CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

The Association of Lipids and Lipoproteins with Hip Fracture Risk: The Cardiovascular Health Study

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ABSTRACT

BACKGROUND: It is uncertain if lipids or lipoproteins are associated with osteoporotic fractures. In this study, incident hip fracture risk according to conventional lipid levels and lipoprotein levels and sizes was examined.

METHODS: We followed 5832 participants aged ≥65 years from the Cardiovascular Health Study for hip fracture for a mean of 13.5 (SD 5.7) years. Standard enzymatic methods were used to determine lipid levels (ie, high-density lipoprotein-cholesterol [HDL-c], low-density lipoprotein-cholesterol [LDL-c], and triglycerides). Nuclear magnetic resonance spectroscopy was used to measure lipoprotein fractions (ie, very-low-density lipoprotein-particle [VLDL-P], low-density lipoprotein-particle [LDL-P], high-density lipoprotein-particle [HDL-P]) in a subset of 1849 participants.

RESULTS: We documented 755 incident hip fractures among women (1.19 fractures per 100 participant years [95% confidence interval, 1.04, 1.35]) and 197 among men (0.67 fractures per 100 participant years [95% CI, 0.41, 1.10]) over an average follow-up. HDL-c and LDL-c levels had statistically significant nonlinear U-shaped relationships with hip fracture risk (HDL-c, $P = .009$; LDL-c, $P = .02$). Triglyceride levels were not significantly associated with hip fracture risk. In fully adjusted conjoint models, higher VLDL-P concentration (hazard ratio [HR] per 1 standard deviation [SD] increment 1.47 [1.13, 1.91] and size [HR per 1 SD increment 1.24 [1.05, 1.46]) and higher high-density lipoprotein particle size (HR per 1 SD increment 1.81 [1.25, 2.62]) were all associated with higher hip fracture risk.

CONCLUSIONS: Lipids and lipoproteins are associated with hip fracture risk in older adults. The associations are complex. Mechanistic studies are needed to understand these findings.

 • The American Journal of Medicine (2022) 135:1101−1108

KEYWORDS: Hip fracture; Lipid; Lipoprotein particle

Funding: This research was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, 75N92021D00006, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interest: None.

Authorship: All authors had access to the data and a role in writing this manuscript.

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0002-9343/
https://doi.org/10.1016/j.amjmed.2022.05.024

INTRODUCTION

There are many reasons to posit a direct or indirect association among serum lipid levels, osteoporosis, and hip fracture risk. Laboratory studies show that cholesterol can extend the survival of osteoclast-like cells, contributing to osteoporosis.[1] High levels of total cholesterol are associated with low 25(OH) vitamin D levels (required for the absorption of calcium[2]) and with inflammatory cytokines (eg, tumor necrosis factor-alpha [TNF-α], interleukin [IL]-1 and IL-6), which uncouple bone remodeling.[3] Metabolomic studies demonstrate low bone mineral density to be associated with lipids.[4] Clinical studies also show an association of lipids with bone disease. Chronic medical conditions associated with dyslipidemia (eg, metabolic syndrome, obesity, and diabetes) are often associated with increased fracture risk.[5-7] Dyslipidemia is a strong risk factor for atherosclerosis. Clinical and subclinical atherosclerosis of large and medium-sized blood vessels is associated with osteoporosis and fracture risk,[8,9] as well as with disrupted distal bone capillary blood flow.[10] Statin medications increase bone mineral density, suggestive of a causal link between the lowering of lipid levels and improved bone health.[11] Last, the skeleton takes up a large proportion of a postprandial lipoprotein load.[12]

Despite these reasons, the reported associations of lipid levels with hip fracture risk and, by extension, with osteoporosis, are mixed.[13-16] Certain data suggest positive associations, some report no associations, and others negative associations. Most studies are cross-sectional and small; the ethnic compositions of the cohorts vary; and the ages of the cohorts often include young people in whom osteoporotic fractures are uncommon. Prior studies examine lipid fractions individually but do not adjust for the effect of the other lipid fractions on fracture risk. Finally, another factor, heretofore not considered, is the variety of lipoprotein subclasses that carry lipids in the blood.

In this longitudinal study from the Cardiovascular Health Study (CHS) the association of baseline lipids and lipoproteins with incident hip fracture risk is examined in a cohort of adults aged ≥65 years at baseline who were well-phenotyped and followed for hip fracture for up to 20 years.

CLINICAL SIGNIFICANCE

- The associations of lipid levels and of lipoprotein levels and size with hip fracture risk are uncertain.
- In this study, high-density lipoprotein-cholesterol (HDL-c) and low-density lipoprotein-cholesterol (LDL-c) levels had significant nonlinear associations with fracture risk.
- Very-low-density lipoprotein (VLDL) number and size and high-density lipoprotein (HDL) particle size were positively associated with risk.
- Elevated lipid and lipoprotein levels are associated with hip fracture risk, suggesting an unanticipated protective benefit of lipid-lowering medications in people with elevated LDL-c levels.

METHODS

The CHS is a prospective observational study of community dwelling adults, aged ≥65 years at study entry, from 4 US communities drawn from Medicare lists.[17] In 1989-1990, 5201 participants were recruited, followed by an additional 687 predominantly African American participants in 1992-1993. All participants gave informed consent prior to study entry. Institutional review board approval was received at all clinical sites. From 1989-1990 to 1998-1999, participants were seen in clinic annually and had telephone contact midway between clinic visits. Following the 1998-1999 visit, participants continued to be contacted biennially to update hospitalizations, incident diagnoses, and medications. Surveillance for hip fractures ended June 30, 2015.

Analytic Cohorts

Lipid Level Cohort. Lipid data collected at the baseline 1989-1990 and 1992-1993 visits were combined for lipid analyses. A total of 56 participants had missing lipid analytes and were excluded from the lipid level cohort. Participants with fractures prior to the baseline date, including hip fractures, were not excluded.

Lipoprotein Cohort. Plasma collected at baseline from a total of 1622 CHS participants from the 1989-1990 cohort, and 228 African American participants from the 1992-1993 cohort underwent nuclear magnetic resonance (NMR) spectroscopy at LipoScience (Raleigh, North Carolina) for determination of lipoprotein subclasses as part of a nested case-cohort study.[18] All participants in the lipoprotein cohort were free of clinical cardiovascular disease at baseline. Participants comprised several groups: 1) 249 who were free of all subclinical atherosclerosis at baseline (as defined in CHS[19]); 2) 492 who were free of incident myocardial infarction or angina through June 30, 1995; 3) 222 with incident angina but not myocardial infarction through June 30, 1995; 4) 213 with incident myocardial infarction through June 30, 1995; 5) 200 with incident stroke through June 30, 1995; and 6) 246 with subclinical cerebral infarcts by cranial magnetic resonance imaging through June 30, 1995. Participants free of incident myocardial infarction or angina and those free of all subclinical disease were sampled randomly from the CHS population. The 228 randomly selected African American participants were free of myocardial infarction or stroke. Participants with fractures prior to study baseline were not excluded.

Study Outcome

The study outcome was incident hip fracture. Fracture data were obtained through participant report and confirmed through hospital medical records, including discharge

summaries, gathered every 6 months from the 1996-1997 visit through June 30, 2015. Data were checked against Medicare claims data to identify any hospitalizations not reported by participants. Hip fracture was defined using the *International Classification of Diseases, Ninth Revision* (ICD-9) code 820.xx. Pathological fractures (ICD-9 code 773.1x) and motor vehicle accidents (E810.xx-E825.xx) were excluded.

Primary Predictors of Hip Fracture. *Lipid Levels.* Standard enzymatic methods were used to determine total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), and triglycerides, standardized according to the Centers for Disease Control and Prevention guidelines as described previously.[20] Low-density lipoprotein-cholesterol (LDL-c) levels were calculated using the Friedewald equation.

Lipoprotein Subclasses. Aliquots (0.5 mL) of EDTA plasma stored at −80°C at the CHS central laboratory were shipped on dry ice to LipoMed, Inc, for NMR lipoprotein subclass analysis. Lipoprotein particle diameters were measured with an automated NMR spectroscopic assay. In brief, lipoprotein subclasses emit characteristic lipid methyl group NMR signals, and the signal amplitude reflects particle concentration. The categories examined were very-low-density lipoprotein particles (VLDL-P), low-density lipoprotein particles (LDL-P), and high-density lipoprotein particles (HDL-P). Particle concentrations are in nanomoles per liter for VLDL-P and LDL-P and micromoles per liter for HDL-P. Weighted-average VLDL-P, LDL-P, and HDL-P sizes (in nanometer diameter units) were calculated as the particle size of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its NMR signal.

Covariates. Analyses were adjusted for baseline factors associated with lipid levels and hip fracture risk. These included: age, sex, race, smoking status (never, past, current), current alcohol intake (none, less than 7 drinks per week, 7 or more drinks per week), presence of self-reported and adjudicated diabetes mellitus and cardiovascular disease (angina, myocardial infarction, angioplasty, bypass surgery or stroke), energy expended per week (kcal), estimated glomerular filtration rate based on cystatin-C level, C-reactive protein level,[20] hypertension, frailty status (none, prefrail, frail) based on Fried criteria,[21] difficulties with activities of daily living and instrumental ADL, weight, and height.

Statistical Analysis

Due to skewed lower and upper tails of the distributions of the lipids, we winsorized HDL-c, LDL-c, and triglycerides at 2% (30, 63.7, 59 mg/dL, respectively) and at 98% (93, 210.8, 352 mg/dL, respectively). Lipoproteins were similarly winsorized.

Incidence rates of hip fracture, total and by sex, were calculated with quasi-Poisson models with offset to accommodate time at risk.

Multivariable Cox hazards models estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) of incident hip fracture associated with a standard deviation higher exposure. We used nested models (M) adjusting for factors as: M0: unadjusted; M1: age, sex, race, clinic. M2: M1 + smoking, alcohol, hypertension, estimated glomerular filtration rate, diabetes mellitus, physical activity score, C-reactive protein (log base 2), estrogen, weight, height, and prevalent cardiovascular. We included models with a single lipid exposure as well as all three lipids simultaneously in the model to estimate mutually adjusted HRs.

To study linearity in the models, the functional association of lipids with incident hip fracture using generalized additive models with splines was examined, observing U-shaped relationships. Using a permutation approach for significance tests,[22] we observed significant nonlinear associations with LDL-c and HDL-c. In follow-up analyses, we categorized LDL-c and HDL-c into quintiles and used the middle quintile as a reference category in the aforementioned model M2 with all 3 exposures included.

Analyses were conducted using R (R Foundation for Statistical Computing).

RESULTS

Baseline characteristics of the cohort, categorized by sex, are shown in Table 1. Women comprised 57.5% of the cohort. Mean age was ∼73 years. Men were more likely to be former smokers and to drink ≥7 alcoholic drinks per week. Slightly less than 50% of men and women had more than 12 years of education. Women had a higher prevalence of difficulties with instrumental activities of daily living than men, but both sexes were equivalent in the prevalence of prefrailty and frailty. Men had a higher prevalence of coronary heart disease than women, but renal function was approximately the same. Diabetes prevalence was roughly equivalent. Women were more likely to use calcium supplements than men. There was low use of vitamin D supplements and statins.

Supplementary Table 1, available online, provides baseline lipid values of men and women winsorized at the 2nd and 98th percentiles. Women had higher LDL-c and HDL-c levels than men. Triglyceride levels were equivalent.

Mean (standard deviation [SD]) follow-up was 13.5 (7.1) years (median 13.2 years [interquartile range, 7.9, 19]). We documented 755 incident hip fractures among women (1.19 fractures per 100 participant years [95% CI, 1.04, 1.35]) and 197 among men (0.67 fractures per 100 participant years [95% CI, 0.41, 1.10]).

Lipid Levels

The risks for hip fracture associated with winsorized individual lipid analytes sequentially adjusted for covariates were not statistically significant as linear associations, together or for men and women separately, or when adjusted for the association of the other lipid analytes with hip fracture risk (Table 2).

Table 1 Baseline Characteristics of the Cardiovascular Health Study Cohort Categorized by Sex

	Women, N = 3351	Men, N = 2481
Demographic		
Black race (%)	16.6	13.6
Age (y) SD	72.5 (5.5)	73.3 (5.7)
Weight (kg)	67.9 (14.2)	79.3 (12.6)
Height (m)	1.6 (0.1)	1.7 (0.1)
Alcohol (drinks/wk)		
0	55.9	41.8
1-6	35.6	40.9
≥7	8.4	17.4
Smoking		
Current	12.5	11.1
Former	30.4	56.9
Never	57.0	32.1
Education level ≥12 y (%)	40.7	47.6
Kcal expended/wk (median, IQR)	412(10-1102)	967(319-2243)
Difficulty ADL (%)	9.7	5.6
Difficulty iADL (%)	30.6	19.0
Diabetes (%)	14.2	18.9
Frail (%)		
None	45.7	48.2
Prefrail	46.4	46.8
Frail	8.0	5.1
Prevalent CVD (%)		
CHD*	15.5	24.9
MI	6.3	14.0
CHF	4.1	5.3
Stroke	3.1	5.6
Hypertension	60.6	55.9
Use of antihypertensive medications	49	45.1
Renal function based on cystatin C (eGFR mL/min/1.73m^2)	79.7 (20.2)	74.3 (18.8)
Medications (%)		
Thiazide	22.6	15.1
Loop diuretic	7.3	6.4
Statin	2.8	1.5
Supplementation Use (%)		
Calcium	26.4	9.4
Vitamin D	0.3	0.1

ADL = activities of daily living; CHF = congestive heart failure; CHD = coronary heart disease; CVD = cardiovascular death; eGFR = estimated glomerular filtration rate; iADL = instrumental activities of daily living; IQR = interquartile range; MI = myocardial infarction; SD = standard deviation.

*angina, MI, angioplasty, bypass surgery.

Generalized additive models of winsorized LDL-c, HDL-c, and triglyceride levels with hip fracture risk, with each lipid fraction adjusted for the effect of the other and for covariates from model 2, are shown in Figure 1. LDL-c and HDL-c levels both had significant nonlinear, U-shaped associations with fracture risk, whereas triglyceride levels showed no significant association with hip fracture (permutation-based *P* values: LDL-c, *P* = .02; HDL-c, *P* = .009; triglyceride, *P* = .92). To further examine the potential nonlinear association of LDL-c and HDL-c with fracture risk, both LDL-c and HDL-c were divided into quintiles of distribution with the third quintile serving as the reference for Cox models (Table 3; model 2). The lowest and highest quintiles of HDL-c were positively associated with hip fracture risk (HR 1.48 [1.12, 1.97]; 1.32 [1.02, 1.71], respectively). The pattern was similar but of lower magnitude for LDL-c.

Table 2 HRs for Hip Fracture Associated with a 1 SD Increase in Standard Lipid Variables in the Cardiovascular Health Study

	All		Women		Men	
	HR	95% CI	HR	95% CI	HR	95% CI
LDL-c						
M0	0.99	0.92, 1.07	0.99	0.91, 1.08	0.88	0.74, 1.03
M1	0.96	0.90, 1.04	0.98	0.90, 1.07	0.92	0.78, 1.09
M2	1.00	0.92, 1.09	1.02	0.93, 1.13	0.92	0.76, 1.11
HDL-c						
M0	1.13	1.05, 1.22	1.07	0.98, 1.17	0.93	0.77, 1.12
M1	1.07	0.98, 1.16	1.10	1.00, 1.21	0.92	0.75, 1.11
M2	1.06	0.96, 1.17	1.08	0.97, 1.21	0.90	0.70, 1.15
TRIG						
M0	0.97	0.89, 1.06	0.97	0.87, 1.07	0.95	0.80, 1.14
M1	0.95	0.87, 1.05	0.94	0.85, 1.05	0.99	0.83, 1.19
M2	0.97	0.88. 1.08	0.96	0.86, 1.09	1.03	0.84, 1.26
HDL-c M0	1.14	1.05, 1.24	1.06	0.96, 1.18	0.88	0.71. 1.08
LDL-c M0	1.00	0.93, 1.09	1.00	0.92, 1.10	0.87	0.74, 1.03
Trig M0	1.00	0.90, 1.11	0.94	0.83, 1.07	0.92	0.74, 1.13
HDL-c M1	1.04	0.95, 1.15	1.08	0.97, 1.21	0.89	0.72, 1.10
LDL-c M1	0.97	0.90, 1.05	1.00	0.91, 1.09	0.92	0.78, 1.08
Trig M1	0.94	0.84, 1.05	0.92	0.81, 1.06	0.96	0.78, 1.19
HDL-c M2	1.05	0.94, 1.17	1.08	0.95, 1.22	0.88	0.67, 1.15
LDL-c M2	1.00	0.92, 1.10	1.04	0.95, 1.15	0.92	0.76, 1.11
Trig M2	0.95	0.84, 1.07	0.93	0.80, 1.07	1.00	0.79, 1.27

ADL = activities of daily living; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular death; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HDL-c= high-density lipoprotein-cholesterol; HR = hazard ratio; HTN = hypertension; iADL = instrumental activities of daily living; LDL-c= low-density lipoprotein-cholesterol; M0 = unadjusted; M1 = age, gender [for "all" only], race adjusted; M2: M1 + smoking, alcohol, HTN, eGFR, DM, energy expended per week, frailty, CRP, ADL, iADL, weight, height, and prevalent CVD; SD = standard deviation; Trig = triglycerides.

Lipoproteins

Lipoprotein particle concentrations and sizes are shown in Supplementary Table 2, available online. The top of Table 4 shows fully adjusted HRs (Model 2) for hip fracture risk for 1 SD higher concentrations and sizes of the individual lipoprotein particles for each individual analyte. HDL-P concentration was associated with lower risk (HR per SD 0.80 [0.66. 0.98], whereas 1 SD higher HDL-P size was associated with an increased risk (HR 1.31 [1.06, 1.63]). In paired analyses (middle Table 4), higher VLDL particle size had a borderline increased risk of fracture, and higher HDL size had a statistically significant association. When all 6 variables were included in a single Cox model (bottom Table 4), 1 SD higher VLDL-P concentration and size and higher

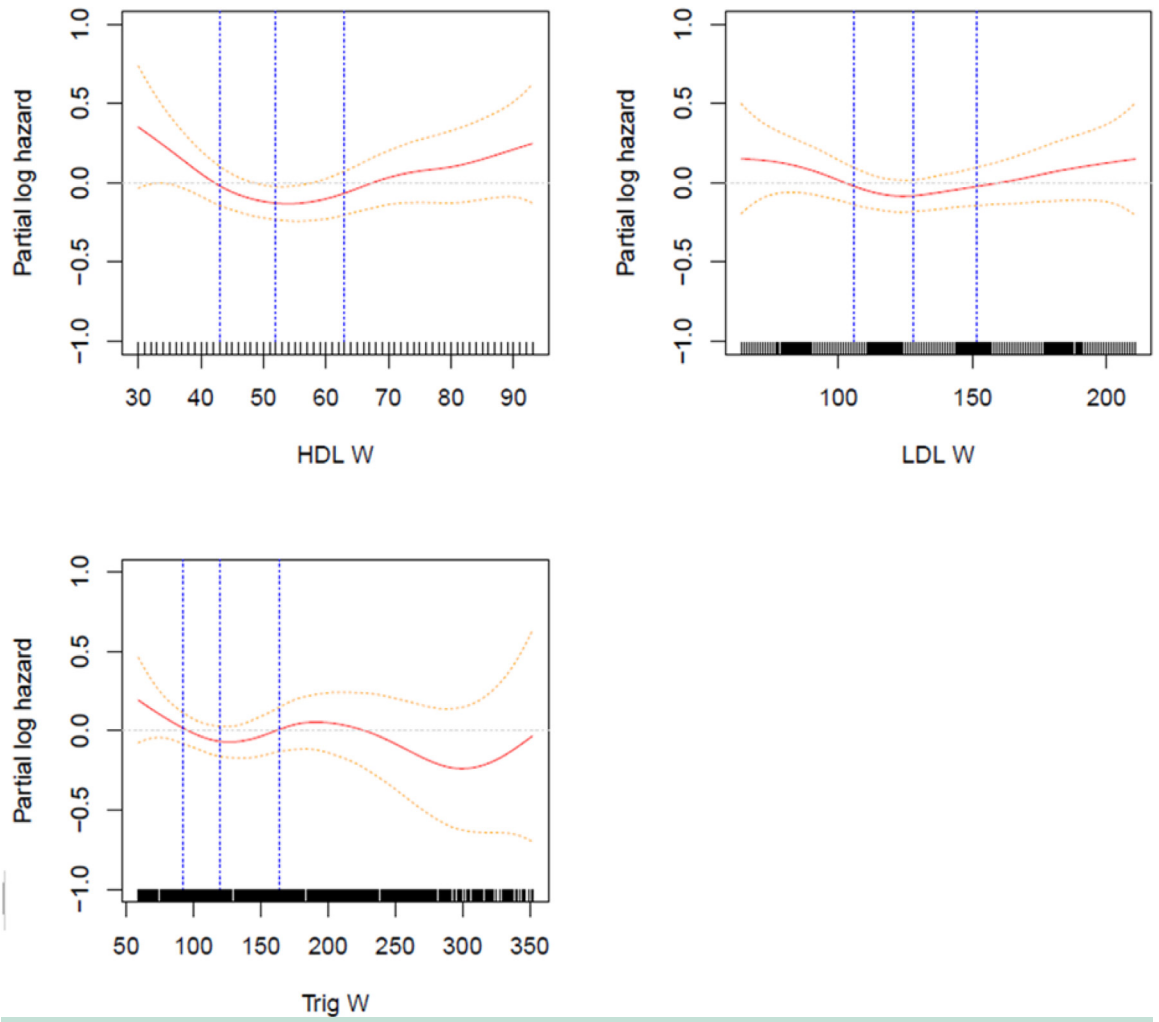

Figure 1 Generalized additive models with splines for winsorized lipid levels in M2 in a single model. W = winsorized.

HDL-P sizes were all associated with statistically significant higher risk of fracture. Figure 2 illustrates these associations in generalized additive models.

DISCUSSION

In this cohort of older adults, there were 2 key findings. First, HDL-c and LDL-c levels were significantly

Table 3 Cox Regression Estimates for Hip Fracture Risk [Model 2] for the 3 Exposures Simultaneously Adjusted for Each Other's Association with Hip Fracture, per 1 SD Higher Value*

	All		Women		Men	
	HR	95% CI	HR	95% CI	HR	95% CI
HDL-c						
Q1	1.48	1.12,1.97	1.66	1.56,2.38	1.05	0.65,1.7
Q2	1.02	0.77,1.34	1.17	0.84,1.61	0.70	0.42,1.17
Q4	1.16	0.90,1.49	1.21	0.91,1.61	1.06	0.61,184
Q5	1.32	1.02,1.71	1.41	1.05,1.87	0.67	0.3,1.48
LDL-c						
Q1	1.22	0.94,1.57	1.17	0.86,1.58	1.38	0.84,2.26
Q2	1.03	0.80,1.33	0.90	0.67,1.20	1.61	0.96,2.69
Q4	1.12	0.87,1.44	1.06	0.8,1.41	1.37	0.79,2.36
Q5	1.14	0.89,1.45	1.10	0.83,1.45	1.21	0.68,2.18
Triglycerides	0.92	0.81,1.04	0.88	0.76,1.02	1.03	0.81,1.31

CI = confidence interval; HDL-c= high-density lipoprotein-cholesterol; HR = hazard ratio; LDL-c= low-density lipoprotein-cholesterol; SD = standard deviation.

*HDL-c and LDL-c values are presented in quintiles; triglyceride values are continuous. The third quintile of HDL-c and LDL-c are the reference group. Quintile values: HDL-c (mg/dL): 20th, 41; 40th, 48; 60th, 56; 80th, 66; LDL-c (mg/dL): 20th 101; 40th 120; 60th 137; 80th 158.

Table 4 Cox Regression Models for the Association of a 1 SD Increase of 3 Lipoprotein Particle Concentrations and Particle Size, Individually, in Pairs, and in 1 Model, with Hip Fracture Risk in the Cardiovascular Health Study*

	All		Women		Men	
	HR	95% CI	HR	95% CI	HR	95% CI
VLDL-P conc	1.09	0.86, 1.38	1.18	0.93, 1.51	0.79	0.45, 1.38
HDL-P conc	**0.80**	**0.66, 0.98**	**0.78**	**0.63, 0.98**	0.84	0.54, 1.30
LDL-P conc	0.94	0.78, 1.13	1.00	0.81, 1.24	0.75	0.51, 1.13
VLDL-P size	1.17	0.97, 1.42	1.19	0.95, 1.49	1.14	0.85, 1.52
HDL-P size	**1.31**	**1.06, 1.63**	1.20	0.94, 1.54	1.85	1.20, 2.86
LDL-P size	1.04	0.85, 1.28	0.95	0.73, 1.22	1.35	0.97, 1.88
VLDL-P conc	1.14	0.90, 1.43	1.24	0.98, 1.57	0.81	0.46, 1.43
VLDL-P size	**1.22**	**1.00, 1.48**	**1.27**	**1.00, 1.60**	1.08	0.80, 1.47
LDL-P conc	0.94	0.72, 1.21	0.93	0.67, 1.29	0.88	0.56, 1.39
LDL-P size	1.00	0.75, 1.32	0.89	0.61, 1.32	1.26	0.88, 1.80
HDL-P conc	0.83	0.67, 1.02	**0.80**	**0.63, 1.00**	0.92	0.60, 1.42
HDL-P size	**1.27**	**1.02, 1.58**	1.16	0.92, 1.48	**1.82**	**1.14, 2.93**
VLDL-P conc	**1.47**	**1.13, 1.91**	**1.57**	**1.19, 2.09**	1.31	0.75, 2.29
VLDL-P size	**1.24**	**1.05, 1.46**	**1.28**	**1.06, 1.54**	1.21	0.91, 1.60
LDL-P conc	0.96	0.74, 1.24	0.96	0.71, 1.30	1.00	0.63, 1.59
LDL-P size	0.85	0.62, 1.17	0.83	0.56, 1.24	0.91	0.55, 1.50
HDL-P conc	0.84	0.68, 1.05	0.81	0.64, 1.03	0.91	0.60, 1.39
HDL-P size	**1.81**	**1.25, 2.62**	**1.82**	**1.23, 2.71**	**2.24**	**1.13, 4.45**

CI = confidence interval; Conc = concentration; HDL-P = high-density lipoprotein-particle; HR = hazard ratio; LDL-P = low-density lipoprotein-particle; SD = standard deviation; VLDL-P = very-low-density lipoprotein-particle.

*Bolded numbers are statistically significant at the $P < .05$ level. Values are adjusted for variables in model 2, Table 1

associated with hip fracture risk; triglyceride levels were not. The associations of HDL-c and LDL-c with hip fracture were nonlinear, with HDL-c and LDL-c levels of 48-56 mg/dL and 120-137 mg/dL, respectively, associated with the lowest risk. Second, we observed novel associations of lipoproteins with hip fracture risk, including positive associations of HDL-P size and VLDL-P concentration and size.

The question arises how to understand these findings. The CHS is an epidemiological study; it does not contain mechanistic data. Hence, explanations are perforce speculative. Nonetheless, several of our findings have precedence. First, the finding that low HDL-c levels are associated with elevated hip fracture risk is not surprising because reduced HDL-c levels are associated with adverse health effects, including low bone mineral density.[23] However, our finding that elevated HDL-P concentrations and HDL-P size are associated with increased hip fracture risk appear to be incongruent with their known health benefits. Reports from Denmark and the UK suggest that the association of HDL-c levels and mortality is U-shaped, with both high and low concentrations associated with elevated all-cause mortality.[24,25] In a meta-analysis of 12 studies of lipid levels in association with osteopenia and osteoporosis, HDL-c levels were elevated in people with osteoporosis in cross-sectional studies.[26] Another previous meta-analysis reported similar findings.[27] Potential factors that may explain the mechanism by which HDL-c and HDL-P could impact bone physiology include adipokines, genetic factors, inflammation, and regulators of lipoprotein metabolism.[28,29]

Second, as to the association of LDL-c levels with hip fracture risk, a Mendelian randomization study demonstrated a significant negative association between LDL-c and bone mineral density.[30] Elevated LDL-c levels are associated with atherosclerosis, a potent risk factor for osteoporosis.[3] LDL-c, when oxidized, is associated with inflammation factors.[31] The association of low LDL-c and hip fracture risk could reflect the decline in LDL-c levels with advanced aging, although our results persisted with adjustment for frailty. The significant nonlinear association of LDL-c levels with hip fracture was generally lesser in magnitude than the association of HDL-c with hip fracture risk and could, therefore, also represent the play of chance. Alternatively, low LDL-c levels in older adults could be related to the presence of chronic illnesses which can increase fracture risk.

Finally, regarding the VLDL-P findings, VLDL-P consist mostly of triglycerides. The availability of triglycerides is the primary determinant of the rate of VLDL synthesis;[32] VLDL production also requires intact hepatic function. Elevated triglyceride levels are associated with high fat diets, insulin resistance, obesity, hepatic steatosis, metabolic syndrome, and inflammation, all of which negatively affect the bone environment and osteoblast function.[33,34] Two clinical studies have reported increased risk of fracture in women with elevated triglyceride levels,[35,36] though no such associations were found here. In 1 study[35] the average age was much younger than in CHS; in the other[36] only vertebral fractures were examined.

This study has several strengths. First, we adjusted the associations of lipids and lipoprotein fractions with hip

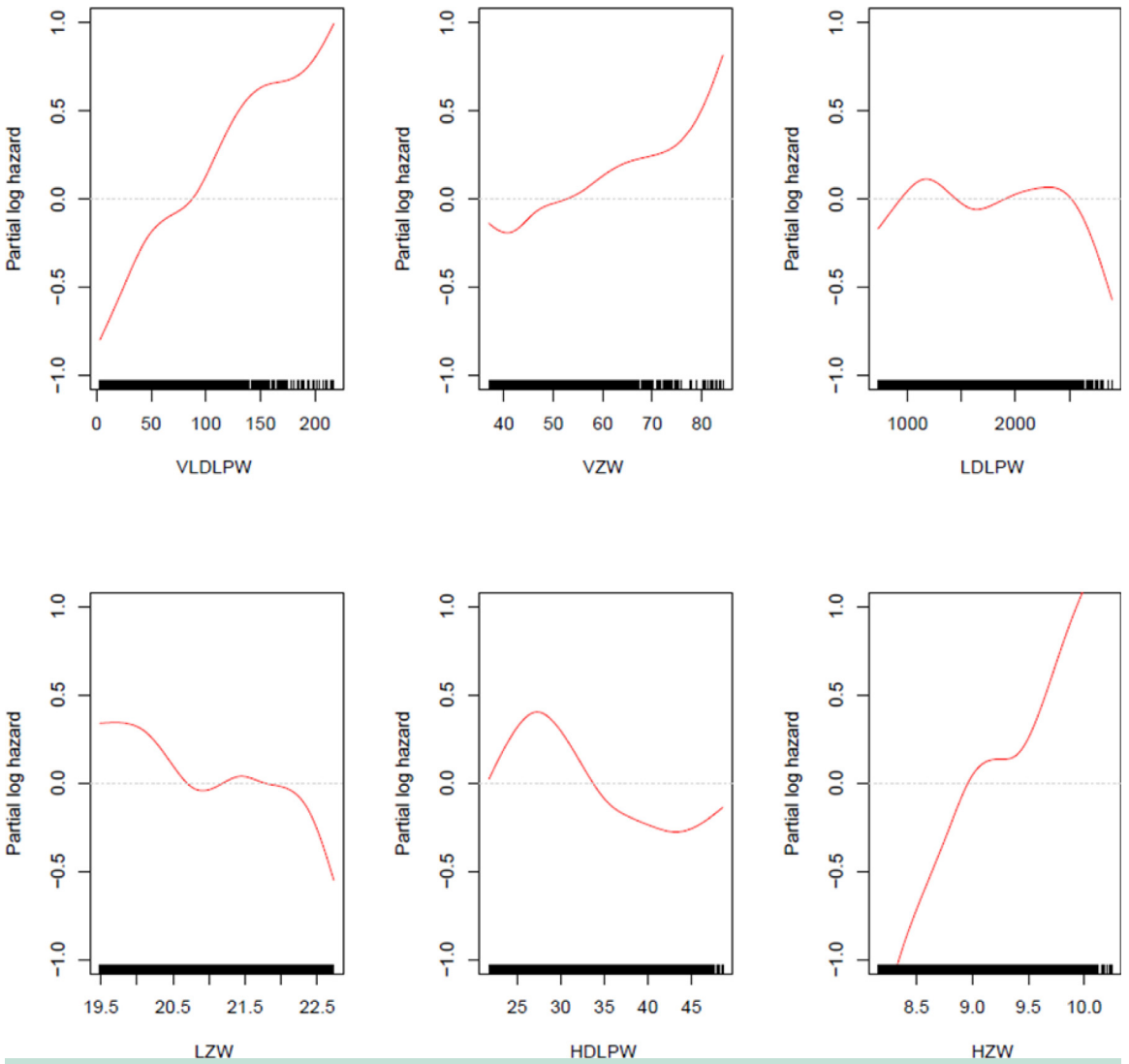

Figure 2 Generalized additive models with splines for winsorized lipoprotein particle levels and sizes in Model 2 in a single model. HDLP = HDL particle concentration; HZ = HDL particle size; LDLP = LDL particle concentration; LZ = LDL particle size; VLDLP = VLDL particle concentration; VZ = VLDL particle size; W = winsorized.

fracture risk for the effects of the associations of other lipid and lipoprotein subfractions with hip fracture risk. Such an approach has not been done previously and may explain in part why our results differ from other studies. We believe our approach represents an accurate representation of the associations of lipids and lipoproteins with hip fracture risk. Second, we measured lipids in 2 complementary ways, including standard clinical values and more novel NMR-based lipoproteins; our results suggest that the latter may be useful for understanding the relationships of lipids with fracture risk. Third, we focused on hip fractures, which are reliably ascertained with data sources like those available in CHS. We documented nearly 1000 hip fractures, providing for precision and the ability to control simultaneously for covariates. Fourth, all the women were menopausal, reducing variability in lipid levels and hip fracture associated with perimenopause. Last, the potentially complex effect of statin medication use was limited in this cohort because much of the follow-up time was in the era prior to its widespread use.

Limitations

There are also important limitations in this study. Not all participants underwent lipoprotein measurement, although we were able to reweight our results to reflect the larger cohort. Nonetheless, confidence intervals for some lipoprotein measurements were wide. As in all observational studies, unmeasured factors that were not captured could have influenced our results. Although we included adjustment for many covariates, the progressive clinical and subclinical comorbidity that accompanies older age could have influenced our results. CHS included few Asian or Latino participants, and we cannot generalize our results to these ethnicities nor to younger adults. Causal factors for fractures are not available in CHS. Finally, only a subset of CHS had bone density testing. This was done 6-7 years after

the baseline examination, far removed from the time of baseline lipid collection.

CONCLUSION

In conclusion, we observed positive associations of HDL-c and LDL-c levels, of VLDL-P number and size, and HDL-P size with hip fracture risk. These findings should be confirmed, and mechanistic studies are needed to understand them. These findings highlight the value of detailed phenotyping to understand the physiological determinants of bone health in older adults. They suggest that a possible unforeseen benefit of LDL-c lowering in those with high LDL-c levels may be fewer incident hip fractures.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.05.024.

Supplementary Table 1 Baseline Lipid Levels in Men and Women from the Cardiovascular Health Study*

	N	Mean	SD	Median	IQR
MEN					
LDL-c	2442	123.4	31.6	122.4	100.8, 143.8
HDL-c	2476	47.7	12.4	46.0	39.0, 54.0
TRIG	2481	136.9	65.2	118.0	90.0, 162.0
WOMEN					
LDL-c	3310	134.3	34.7	132.0	109.8, 157.8
HDL-c	3348	58.7	14.8	57.0	48.0, 68.0
TRIG	3351	137.8	62.9	121.0	93.0, 166.0

HDL-c= high-density lipoprotein-cholesterol; IQR = interquartile range; LDL-c= low-density lipoprotein-cholesterol; SD = standard deviation; TRIG = triglycerides.

*Values are winsorized at the 2nd and 98th percentiles. Values are in mg/dL.

Supplementary Table 2 Lipoprotein Concentrations and Sizes as Determined from NMR at the Baseline Examination for the Cardiovascular Health Study Cohort*

Concentration	Mean (SD)	Median (IQ Range)
VLDL-P	82.4 (51.0)	78.2 (44.5, 111.5)
LDL-P	1516.6 (534.5)	1420.7 (1143.7, 1767.7)
HDL-P	34.5 (6.4)	34.4 (30.4, 38.4)
Size		
VLDL-P	51.7 (12.0)	49.4 (44.9, 55.5)
LDL-P	21.4 (12.0)	21.6 (20.7, 22.1)
HDL-P	9.1 (0.5)	9.1 (8.7, 9.5)

HDL-P = high-density lipoprotein-particle; IQR = interquartile range; LDL-P = low-density lipoprotein-particle; NMR = nuclear magnetic resonance; VLDL-P = very-low-density lipoprotein-particle.

*Subclass particle concentrations are given in units of nanomoles per liter for VLDL-P and LDL-P (including intermediate-density lipoprotein particles) and micromoles per liter for HDL-P. Average VLDL-P, LDL-P, and HDL-P sizes (in nanometer diameter units) were calculated as the particle size of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its NMR signal.