Increases in Serum Non-High-Density Lipoprotein Cholesterol May Be Beneficial in Some High-Functioning Older Adults: MacArthur Studies of Successful Aging

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(See editorial comments by Dr. Tamara Harris on pp 639–640.)

OBJECTIVES: To examine the association between changes in serum non-high-density lipoprotein cholesterol (non-HDL-C) over a 2.5-year period and risk of adverse health outcomes in the following 4.5 years in high-functioning older adults.

DESIGN: Prospective cohort, established in 1988, with a follow-up in 1991 and 1995.

SETTING: Population-based, community-dwelling men and women.

PARTICIPANTS: A random sample (n = 267) from the MacArthur cohort (N = 1,189). The cohort represented the highest-functioning tertile of 4,030 screened candidates aged 70 to 79.

MEASUREMENTS: Change in non-HDL-C between 1988 and 1991 was measured as a predictor of health outcomes between 1991 and 1995, including all-cause mortality, and among survivors, incident heart attack or stroke, development of new disability in basic activities of daily living, and decline in performance on the Short Portable Mental Status Questionnaire.

RESULTS: More-positive change in non-HDL-C between 1988 and 1991 was associated with fewer adverse outcomes between 1991 and 1995. In individuals whose total cholesterol at baseline was in the middle two quartiles (195–244 mg/dL), each 10-mg/dL increase in the 1988-to-1991 change in non-HDL-C was associated with an adjusted mortality odds ratio (OR) of 0.67 (95% confidence interval (CI) = 0.51–0.88). In individuals without cardiovascular disease at baseline, the adjusted OR for new physical disability was 0.79 (95% CI = 0.65–0.95) and for cognitive decline was 0.81 (95% CI = 0.67–0.98).

CONCLUSION: Increases in cholesterol over time have beneficial associations in some older adults. The role of cholesterol changes in the health of older individuals needs further exploration. **J Am Geriatr Soc 52:487–494, 2004.**

Key words: cholesterol; mortality; older adults; functional decline

Randomized clinical trials in elderly individuals, subgroup analysis of data from broader-based clinical trials, and cohort studies in older adults have demonstrated that treatment of elderly adults with 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk of major vascular events[1–3] and all-cause mortality.[4–6] This benefit of statin therapy is presumed to be the result of the lipid-lowering effect of statins, but many large prospective studies of older adults have found no statistically significant association between elevated levels of total serum cholesterol and all-cause mortality risk,[7–9] and several have found hypercholesterolemia to be protective against mortality in older individuals,[10] even after adjusting for serum albumin,[11] excluding individuals with low serum total cholesterol,[12] and excluding individuals who died within the first few years of cholesterol measurement.[11–13] With respect to the low-density lipoprotein (LDL) fraction of cholesterol, perhaps the main culprit in cardiovascular disease (CVD), Framingham analyses found an inverse association between serum LDL-C and all-cause mortality risk in those who were aged 66 and older at the time of

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Work on this article was supported by National Institutes of Health/National Institute on Aging (NIA) Mentored Clinical Scientist Development Award 1K12AG01004 and NIA Grants AG-17056 and AG-17265 and by the MacArthur Research Network on Successful Aging and the MacArthur Research Network on Socioeconomic Status and Health through grants from the John D. and Catherine T. MacArthur Foundation.

This research was previously presented at the 2002 Annual Meeting of the American Geriatrics Society.

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0002-8614/04/$15.00

cholesterol determination,[12] but other large cohort studies of older adults have found no statistically significant association between serum LDL-C and mortality risk, after adjusting for other risk factors.[13,14]

This contrast between the benefits of statin therapy and the questionable role of hypercholesterolemia as a marker of increased mortality risk in older individuals raises the possibility that the benefits of statin therapy result less from the effects of statins on serum cholesterol levels and more from their antiinflammatory, plaque-stabilizing, and other beneficial effects.[15,16] In fact, the benefits of statin therapy in clinical trials were independent of the LDL response to therapy,[1] were greater than that expected from the magnitude of LDL-C reduction,[17] and occurred faster than predicted from lipid-lowering alone.[18] Thus, the effects of changes in cholesterol levels in older adults are unclear.

Examining the health effects of recent change in serum cholesterol may resolve this lingering question about the role of lipid lowering in the care of older adults to some extent. The work reported here examines the association between changes in serum cholesterol over an initial 2.5-year period and health outcomes over the subsequent 4.5 years in a cohort of high-functioning elderly men and women.

METHODS

The Study Sample

Data for this study came from the MacArthur Studies of Successful Aging, a longitudinal study of high-functioning, community-dwelling women and men, aged 70 to 79. Detailed descriptions of the study have been published elsewhere.[19] Briefly, more than 4,000 men and women in this age group from three communities in the eastern United States (Durham, North Carolina; East Boston, Massachusetts; and New Haven, Connecticut) were screened on the basis of four criteria of physical functioning and two criteria of cognitive functioning to identify within the study sample the top functioning one-third. Of the 1,313 subjects who met all screening criteria, 91% (1,189) agreed to participate in the study and provided informed consent.

Baseline data (including age, sex, lifestyle characteristics, medications, body measurements, vital signs, performance tests of functioning ability, and a battery of blood tests) were collected beginning in May 1988. Repeat data were collected for the surviving men and women between 24 and 32 months (mean 28 months) after baseline, starting in May 1991. Attrition was 177 of 1,189 or 15%: 71 deaths (6%), 47 refusals to follow up (4%), and 59 partial or proxy interviews (5%). Because of financial constraints, the complete battery of blood tests was performed only on a random subsample (n = 267) of the remainder. Comparison of this sample with the full cohort suggests that they did not differ significantly on major characteristics of interest. A third set of data was collected after a mean interval of 57 months from first follow-up (standard deviation $\pm$ 7 months), beginning in October 1995.

Measurements

Primary Predictor

Serum levels of total and high-density-lipoprotein cholesterol (HDL-C) were measured at baseline and at first follow-up. Nonfasting blood samples were collected at participants' homes around 8 a.m. on the day after the interview and sent to Nichols Laboratories (San Juan Capistrano, CA). Total serum cholesterol was measured using enzymatic colorimetry,[20] and HDL-C was measured using the direct homogeneous method (Genzyme Diagnostics, Cambridge, MA), and rounded to the nearest 1 mg/dL. Total cholesterol and HDL-C are relatively insensitive to nonfasting versus fasting state at the time of the blood draw.[21] Because high levels of HDL-C are known to be beneficial in elderly men and women,[8,11] the health effects of changes over time in the non-HDL component of serum total cholesterol were examined. Accordingly, the primary predictor in this study was

$$(\text{1991 total cholesterol} - \text{1991 HDL-C}) - (\text{1988 total cholesterol} - \text{1988 HDL-C})$$

a positive value for which corresponds to an increase and a negative value to a decrease in non-HDL-C between 1988 and 1991.

Outcomes

The primary outcome analyzed in this study was mortality between first and second follow-up, from 1991 to 1995. Deaths were identified through contact with next of kin at the time of follow-up interviews, ongoing local monitoring of obituary notices, and National Death Index searches. The second outcome examined in this study was self-reported occurrence of physician-diagnosed myocardial infarction (MI) or stroke between first and second follow-up (1991–95) in those who were alive at the time of the second follow-up. Participants were asked, "Since the time of the last interview, has a doctor told you that you had a heart attack, coronary, MI, coronary thrombosis, or coronary occlusion?" A similar question was asked regarding stroke or brain hemorrhage. Self-reports of cardiovascular events by older adults have been found to have 86% or higher agreement with medical records ($\kappa \geq 0.70$).[22] The third outcome examined in this study was decline in physical functioning in survivors, defined as an increase in the Katz activity of daily living (ADL) disability score between first and second follow-up. The ADL disability score (range 0–7) is a simple count of the number of basic physical activities (such as bathing, dressing, and feeding) with which an individual needs assistance.[23] Cognitive functioning was assessed at both follow-up interviews using performance on a nine-item test adapted from the Short Portable Mental Status Questionnaire (SPMSQ).[24] The fourth outcome examined was decline in cognitive functioning between first and second follow-up, defined as a drop in the SPMSQ score to 6 or less (three or more errors on the test), because this has been found to be sensitive and specific for moderate cognitive impairment.[25]

Covariates

Sex, ethnicity (white vs black), age, use of lipid-lowering medications, number of pack-years of smoking, and body weight (in pounds, rounded to the nearest integer) were all obtained at the time of the baseline examination from participant self-reports. Body weight information was also collected at the first follow-up, and weight loss between

baseline and first follow-up was computed as the difference. Prevalent CVD status was assessed based on self-reports of prior diagnoses of one or more of diabetes mellitus, MI, or stroke, at baseline. Three seated blood pressure readings were taken at baseline and at first follow-up, using the Hypertension Detection and Follow-up Program protocol;[26] average systolic and diastolic blood pressures were computed from the second and third readings. Blood pressure was measured again at first follow-up in 1991, and changes in systolic and diastolic pressure between baseline and first follow-up were calculated. Blood samples in heparinized tubes were assayed for serum albumin and blood glycosylated hemoglobin. Serum levels of albumin were measured using an automated sequential multiple analyzer, and glycosylated hemoglobin levels were measured using affinity chromatography.[27] These measurements were repeated at first follow-up, and changes in albumin and glycosylated hemoglobin between baseline and first follow-up were calculated.

Analyses

The risks for the four health outcomes by quartiles of the 1988-to-1991 change in non-HDL-C were examined and linear trends were tested for using the Cochran Armitage test. These analyses were repeated within strata of the study sample, defined by the first and third quartile cutoff points of baseline total cholesterol (bottom quartile ≤ 191 mg/dL, middle two quartiles = 191–244 mg/dL, and top quartile ≥ 245 mg/dL). This stratification is close to the clinical stratification for hypercholesterolemia, recommended by the National Cholesterol Education Program Adult Treatment Panel III. The analyses were also repeated within strata defined by prevalence of CVD at baseline.

To assess the health effects of the magnitude of change in non-HDL-C, a logistic regression model was fitted to the odds of health outcomes, using the 1988-to-1991 change in non-HDL-C as a continuous predictor. To minimize confounding, the following covariates were included in the model: sex, ethnicity, prevalent CVD status at baseline, baseline level of non-HDL-C, body weight at baseline, and 1988-to-1991 weight loss (continuous term and squared term). Because only five participants reported taking lipid-lowering medications, adjustment for lipid-lowering drug status did not substantially affect the odds ratio (OR) estimates or confidence intervals (CIs). Other risk factors listed under Measurements-Covariates, the baseline (1988) HDL-C level, 1988-to-1991 change in HDL-C, and 1988-to-1991 health declines (specifically, incident cardiovascular events, increase in Katz ADL disability, and fall in the SPMSQ score) were introduced in the model one at a time and were retained in the model if they altered the primary association. To test for effect modification, interaction terms were also introduced one at a time. Stability of estimates was assessed using bootstrapping. SAS version 8 (SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

The study sample (n = 267) did not differ significantly from the complete MacArthur cohort in demographic and lifestyle characteristics, cardiovascular risk factors, CVD prevalence, or use of lipid-lowering medications (Tables 1 and 2). Median levels of total cholesterol and HDL-C at baseline were 218 mg/dL and 47 mg/dL, respectively. Changes in risk factors between baseline and first follow-up and event probabilities in the periods between baseline and first follow-up and between first and second follow-up were also similar for the two groups (Tables 3 and 4).

The median change in non-HDL-C between 1988 and 1991 was -6 mg/dL, but there was a wide range of change values. The first quartile cutoff was -22 mg/dL; 67 people in the sample experienced a fall of 22 mg/dL or more. The

Table 1. Descriptive Statistics for Baseline Variables in the MacArthur Cohort and the Study Sample

Variable	MacArthur Cohort* n = 1,189	Study Sample† n = 267
	Median (Q1, Q3)	
Age	74 (72, 76)	74 (72, 76)
Smoking, pack-years‡	0 (0, 37)	0 (0, 28)
Body weight, kg	72 (63, 79)	73 (63, 82)
Systolic blood pressure, mmHg	136 (125, 148)	136 (125, 148)
Diastolic blood pressure, mmHg	76 (70, 83)	76 (70, 81)
Serum albumin, g/L	41 (39, 43)	41 (39, 43)
Glycosylated hemoglobin, %‡	6.4 (5.9, 7.1)	6.2 (5.7, 6.9)
Serum HDL cholesterol, mg/dL	47 (37, 54)	47 (37, 58)
Serum total cholesterol, mg/dL	218 (191, 245)	218 (191, 247)

* Participants who had measurements at baseline (1988).
† Participants who had measurements at baseline and measurements of total and high-density lipoprotein (HDL) cholesterol in 1991.
‡ Two-sided $P < .05$ for t test of difference between means of (transformed) variables in the study sample and the rest of the MacArthur cohort.
Q1 = first quartile cutoff point (i.e., the 25th percentile); Q3 = third quartile cutoff point (i.e., the 75th percentile).

Table 2. Demographics of the MacArthur Cohort and the Study Sample

Variable	MacArthur Cohort* n = 1,189	Study Sample† n = 267
	%	
Female	55.4	58.4
White‡	81.1	85.7
Prevalent cardiovascular disease§	23.9	25.5
Use of statins for lipid lowering	1.0	0.4
Use of other lipid lowering agents	1.3	1.5

* Participants who had measurements at baseline (1988).
† Participants who had measurements at baseline and measurements of total and high-density lipoprotein (HDL) cholesterol in 1991.
‡ Two-sided $P < .05$ for chi-square test of difference between study sample and rest of MacArthur cohort.
§ Previous diagnosis of diabetes mellitus, heart attack, or stroke.

Table 3. Descriptive Statistics for Change Variables in the MacArthur Cohort Versus the Study Sample

Variable	MacArthur Cohort* n = 1,189	Study Sample† n = 267
	Median (Q1, Q3)	
Change, 1988–1991‡		
Body weight, kg	0.0 (−2.7, 1.4)	0.0 (−2.7, 1.8)
Systolic blood pressure, mmHg	−1.0 (−13,9)	−1.0 (−14, 9)
Diastolic blood pressure, mmHg	−4.0 (−10,3)	−4.0 (−10, 1)
Serum albumin, g/L	0.0 (−2, 2)	0.0 (−2, 2)
Glycosylated hemoglobin, %	— —	0.4 (−0.2, 0.8)
Serum HDL cholesterol, mg/dL	— —	−2.0 (−6, 2)
Serum total cholesterol, mg/dL	— —	−9.0 (−22, 5)

* Everyone with measurements at baseline (1988).
† People with measurements of total and high-density lipoprotein (HDL) cholesterol in 1988 and 1991.
‡ Change refers to the 1991 value minus the 1988 value.
Q1 = first quartile cutoff point (i.e., the 25th percentile); Q3 = third quartile cutoff point (i.e., the 75th percentile).

third quartile cutoff was 9 mg/dL; 60 participants had a rise of more than 9 mg/dL. The distribution of the 1988-to-1991 change in non-HDL-C was similar in men and women, whites and blacks, and in those with and without prevalent CVD at baseline, but those who started with a lower level of serum total cholesterol at baseline had a greater rise in non-HDL-C between baseline and first follow-up (analysis of variance $P < .0001$).

Table 4. Outcomes in the MacArthur Cohort Versus the Study Sample

Event	MacArthur Cohort* n = 1,189	Study Sample† n = 267
	%	
1988 to 1991		
Myocardial infarction or stroke	6.2	4.5
Increase in ADL disability	4.6	2.6
Decrease in SPMSQ score to ≤ 6	3.8	3.4
1991 to 1995		
Mortality	18.1	14.2
Myocardial infarction or stroke	11.2	12.8
Increase in ADL disability	16.7	17.0
Decrease in SPMSQ score to ≤ 6	12.6	13.9

* Everyone with measurements at baseline (1988).
† People with measurements of total and high-density lipoprotein cholesterol in 1988 and 1991.
ADL = activity of daily living; SPMSQ = Short Portable Mental Status Questionnaire.

Results of Categorical Analyses

Analyses focused first on examining the risks for the four outcomes by quartiles of the primary predictor: the 1988-to-1991 change in non-HDL-C. The change was negative (meaning a fall) in the bottom two quartiles and positive (meaning a rise) in the top quartile. As indicated in Figure 1, there were statistically significant downward trends in unadjusted risks for mortality ($P = .049$) and cognitive decline ($P = .037$) progressing from lower to higher quartiles of the primary predictor (i.e., from individuals whose non-HDL-C declined to those whose non-HDL-C increased). A similar trend was seen for onset of new ADL disability, although this trend was only marginally significant ($P = .071$).

Similar trends were seen in stratified analyses. In the middle stratum of baseline total cholesterol (191–244 mg/dL), there was a statistically significant downward trend in the unadjusted risk for mortality ($P = .009$) and a marginally significant downward trend in the risk for incident physical disability ($P = .110$). Similarly, in those without prevalent CVD at baseline, there were statistically significant downward trends in unadjusted risks for new ADL disability ($P = .027$) and cognitive decline ($P = .020$).

Results of Continuous Analyses

In unadjusted analyses with the 1988-to-1991 change in non-HDL-C treated as a continuous predictor, each 10-mg/dL increase in the change score was associated with ORs of 0.85 for physical decline (95% CI = 0.74–0.97) and 0.83 for cognitive decline in survivors (95% CI = 0.72–0.97), as indicated in Table 5. An increase in the change score (the primary predictor)

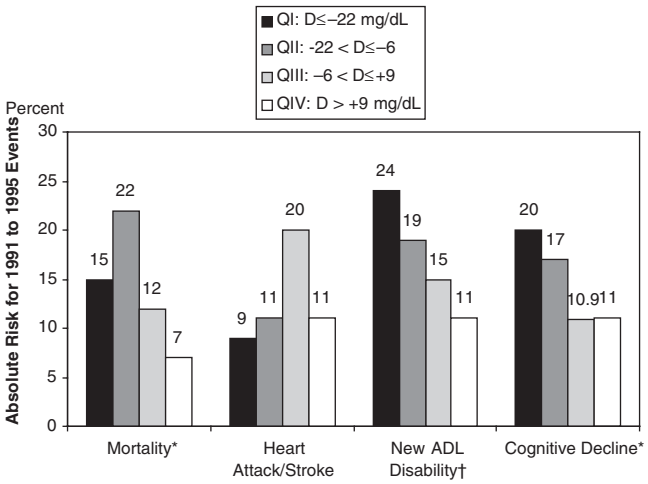

Figure 1. Unadjusted absolute risks for health outcomes between 1991 and 1995 by quartiles of the change (D) in non-high-density lipoprotein cholesterol (non-HDL-C) between 1988 and 1991. QI refers to the bottom quartile of change in non-HDL-C (decrease of ≥ 22 mg/dL), and QIV refers to the top quartile of change in non-HDL-C (increase of ≥ 9 mg/dL). Two-sided *P*-value for trend * < .050; † < .100 but not < .050. ADL = activities of daily living.

Table 5. Unadjusted and Adjusted Odds Ratios for Each 10 mg/dL Increase in the 1988-to-1991 Change in Non-High-Density Lipoprotein Cholesterol for 1991 to 1995 Events

	Mortality	Heart Attack or Stroke	New Activity of Daily Living Disability	Cognitive Decline
Model	Odds Ratio (95% Confidence Interval)			
Unadjusted	0.92 (0.80–1.06)	1.07 (0.91–1.27)	0.85 (0.74–0.97)†	0.83 (0.72–0.97)†
Adjusted*	0.84 (0.62–1.00)†	1.16 (0.95–1.40)	0.84 (0.71–0.99)†	0.86 (0.73–1.02)

* Adjusted for sex, ethnicity, baseline level of total cholesterol, prevalent cardiovascular disease status at baseline, baseline weight (continuous), and 1988-to-1991 weight loss (continuous and squared term).
† Confidence intervals do not cross 1.

corresponds to a more-positive change, which can mean a larger rise or a smaller fall in non-HDL-C in the first period.

Multivariate analyses revealed that, after adjustment, more-positive changes in non-HDL-C were associated with significantly lower odds of mortality and of incident physical disability in survivors but were not significantly associated with odds of cardiovascular events (heart attack or stroke) or cognitive decline. For each 10-mg/dL increase in the change score, the adjusted OR for all-cause mortality was 0.84 (95% CI = 0.69–1.00) and for new ADL disability in survivors was 0.84 (95% CI = 0.71–0.99). According to this model, a person whose non-HDL-C rose by 15 mg/dL between baseline and first follow-up had adjusted mortality odds between first and second follow-up that was 0.84 times the adjusted mortality odds of a person whose non-HDL-C rose by only 5 mg/dL. The same can be said of an individual whose non-HDL-C fell by 10 mg/dL relative to one whose non-HDL-C fell by 20 mg/dL. Other potential confounders (including change in HDL-C and health declines in the first period) were introduced in the model one at a time (described in Methods-Analysis); they did not substantially alter the associations between the primary predictor and outcomes.

Results of Effect Modification Testing

There was no evidence of effect modification by the direction of change (fall vs rise) in non-HDL-C ($P > .250$ for all outcomes). Thus, regardless of the direction of change, a more-positive change in non-HDL-C (a larger rise or a smaller fall) was associated with lower mortality and less incident ADL disability.

Tests of effect modification by baseline cholesterol strata were statistically significant only for mortality odds ($P = .027$). As indicated in Table 6, in the middle stratum of baseline total cholesterol (191–244 mg/dL), more-positive change in non-HDL-C was still associated with significantly lower odds of mortality (OR = 0.67, 95% CI = 0.51–0.88). The top stratum of baseline total cholesterol ($\geq$ 245 mg/dL), alternatively, appears to be substantially different from the other two strata, in that the OR for mortality is higher in the top stratum than in the other two strata.

There was a suggestion of effect modification by baseline CVD prevalence status for physical decline odds ($P = .147$) and cognitive decline odds ($P = .150$). As indicated in Table 6, only in those who had no prevalent CVD at baseline was more-positive change in non-HDL-C associated with lower odds of physical decline (OR = 0.79, 95% CI = 0.65–0.95) and cognitive decline (OR = 0.81, 95% CI = 0.67–0.98), whereas in those who had prevalent CVD at baseline, the ORs were greater than 1.

Results of Stability Analyses

Stability of the OR estimates obtained from the multivariate models was assessed in two ways—by bootstrapping and by using an alternate adjustment for baseline cholesterol. Results from bootstrapped model fitting were similar to the corresponding results in Tables 5 and 6. For instance, the median of 1,000 bootstrapped estimates of the adjusted OR

Table 6. Adjusted Odds Ratios Within Strata for Each 10 mg/dL Increase in the 1988-to-1991 Change in Non-High-Density Lipoprotein Cholesterol from Models Including Effect Modification

	Mortality	Heart Attack or Stroke	New ADL Disability	Cognitive Decline
Stratum	Point Estimate of Odds Ratio (95% Confidence Interval)			
Baseline total cholesterol stratum, mg/dL	$P = .027$	$P = .40$	$P = .62$	$P = .41$
<191	0.90 (0.61–1.32)	—	—	—
191–244	0.67 (0.51–0.88)*	—	—	—
≥245	1.42 (0.89–2.27)	—	—	—
Prevalent CVD status	$P = .65$	$P = .38$	$P = .147$	$P = .150$
No CVD at baseline	—	—	0.79 (0.65–0.95)*	0.81 (0.67–0.98)*
With CVD at baseline	—	—	1.05 (0.75–1.48)	1.13 (0.76–1.71)

Note: Adjusted for sex, ethnicity, baseline level of total cholesterol, prevalent cardiovascular disease status at baseline, baseline weight (continuous), 1988-to-1991 weight loss (continuous and squared term), and an interaction (product) between the stratification variable (categories of baseline total cholesterol or prevalent cardiovascular disease (CVD) status) and the 1988-to-1991 change in non-high-density lipoprotein cholesterol.
Odds ratios within strata are shown only when interaction *P*-values are <.2.
* Confidence intervals do not cross 1.

was 0.64 (95 percentile interval (95%I) = 0.39–0.87) for mortality in the middle stratum of baseline total cholesterol, 0.77 (95% I = 0.62–0.95) for new ADL disability in those without prevalent CVD at baseline, and 0.80 (95% I = 0.64–0.99) for cognitive decline in those without prevalent CVD at baseline.

Because methodologists have felt that adjusting for the baseline level of a risk factor, when studying the effect of risk factor change on disease risk, can lead to overestimates of effect, the multivariate analyses were repeated to adjust instead for the mean of the baseline and final values of non-HDL-C,[28] and the results were similar. For instance, the adjusted OR for mortality in the middle stratum of baseline total cholesterol was 0.65 (95% CI = 0.49–0.86), for new ADL disability in those without prevalent CVD at baseline was 0.79 (95% CI = 0.67–0.94), and for cognitive decline in those without prevalent CVD at baseline was 0.80 (95% CI = 0.67–0.95).

DISCUSSION

The objective of this study was to investigate the association between changes in serum cholesterol over a 2.5-year period and risk of adverse health outcomes over the following 4.5 years in a cohort of high-functioning older adults. The analyses indicated that more-positive changes in non-HDL-C from 1988 to 1991 were associated with lower risk of mortality in 1991 to 1995 and lower risk of physical and cognitive decline in survivors, even after adjusting for potential confounders. In particular, these associations were independent of changes in HDL-C and health declines over the first period (1988–91). Baseline level of total cholesterol modified the mortality effect, yet the direction and strength of the association persisted in the middle stratum of baseline total cholesterol. CVD prevalence status at baseline appeared to modify the effect on functional decline, yet the direction and strength of the associations were retained in those without clinically apparent CVD at baseline. There was no evidence of effect modification by the direction of change (fall vs rise) in non-HDL-C in the first period. Thus, the benefits associated with a more-positive change in non-HDL-C were seen not only for a smaller fall, but also for a larger rise in non-HDL-C. This suggests that ill and dying individuals experiencing a fall in cholesterol in the first period did not determine the associations seen in this study. In fact, in this high-functioning population, the number of people experiencing clinically apparent health declines was small; fewer than 5% had incident cardiovascular events, new ADL disability, or cognitive decline in the first period.

Several plausible explanations of the findings can be hypothesized. Cholesterol has many important roles in humans, one of them being maintenance of the integrity of cell membranes. In vitro studies have suggested that cholesterol acts as an antioxidant and has a protective role.[29,30] At the same time, elevated levels of cholesterol in the blood can promote atherosclerosis and lead to CVD. It has been postulated that higher levels of cholesterol may be needed to maintain the cell membranes of aging cells[31] and that older calcified vessel walls may be less susceptible to the deleterious effects of elevated cholesterol.[11] A "harvest" phenomenon has also been suggested wherein older individuals with hypercholesterolemia are those who are less susceptible to the ill effects of cholesterol and have therefore survived into old age.[7]

These findings may appear to contradict findings in recent trials that statin therapy has benefits even in elderly men and women, but there is no conflict because statins have pleiotropic effects that beneficially affect vascular disease, independent of their classical effects on lipids. In humans, these include reduction in C-reactive protein levels,[32] stabilization of atheromatous plaques,[33] improvement of endothelial function,[34] and reduction in the hypertensive response to angiotensin II.[35] Other effects seen in animal models and in vitro include reduced platelet aggregation, reduced thrombin generation, reduced oxidation of LDL-C, and accelerated re-endothelialization after intravascular injury.[36,37] Although the findings of this study are in sharp contrast to those in young and middle-aged adults, they are consistent with previous studies in older cohorts that have found that elevated levels of total cholesterol and even LDL-C are associated with lower all-cause mortality.[11–13] This dichotomy between younger and older age groups was seen in a Finnish study of men without prevalent CVD, in which increases in serum total cholesterol over a prior 10-year period were associated with increased all-cause mortality in those aged 55 to 65 but not in those aged 65 to 74.[38] Several of the findings of the current study are similar to those in younger cohorts. For instance, there was a trend for increased risk of nonfatal cardiovascular events with increases in non-HDL-C over time. This is consistent with earlier studies that have documented a strong, positive association between hypercholesterolemia and CVD in older cohorts.[9,39,40] The specter of increased CVD raises the possibility that older individuals with hypercholesterolemia have greater risk of functional disability, resulting from heart attacks and strokes. Nevertheless, the current study found that more-positive changes in non-HDL-C were associated with lower risk of subsequent functional decline. This is consistent with previous studies in older cohorts that have found that high levels of total cholesterol are associated with decreased risk of physical disability[41] and mortality[42] after a stroke.

There are some limitations of this study that need to be acknowledged. First, the study sample consisted entirely of high-functioning older adults, and the results may not be generalizable to individuals who are not functioning as well at baseline. Nevertheless, the deliberate choice of a high-functioning cohort minimized any confounding by possible reverse effects of poor health on changes in cholesterol, and means of baseline levels and rate of change in total and HDL-C were similar to the means in other more-representative cohorts of similar age.[43–45] Moreover, high-functioning older adults may have the most to gain or lose from cholesterol management and represent an important group in whom the role of lipid lowering in primary prevention needs to be understood. Second, the LDL fraction of cholesterol was not measured. The effects of change in non-HDL-C were therefore studied, and no confounding by increases in HDL-C was found. Incidentally, optimization of non-HDL-C levels is a secondary goal of cholesterol management in recent guidelines from the National Cholesterol Education Program Adult Treatment Panel III.[46] Third, interim cardiovascular events and incident ADL disability were gauged using self-reports. Nevertheless,

evaluations of the consistency of self-reports of such events with medical records have confirmed the reliability of such self reports.[47] Fourth, the sample size was only 267, and the study had 80% power at significance level (alpha) of 0.05 only to detect ORs less than 0.6 or greater than 1.7. This limited the ability to detect more-moderate effects. Because of the risk of overfitting in a small sample, the stability of model fitting was assessed using bootstrapping, which showed the OR estimates to be stable.

One of the strengths of this study is that the effect of increases in cholesterol, not only on mortality, but also on functional status, a key contributor to quality of life in elderly survivors, was examined. These findings have implications for the diagnosis and treatment of hypercholesterolemia in older adults. They suggest that the threshold value for the diagnosis of hypercholesterolemia may be higher in elderly individuals than in young and middle-aged adults. Other studies have also hinted at this,[48] and some have suggested that the threshold may be higher in elderly women than in elderly men.[49,50] Below this threshold, increases in serum cholesterol may be beneficial in high-functioning older adults without prior diagnosis of diabetes mellitus, heart attacks, or strokes. Nevertheless, there are some caveats. First, it is possible that there are substrata of individuals in whom the effects of increase in cholesterol are different; the current study sample was not large enough to stratify by more than one variable at a time. A larger study will be needed to look, for instance, at the differences in the effects of change in cholesterol between those with and without prevalent CVD, within each stratum of baseline total cholesterol. Second, there are differences between the effects of spontaneous changes in serum cholesterol level and intentional changes that result from clinical interventions. Clinical interventions, whether in the form of statin therapy or regular physical exercise, can have direct health benefits independent of their effects on cholesterol levels. Third, observational data can only suggest, not confirm, a causal relationship. These findings cannot therefore be translated into clinical practice until they are confirmed in clinical trials. Nevertheless, they raise important questions regarding the role of cholesterol reduction in older individuals with average or borderline cholesterol levels and no clinically evident CVD.

ACKNOWLEDGMENTS

The authors would like to gratefully acknowledge the assistance of Drs. Ralph Horwitz of the Department of Internal Medicine, Yale University, and Emmett Keeler of RAND, Santa Monica, California, for their critical reading of the manuscript and invaluable suggestions.

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