174.8 ± 27.1	134.6 ± 36.6†	101.7 ± 20.3	139.9 ± 16.1	180.6 ± 26.4	123.9 ± 33.0†
Triglycerides , mg/dL, mean ± SD	123.7 ± 67.0	133.5 ± 67.2	159.1 ± 75.8	138.1 ± 71.2†	125.9 ± 67.1	146.6 ± 85.4	159.8 ± 76.4	137.0 ± 76.2†
Fasting glucose, mg/dL, mean ± SD	109.4 ± 37.8	106.6 ± 31.1	108.9 ± 38.0	108.1 ± 35.3	111.8 ± 34.1	111.7 ± 31.5	114.1 ± 39.9	112.0 ± 33.8
C-reactive protein, mean ± SD	3.80 ± 6.09	3.22 ± 4.67	3.27 ± 4.51	3.40 ± 5.09*	3.76 ± 8.24	2.89 ± 4.06	2.95 ± 3.52	3.36 ± 6.60*
Lipid-lowering medications, %	3.7	6.0	7.4	5.7*	2.6	5.5	5.7	4.0*
Ankle-arm index, mean ± SD	1.07 ± 0.14	1.06 ± 0.14	1.04 ± 0.16	1.06 ± 0.14†	1.11 ± 0.19	1.09 ± 0.18	1.08 ± 0.18)	1.10 ± 0.18
Maximum intimal-medial thickness, mean ± SD								
Common carotid	1.01 ± 0.18	1.02 ± 0.19	1.03 ± 0.19	1.02 ± 0.19*	1.10 ± 0.22	1.11 ± 0.23	1.12 ± 0.23	1.10 ± 0.23
Internal carotid	1.24 ± 0.47	1.30 ± 0.50	1.38 ± 0.53	1.31 ± 0.50†	1.51 ± 0.60	1.56 ± 0.57	1.57 ± 0.57	1.53 ± 0.59
History of cardiovascular disease, %	9.7	9.3	10.8	9.9	13.0	15.4	13.7	13.9
Angioplasty	0.3	0.5	1.1	0.6	1.1	1.4	0.0	1.1
Bypass surgery	0.2	0.9	0.9	0.7	4.2	4.3	3.3	4.1
Angina pectoris	8.0	8.2	9.6	8.5	10.8	12.4	10.4	11.3
Carotid endarterectomy	0.7	0.3	0.6	0.5	1.1	1.7	2.9	1.5
Peripheral vascular disease surgery	1.1	1.2	1.1	1.1	1.4	1.9	2.4	1.7
African American, %	19.2	15.1	12.5	15.6†	12.7	14.7	11.4	13.3
Self-reported hypertension, %	46.7	46.9	47.1	46.9	42.6	43.2	38.6	42.4
Treated hypertension, %	39.7	37.0	37.2	37.8	31.3	32.0	32.2	31.7
Insulin or oral hypoglycemic agents, %	8.3	5.2	5.4	6.2*	10.9	6.8	7.1	9.0*
Diabetes mellitus or impaired fasting glucose, %	15.1	10.8	13.2	12.8*	18.6	14.7	14.7	16.7
Current smoker, %	13.6	12.0	12.6	12.7	12.2	10.8	5.2	11.0*
≥High school education, %	72.8	73.4	72.0	72.8	71.6	70.9	70.6	71.3
Self-reported health very good or excellent, %	38.6	42.9	39.3	40.6	42.6	44.1	41.7	43.0
Married, %	54.7	56.5	55.7	55.7	82.1	83.6	86.7	83.1

Note: To convert from mg/dL to mmol/L, multiply by 0.0259 for cholesterol, 0.0555 for glucose, and 0.0113 for triglycerides.
P-value <* .05; † .001. The *P* = values refer to sex-specific differences among the lipid groups.

Table 2. Rates (Per 1,000 Person Years (PY)) of Myocardial Infarction, Stroke, and Total Mortality by Traditional Levels of Total, High-Density Lipoprotein Cholesterol (HDL-C), and Low-Density Lipoprotein Cholesterol (LDL-C), and Triglycerides in Women

		Myocardial Infarction			Hemorrhagic Stroke			Ischemic Stroke			Total Mortality		
Lipid Range	N	n	PY	Rate*	n	PY	Rate*	n	PY	Rate*	n	PY	Rate*
Total cholesterol													
<160 (optimal)	142	5	1,009	5.0	5	1,015	4.9	8	1,015	7.9	38	1,033	36.8
160–199 (desirable)	723	37	5,336	6.9	15	5,301	2.8	38	5,290	7.2	139	5,437	25.6
200–239 (borderline)	1,208	78	9,070	8.6	24	9,002	2.7	86	9,000	9.6	205	9,323	22.0
≥240 (high)	858	66	6,376	10.4	11	6,356	1.7	64	6,355	10.1	149	6,586	22.6
LDL-C													
≤100 (optimal)	463	26	3,363	7.7	13	3,351	3.9	26	3,347	7.8	111	3,446	32.2
100–129 (near optimal)	896	47	6,722	7.0	20	6,657	3.0	56	6,650	8.4	148	6,873	21.5
130–159 (borderline high)	887	54	6,632	8.1	12	6,621	1.8	58	6,620	8.8	143	6,817	21.0
160–189 (high)	456	43	3,400	12.6	6	3,374	1.8	37	3,374	11.0	82	3,514	23.3
≥190 (very high)	198	13	1,456	8.9	3	1,449	2.1	16	1,447	11.1	37	1,491	24.8
HDL-C													
<40 (low)	206	16	1,528	10.5	2	1,508	1.3	19	1,503	12.6	44	1,592	27.6
40–59 (normal)	1,432	106	10,575	10.0	22	10,540	2.1	96	10,534	9.1	276	10,868	25.4
≥60 (high)	1,293	64	9,686	6.6	31	9,626	3.2	81	9,623	8.4	211	9,918	21.3
Triglycerides													
<150) (normal	2,018	123	14,961	8.2	45	14,892	3.0	125	14,884	8.4	365	15,336	23.8
150–199 (borderline)	511	30	3,814	7.9	5	3,787	1.3	37	3,786	9.8	93	3,900	23.8
200–399 (high	370	30	2,787	10.8	4	2,764	1.4	31	2,760	11.2	63	2,896	21.8
≥400 (very high)	32	3	227	13.2	1	230	4.3	3	230	13.0	10	245	40.8

* Cases per 1,000 PY.
N = number of subjects; n = number of events.

remained weak and no consistent pattern emerged. For the outcome of MI, there was no evidence of an interaction between HDL-C or total cholesterol and common carotid IMT ($P = .52$ and $P = .98$, respectively), nor was there an interaction between these two lipid measures and CRP ($P = .61$ and $P = .28$, respectively). Excluding subjects on lipid treatment and additional adjustment for CRP affected the point estimates in only trivial ways.

DISCUSSION

In this population-based study of 4,885 older adults at risk for incident CHD or stroke, lipid measures were not the major predictors of the outcomes of MI, ischemic stroke, hemorrhagic stroke, and total mortality during 7.5 years of follow-up. None of lipid measures was significantly associated with total mortality. The associations between total cholesterol and LDL-C and MI and ischemic stroke were marginally significant despite large numbers of cardiovascular events—436 MIs and 332 ischemic strokes. HDL-C was strongly and inversely associated with the risk of MI (HR = 0.85, 95% CI = 0.76–0.96); this association was consistent in men and women. For the outcome of ischemic stroke, high levels of HDL-C were associated with a decreased risk in men but not women. Lipid measures were only weakly associated with the risks of hemorrhagic stroke or total mortality. With the exception of the combination of total and HDL-C and MI risk, the models with multiple lipid measures did not improve the prediction. In sensitivity analyses, there were not more interactions than expected by chance alone.

This population-based study included a more representative sample than is typically recruited for clinical trials, measurements were done in a standardized fashion, and event follow-up was long-term and complete. Because the primary effort was to describe associations with cardiovascular events and to test in CHS findings previously reported in the literature, no adjustment was made for multiple testing. At baseline, lipids were assessed only once; measurement error and biological variability of a single baseline measure would make it more difficult to detect associations.

Findings from the CHS were similar to those reported by some other cohort studies of older adults. Many studies have identified weak associations between lipids and cardiovascular events or total mortality in older adults.[3,4,12,13,36] In the CHS, lipid levels were not associated with total mortality; chronic inflammation, which reduces lipid levels, may be partly responsible for the lack of association.[37,38] In the CHS, total and calculated LDL-C levels were so weakly related to MI and stroke risk that their levels measured in adults aged 65 and older are not likely to improve risk prediction in older adults. Similarly, the small risk differences between lipid categories suggest that the number needed to treat to prevent one event is large. The findings are in contrast to recent reports of CHD risk in diverse middle-aged cohorts, in whom direct LDL-C associations and indirect HDL-C associations are typically strong and linear.[39]

Risk stratification is an important effort in targeting therapies to patients most likely to benefit.[40] The use of clinical conditions—diabetes mellitus or chronic renal disease—as CHD risk equivalents is easy to understand and

Table 3. Rates (Per 1,000 Person Years (PY)) of Myocardial Infarction, Stroke, and Total Mortality by Traditional Levels of Total, High-Density Lipoprotein Cholesterol (HDL-C), and Low-Density Lipoprotein Cholesterol (LDL-C), and Triglycerides in Men

		Myocardial Infarction			Hemorrhagic Stroke			Ischemic Stroke			Total Mortality		
Lipid Range	N	n	PY	Rate*	n	PY	Rate*	n	PY	Rate*	n	PY	Rate*
Total cholesterol													
<160 (optimal)	262	32	1,747	18.3	7	1,773	3.9	18	1,767	10.2	88	1,835	48.0
160–199 (desirable)	778	100	5,338	18.7	22	5,464	4.0	48	5,466	8.8	222	5,637	39.4
200–239 (borderline)	703	93	4,746	19.6	16	4,812	3.3	56	4,808	11.6	197	5,052	39.0
≥240 (high)	211	25	1,446	17.3	4	1,492	2.7	14	1,486	9.4	58	1,538	37.7
LDL-C													
≤100 (optimal)	461	50	3,160	15.8	13	3,207	4.1	32	3,199	10.0	145	3,306	43.9
100–129 (near optimal)	675	90	4,561	19.7	13	4,679	2.8	41	4,680	8.8	197	4,831	40.8
130–159 (borderline high)	549	74	3,713	19.9	15	3,751	4.0	47	3,752	12.5	148	3,970	37.3
160–189 (high)	196	28	1,351	20.7	6	1,398	4.3	8	1,397	5.7	51	1,428	35.7
≥190 (very high)	51	6	345	17.4	2	351	5.7	8	345	23.2	16	372	43.0
HDL-C													
<40 (low)	503	80	3,395	23.6	15	3,461	4.3	46	3,452	13.3	158	2,650	43.3
40–59 (normal)	1,123	140	7,694	18.2	27	7,841	3.4	74	7,837	9.4	306	8,123	37.7
≥60 (high)	328	30	2,188	13.7	7	2,239	3.1	16	2,239	7.1	101	2,289	44.1
Triglycerides													
<150) (normal	1,364	163	9,271	17.6	33	9,437	3.5	81	9,437	8.6	388	9,763	39.7
150–199 (borderline)	322	48	2,156	22.3	12	2,233	5.4	27	2,222	12.2	91	2,318	39.3
200–399 (high	247	37	1,703	21.7	4	1,717	2.3	28	1,714	16.3	78	1,826	42.7
≥400 (very high)	22	2	146	13.7	0	155	0.0	0	155	0.0	8	155	51.7

* Cases per 1,000 PY.
N = number of subjects; n = number of events.

apply. CHS includes objective, validated measures of these risk-related conditions, as well as subclinical disease measures that may help unravel the complex relationship of cholesterol levels to asymptomatic atherosclerosis and clinical CHD events in older adults. Although subclinical disease measures such as carotid wall thickness and coronary calcium may eventually count as CHD risk equivalents and aid in risk stratification, total and HDL-C levels in CHS

Table 4. Risk of Myocardial Infarction, Stroke, and Total Mortality by Lipid Level

		Unadjusted Model			Adjusted Model*		
Outcome	Linear Term†	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Myocardial infarction	Total C	0.95	0.86–1.04	.24	1.09	0.98–1.20	.10
	LDL-C	1.02	0.93–1.12	.71	1.10	1.00–1.21	.053
	HDL-C	0.71	0.64, 0.79	<.001	0.85	0.76–0.96	.006
	Triglycerides	1.11	1.03, 1.20	.015	1.07	0.99–1.16	.10
Hemorrhagic stroke	Total C	0.87	0.71–1.05	.25	0.92	0.75–1.13	.45
	LDL-C	0.89	0.73–1.09	.27	0.94	0.76–1.15	.53
	HDL-C	0.95	0.78–1.16	.60	1.00	0.81–1.24	.99
	Triglycerides	0.84	0.66–1.07	.13	0.86	0.68–1.08	.17
Ischemic stroke	Total C	1.07	0.96–1.19	.22	1.13	1.01–1.26	.031
	LDL-C	1.08	0.97–1.20	.17	1.12	1.01–1.25	.038
	HDL-C	0.88	0.78–0.98	.019	0.92	0.81–1.04	.15
	Triglycerides	1.13	1.04–1.24	.009	1.10	1.01–1.20	.046
Death	Total C	0.86	0.81–0.91	<.001	0.98	0.92–1.04	.50
	LDL-C	0.89	0.84–0.95	<.001	0.97	0.92–1.04	.38
	HDL-C	0.86	0.81–0.92	<.001	0.99	0.92–1.06	.73
	Triglycerides	1.05	0.99–1.11	.11	1.05	0.99–1.11	.13

* Adjusted for age, sex, diabetes mellitus, smoking status, cardiovascular disease, and systolic blood pressure.
† Linear terms entered in units of standard deviation (SD): 38.3 for total cholesterol, 35.6 for low-density lipoprotein cholesterol (LDL-C), 15.7 for high-density lipoprotein cholesterol (HDL-C), and 73.2 for triglycerides.
CI = confidence interval; HR = hazard ratio.

Table 5. Risk of Events with Multiple Lipids in the Same Model

Outcome-Model	Lipid*	Unadjusted Model			Adjusted Model†		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
MI-1	Total C	0.95	0.86–1.04	.24	1.09	0.98–1.20	.10
MI-2	LDL-C	1.02	0.93–1.12	.71	1.10	1.00–1.21	.053
MI-3	HDL-C	0.71	0.64–0.79	<.001	0.85	0.76–0.96	.006
MI-4	Triglycerides	1.11	1.03–1.20	.015	1.07	0.99–1.16	.10
MI-5‡	Total C	1.01	0.92–1.11	.80	1.11	1.00–1.22	.043
	HDL-C	0.71	0.63–0.79	<.001	0.84	0.75–0.94	.003
MI-6‡	LDL-C	1.01	0.91–1.10	.92	1.09	0.99–1.20	.10
	HDL-C	0.71	0.63–0.79	<.001	0.86	0.76–0.96	.009
MI-7‡	Total C	0.93	0.84–1.02	.12	1.07	0.97–1.18	.17
	Triglycerides	1.12	1.04–1.21	.004	1.06	0.98–1.15	.16
Hemorrhagic Stroke-1	Total C	0.87	0.71–1.05	.25	0.92	0.75–1.13	.45
Hemorrhagic Stroke-2	LDL-C	0.89	0.73–1.09	.27	0.94	0.76–1.15	.53
Hemorrhagic Stroke-3	HDL-C	0.95	0.78–1.16	.60	1.00	0.81–1.24	.99
Hemorrhagic Stroke-4	Triglycerides	0.84	0.66–1.07	.13	0.86	0.68–1.08	.17
Hemorrhagic Stroke-5‡	Total C	0.87	0.71–1.06	.17	0.92	0.75–1.13	.44
	HDL-C	0.98	0.80–1.20	.84	1.01	0.82–1.25	.91
Hemorrhagic Stroke-6‡	LDL-C	0.89	0.73–1.09	.25	0.93	0.76–1.15	.52
	HDL-C	0.93	0.76–1.13	.47	0.98	0.79–1.21	.84
Hemorrhagic Stroke-7‡	Total C	0.89	0.73–1.08	.24	0.95	0.77–1.18	.64
	Triglycerides	0.87	0.68–1.10	.24	0.87	0.68–1.10	.25
Ischemic Stroke-1	Total C	1.07	0.96–1.19	.22	1.13	1.01–1.26	.031
Ischemic Stroke-2	LDL-C	1.08	0.97–1.20	.17	1.12	1.01–1.25	.038
Ischemic Stroke-3	HDL-C	0.88	0.78–0.98	.019	0.92	0.81–1.04	.15
Ischemic Stroke-4	Triglycerides	1.13	1.04–1.24	.009	1.10	1.01–1.20	.046
Ischemic Stroke-5‡	Total C	1.10	0.99–1.22	.08	1.14	1.02–1.27	.018
	HDL-C	0.86	0.76–0.96	.010	0.90	0.79–1.02	.10
Ischemic Stroke-6‡	LDL-C	1.07	0.96–1.19	.22	1.11	1.00–1.24	.05
	HDL-C	0.88	0.78–0.98	.026	0.93	0.82–1.05	.24
Ischemic Stroke-7‡	Total C	1.05	0.94–1.16	.42	1.11	0.99–1.24	.06
	Triglycerides	1.13	1.03–1.23	.008	1.08	0.99–1.18	.09
Total mortality-1	Total C	0.86	0.81–0.91	<.001	0.98	0.92–1.04	.50
Total mortality-2	LDL-C	0.89	0.84–0.95	<.001	0.97	0.92–1.04	.38
Total mortality-3	HDL-C	0.86	0.81–0.92	<.001	0.99	0.92–1.06	.73
Total mortality-4	Triglycerides	1.05	0.99–1.11	.11	1.05	0.99–1.11	.13
Total mortality-5‡	Total C	0.88	0.83–0.94	<.001	0.98	0.92–1.04	.53
	HDL-C	0.89	0.83–0.95	<.001	0.99	0.93–1.06	.79
Total mortality-6‡	LDL-C	0.88	0.83–0.94	<.001	0.97	0.91–1.03	.37
	HDL-C	0.86	0.81–0.92	<.001	0.99	0.93–1.06	.76
Total mortality-7‡	Total C	0.85	0.80–0.90	<.001	0.97	0.91–1.03	.32
	Triglycerides	1.07	1.02–1.13	.011	1.05	0.99–1.11	.09

* Linear terms entered in units of standard deviation: 38.3 for total cholesterol, 35.6 for low-density lipoprotein cholesterol (LDL-C), 15.7 for high-density lipoprotein cholesterol (HDL-C), and 73.2 for triglycerides.
† Adjusted for age, sex, diabetes mellitus, smoking status, cardiovascular disease, and systolic blood pressure.
‡ The two terms were entered into the model simultaneously.
CI = confidence interval; HR = hazard ratio; MI = myocardial infraction.

were weak predictors in those with and without high values of carotid IMT at baseline.

HDL-C in older adults has been an important predictor of events in several studies. In the Established Populations for Epidemiologic Studies in the Elderly, low HDL-C was associated with a greater risk of CHD mortality and new CHD events.[6] In a case-control study of stroke survivors that included a large proportion of adults aged 65 and older, high levels of HDL-C were associated with a reduced risk of ischemic stroke.[11] The findings were similar in men and women. The interaction between sex and HDL-C and ischemic stroke in the CHS may represent a chance finding, because a large number of statistical tests for interactions were conducted.

The new ATP III guidelines reflect the accumulating clinical trial evidence that statins reduce the risk of cardiovascular events.[15–18] The evidence for statin treatment is so strong in the secondary prevention setting[41] that additional trials in secondary prevention[17] seem unnecessary. Few studies in the primary prevention setting have included adults aged 65 and older.[18] In one trial in 5,804 older adults,[19] pravastatin was associated with a greater risk

reduction in those with vascular disease (HR = 0.78, 95% CI = 0.66–0.93) than in those without (HR = 0.94, 95% CI = 0.77–1.15; *P* for interaction = .109).

The ATP III recommendations have appropriately and cautiously extrapolated the clinical trial findings to older adults without established CHD. Compared with the previous guidelines, the new ATP III recommendations have nonetheless increased the number of treatment-eligible older adults in the United States from 4.2 million to 9.7 million.[42] One study[42] suggests that this increase in the number of treatment-eligible older adults is not based on new evidence about the strength of the associations between lipids and events in older adults or on new evidence about the effectiveness of statins in primary prevention for older adults[19] but on the increase in risk associated with the weights given to age by the Framingham score. Moreover, several commentators have noted that the multiplicative risk associated with cholesterol declines with age.[8,9]

Epidemiological studies typically provide evidence of associations such as those between lipids and CVD risk. The resulting hypothesis that lowering lipids might reduce risk is a physiological extrapolation from epidemiologic data—one that can only be definitively evaluated in clinical trials. Subjects entered the CHS at age 65 and older, and the weak associations frequently observed in this study could be a result of loss to mortality before age 65 of those who had had high lipid levels. In the CHS, the use of statins was associated with a decreased risk of cardiovascular events.[35] Given the body of animal, human, clinical-trial, and observational evidence, the weak lipid-CVD associations in older adults reported here demonstrate the need for additional experimental evidence of primary prevention in older adults.[43] Indeed, the mechanisms of benefit for the statins may be in part unrelated to their ability to lower lipids.[44–47] If so, the risk reductions in older adults might be pronounced even though their lipid levels are only weakly associated with cardiovascular events. Further research needs to identify those older adults most likely to benefit from statin therapy.

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Participating Institutions, Principal Investigators, CHS: Wake Forest University School of Medicine: Curt D. Furberg, MD, PhD; Gregory L. Burke MD. Wake Forest University—ECG Reading Center: Pentti M. Rautaharju, MD, PhD. University of California, Davis: John Robbins, MD, MHS. The Johns Hopkins University: Linda P. Fried, MD, MPH. The Johns Hopkins University—MRI Reading Center: Nick Bryan, MD, PhD; Norman J. Beauchamp, MD. University of Pittsburgh: Lewis H. Kuller, MD, DrPH. University of California, Irvine—Echocardiography Reading Center (baseline): Julius M. Gardin, MD. Georgetown Medical Center—Echocardiography Reading Center (follow-up): John S. Gottdiener, MD. New England Medical Center, Boston—Ultrasound Reading Center: Daniel H. O'Leary, MD. University of Vermont—Central Blood Analysis Laboratory: Russell P. Tracy, PhD. University of Arizona, Tucson—Pulmonary Reading Center: Paul Enright, MD. University of Wisconsin—Retinal Reading Center: Ronald Klein, MD. University of Washington—Coordinating Center: Richard A. Kronmal, PhD. NHLBI Project Office: Teri A. Manolio, MD, PhD; Jean Olson, MD, MPH.

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