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Authors

Ferguson, Erin L
Zimmerman, Scott C
Jiang, Chen
et al.

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RESEARCH ARTICLE

Low- and High-Density Lipoprotein Cholesterol and Dementia Risk Over 17 Years of Follow-up Among Members of a Large Health Care Plan

Erin L. Ferguson, MPH, Scott C. Zimmerman, MPH, Chen Jiang, PhD, Minhyuk Choi, MPH, Kaitlin Swinnerton, MIDS, Vidhu Choudhary, MA, Travis J. Meyers, PhD, MPH, Thomas J. Hoffmann, PhD, Paola Gilsanz, ScD, Akinyemi Oni-Orisan, PharmD, PhD, Rachel A. Whitmer, PhD, Neil Risch, PhD, Ronald M. Krauss, MD, Catherine A. Schaefer, PhD, and M. Maria Glymour, ScD, MS

Correspondence
Ms. Ferguson
erin.ferguson@ucsf.edu

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Abstract

Background and Objectives

The associations of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) with dementia risk in later life may be complex, and few studies have sufficient data to model nonlinearities or adequately adjust for statin use. We evaluated the observational associations of HDL-C and LDL-C with incident dementia in a large and well-characterized cohort with linked survey and electronic health record (EHR) data.

Methods

Kaiser Permanente Northern California health plan members aged 55 years and older who completed a health behavior survey between 2002 and 2007, had no history of dementia before the survey, and had laboratory measurements of cholesterol within 2 years after survey completion were followed up through December 2020 for incident dementia (Alzheimer disease–related dementia [ADRD]; Alzheimer disease, vascular dementia, and/or nonspecific dementia) based on ICD-9 or ICD-10 codes in EHRs. We used Cox models for incident dementia with follow-up time beginning 2 years postsurvey (after cholesterol measurement) and censoring at end of membership, death, or end of study period. We evaluated nonlinearities using B-splines, adjusted for demographic, clinical, and survey confounders, and tested for effect modification by baseline age or prior statin use.

Results

A total of 184,367 participants [mean age at survey = 69.5 years, mean HDL-C = 53.7 mg/dL (SD = 15.0), mean LDL-C = 108 mg/dL (SD = 30.6)] were included. Higher and lower HDL-C values were associated with elevated ADRD risk compared with the middle quantile: HDL-C in the lowest quintile was associated with an HR of 1.07 (95% CI 1.03–1.11), and HDL-C in the highest quintile was associated with an HR of 1.15 (95% CI 1.11–1.20). LDL-C was not associated with dementia risk overall, but statin use qualitatively modified the association. Higher LDL-C was associated with a slightly greater risk of ADRD for statin users (53% of the sample, HR per 10 mg/dL increase = 1.01, 95% CI 1.01–1.02) and a lower risk for nonusers (HR per 10 mg/dL increase = 0.98; 95% CI 0.97–0.99). There was evidence for effect modification by age with linear HDL-C (p = 0.003) but not LDL-C (p = 0.59).

Discussion

Both low and high levels of HDL-C were associated with elevated dementia risk. The association between LDL-C and dementia risk was modest.

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Infographic
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From the Department of Epidemiology and Biostatistics (E.L.F., S.C.Z., M.C., K.S., T.J.H., N.R., M.M.G.), University of California, San Francisco; Kaiser Permanente Division of Research (C.J., V.C., T.J.M., P.G., C.A.S.), Oakland; Institute for Human Genetics (A.O.-O., N.R.); Department of Clinical Pharmacy (A.O.-O.), University of California, San Francisco; Department of Public Health Sciences (R.A.W.), University of California, Davis; and Departments of Pediatrics and Medicine (R.M.K.), University of California, San Francisco. K.S. is currently affiliated with the VA Boston Healthcare System, MA. T.J.H. is currently affiliated with the Department of Epidemiology and Biostatistics, University of California, San Francisco, and the Institute for Human Genetics, University of California, San Francisco. P.G. is currently affiliated with the Kaiser Permanente Division of Research, Oakland, CA, and the Department of Epidemiology and Biostatistics, University of California, San Francisco. N.R. is currently affiliated with the Department of Epidemiology and Biostatistics, the Institute for Human Genetics, University of California, San Francisco, and the Kaiser Permanente Division of Research, Oakland, CA. M.M.G. is currently affiliated with the Department of Epidemiology, Boston University School of Public Health, MA.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = Alzheimer disease; **ADRD** = Alzheimer disease–related dementia; **BMI** = body mass index; **EHR** = electronic health record; **HDL-C** = high-density lipoprotein cholesterol; **KPNC** = Kaiser Permanente Northern California; **LDL-C** = low-density lipoprotein cholesterol; **RPGEH** = Research Program on Genes, Environment, and Health.

Introduction

Despite years of inquiry, evidence for a role of lipids and lipoproteins in the development of dementia remains ambiguous. Approximately 30% of older adults in the United States are estimated to have high levels of low-density lipoprotein cholesterol (LDL-C).[1] Thus, even small individual-level effects of dysregulated cholesterol on dementia may cause a large number of excess cases. Because high-density lipoprotein cholesterol (HDL-C) and LDL-C are strongly associated with stroke and cardiovascular disease,[2-4] they also likely influence the risk of dementia. However, prior evidence is inconsistent. A recent meta-analysis suggested no significant association of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or total cholesterol with dementia risk among older adults (aged 60 years and older), but CIs were too wide to rule out small-to-moderate effects.[5] A subsequent UK study, with a larger sample than the prior meta-analyses, suggested that elevated LDL-C increased dementia risk, but there was no relationship with HDL-C.[6] The potential for detecting associations may be affected by limitations of prior studies, including variation in how cholesterol was measured, incomplete control for major confounders, limited diversity in some samples, and lack of statistical power to evaluate nonlinear relationships or deliver precise estimates.

Measurement error is a concern because both laboratory measurement error[7] and short-term individual fluctuations contribute to variability in measured serum cholesterol.[8] Repeated measures of cholesterol may be needed to adequately assess cholesterol-related risk, but most prior studies have had only a single laboratory measurement.[6,9,10] Strong links between lipoprotein cholesterol levels and social, behavioral, and clinical risk factors of dementia (eFigure 1, links.lww.com/WNL/D135) require careful control for confounders, but many prior studies used administrative data without detailed confounder assessments.[11,12] Finally, only a few studies have investigated nonlinear relationships between cholesterol measures and dementia, despite evidence of nonlinearities in effects of HDL-C[13,14] and LDL-C[15] on cardiovascular outcomes. A combination of these limiting factors has likely contributed to discrepancies in the literature on cholesterol and dementia risk.[10,11,16-20]

This analysis leveraged an exceptional cohort combining survey data from a large diverse sample of older Kaiser Permanente Northern California (KPNC) members with comprehensive longitudinal electronic health record follow-up for dementia incidence up to 17 years to rigorously investigate associations between cholesterol and dementia incidence. The large sample, repeated cholesterol measures, and detailed covariate assessments allowed us to address many limitations in prior work.

Methods

Study Population

We pooled electronic health record (EHR) and survey data collected from 2 large survey cohorts of KPNC members. KPNC is a large integrated health care delivery system, attending to more than 4.6 million members in Northern California. The older population in KPNC, specifically those older than 65 years, are generally similar to seniors living in California regarding relevant characteristics of this analysis, including history of chronic disease (cardiovascular disease, diabetes, and hypertension) and lifestyle factors (smoking and sedentary lifestyle), although the most advantaged and disadvantaged groups may be underrepresented.[21]

The 2 survey cohorts included in these analyses are the California Men's Health Study (CMH) cohort and the Kaiser Research Program on Genes, Environment, and Health (RPGEH) cohort. The CMH enrolled men aged 45–69 years in 2000 who completed a demographics and health behavior survey in 2002–2003.[22] The RPGEH included KPNC members who completed a similar demographics and health behavior survey in 2007.[23] Full medical, laboratory, and pharmacy information for participants eligible for these analyses were obtained from KPNC EHRs from 1996 to 2020.

From 265,224 participants who completed either survey, we excluded participants (eFigure 2, links.lww.com/WNL/D135) who were younger than 55 years at survey completion (n = 5,915, 2.2%), did not have at least 1 LDL-C and HDL-C measurement within 2 years after survey completion (n = 53,016, 20.0%), or had a diagnosis of any dementia (including frontotemporal dementia and dementia with Lewy bodies), Parkinson disease, or amyotrophic lateral sclerosis before baseline (defined as 2 years after survey completion) (n = 4,295, 1.6%). By design, surviving participants were at least 68 years of age by the end of the study period given the low incidence of dementia before this age. To avoid immortal time bias and define a consistent starting point for all participants, follow-up time for dementia began 2 years after completion of the survey (eFigure 3); 15,061 participants (5.7%) who were lost to follow-up or ended KPNC membership in this time interval were excluded from analyses. Participants with missing sex information (n = 57, 0.03%) or no documented

measurements of systolic blood pressure in the EHR were excluded (n = 2,513, 1.3%), which resulted in a final analytic sample of 184,367 participants. We considered missing survey questions on education (7.9% missing), income (13.3% missing), and alcohol use (21.7% missing) likely to be informative and retained nonresponders by including "missing" indicator variables for all survey covariates. We additionally conducted a sensitivity analysis dropping all observations with missing covariates (n of complete cases = 110,940).

Serum Cholesterol Levels: LDL-C and HDL-C

We used all lipid panel measurements from eligible participants recorded in the KPNC EHR system in the 2 years after survey completion (n = 466,911; range 1–26 panels per participant). Each fasted lipid panel included total cholesterol, LDL-C, triglycerides, and HDL-C levels (mg/dL).[24] LDL-C levels were available in the EHR primarily as calculated values from the traditional Friedewald formula (based on total cholesterol, triglycerides, and HDL-C).[25] Other LDL-C levels were available in the EHR as direct measurements when triglyceride levels were >400 mg/dL consistent with routine clinical care. All other lipid types were available in the EHR as direct measurements. We excluded 3.9% of laboratory records with values outside of plausible ranges (10–200 mg/dL for HDL-C and 10–500 mg/dL for LDL-C), which indicated potential data entry errors or equipment malfunction.

Dementia Outcomes

We defined an incident dementia diagnosis in the KPNC EHR as first documented diagnosis of Alzheimer disease (AD), vascular dementia, or nonspecific dementia (ICD-9 or ICD-10 codes listed in eTable 1, links.lww.com/WNL/D136) from any encounter type (inpatient, outpatient, ambulatory, virtual care, etc.) except for laboratory-only and radiology-only encounters. Other types of dementia, such as frontotemporal dementia and dementia with Lewy bodies, were used as censoring variables but were not included in the primary outcome.

Covariates

We sought to control for clinical, demographic, and behavioral covariates recorded before cholesterol measurement and posited to potentially influence both cholesterol and dementia risk. To assess the impact of additional confounding variables, we compared estimates from 3 models for each cholesterol measure, with controls for the following: (1) basic demographics and known confounders (age at survey, sex [male, female], race/ethnicity [Asian, Black, Hispanic, Other, White, or unknown racial identity], education [less than high school, high school completion, more than high school, or missing], income [reported in 5 categories and coded as ordinal or missing], US nativity, and marital status [never married, married, separated, widowed, or missing]); (2) model 1 covariates plus probable confounders (binary indicator for clinical history of diabetes, major depression, or head injury, systolic blood pressure [continuous; an average of all SBP measurements in the 2 years after survey completion], current alcohol use based on the National Institute on Alcohol Abuse and Alcoholism guidelines[26] [none, light to moderate, heavy, or missing], current smoking status [yes, no, or missing], body mass index [continuous], and number of lipid measurements in the 2 years after survey completion [continuous]); (3) model 2 covariates plus confounders that might also be influenced by cholesterol and were therefore potential mediators (binary indicators for clinical history of cardiovascular disease [myocardial infarction, ischemic heart disease, or revascularization procedures], stroke [either ischemic or hemorrhagic, pooled], hypertension, any history of statin use, and general health measure self-reported on a 5-point scale [poor, fair, good, very good, and excellent]). Basic demographics, including racial-ethnic identity and sex, were obtained from administrative records, which are a compilation of self-report and legacy administrative records. In supplemental analyses, we structured covariate sets based on variable availability in the EHR or survey (see eTable 2, links.lww.com/WNL/D136). We also conducted 2 supplemental analyses with additional covariates. The first uses the number of statin prescription months in the 5 years before survey completion, obtained from prescription records. The other uses categorical body mass index (BMI) calculated from self-reported weight and height on the survey (underweight, healthy, overweight, obese, and missing).

Statistical Analysis

We estimated Cox proportional hazard models of time to incident dementia diagnosis predicted by LDL-C and HDL-C (modeled as described further). Participants were censored at death, end of KPNC membership, end of study period (12/2020), or a diagnosis of other dementias or neurodegenerative diseases.

To evaluate potential nonlinearities in the relationships between serum cholesterol measures and the hazard of Alzheimer disease–related dementia (ADRD), we assessed the relationship between quintiles of cholesterol and ADRD risk. Separately, we introduced cubic B-splines (basis splines) of LDL-C and HDL-C, creating piecewise cubic line segments between knots at the 25th, 50th, and 75th percentiles. Likelihood ratio tests were used to statistically compare the models with splines with the models without splines (i.e., models imposing a linearity assumption).

Based on prior evidence for heterogeneous effects by age,[6,27] we checked for effect measure modification between each of the cholesterol measures (linear and using splines) with a binary measurement of age (younger than or older than 65 years). Binary age was only used for this interaction analysis. In addition, because HDL-C cutoffs for metabolic syndrome differ by sex (<40 mg/dL for men and <50 mg/dL for women),[28] we checked for effect measure modification between HDL-C (linear and using splines) and sex. Using binary indicators for being above and below this threshold by sex, we tested for statistically significant discontinuities in risk of dementia at the threshold. Finally, we also evaluated models

stratified by whether the participant was using statins before the survey. In post hoc analyses, we evaluated interactions with racial/ethnic identity with adjustment for multiple comparisons.

Previous literature reported that an HDL-C to LDL-C ratio could be a stronger predictor of cardiovascular risk than either component alone,[29,30] but prior work did not evaluate this ratio as a predictor of dementia risk. In secondary analyses, we therefore evaluated the association between the ratio and dementia. We calculated an HDL-LDL ratio based on each participant's HDL-C and LDL-C measures recorded for the same date and averaged over all available ratio measures for the participant.

To allow direct comparisons with previous studies that only measured cholesterol at a single time point,[6,9,10] we also considered the first available postsurvey measurement of LDL-C, HDL-C, and ratio measures and compared these results with findings when using the 2-year postsurvey average of all available LDL-C, HDL-C, and ratio measurements. The agreement between the single measurement and the 2-year average of all measurements was quantified using an intraclass correlation coefficient for each cholesterol type, using 2-way random effects models and absolute agreement.

Because prior studies of the association between cholesterol and dementia additionally adjusted for BMI,[6,12] we included a supplementary analysis for the association between quintiles of cholesterol and risk of ADRD additionally adjusted for BMI. Due to concerns about measurement error of the self-reported measure,[31] we did not include BMI in the primary covariate set.

In older populations, statin use is highly prevalent.[32] Because statin use is strongly associated with LDL-C, residual confounding by statin use could be a concern in the primary analysis. To address this concern in a sensitivity analysis, we used the first-ever recorded measurement of LDL-C and HDL-C as a proxy for cholesterol under no statin treatment. Most patients receive an LDL-C measurement before statin initiation because guidelines from the American College of Cardiology and the American Heart Association recommend prescribing statins for lowering LDL-C levels.[28] The correlation between the first-ever measurement and the 2-year postsurvey average was calculated using the Pearson correlation coefficient. To account for potential residual confounding by statin dosage or length of use, we conducted a supplementary analysis adjusting for number of prescription months on statins in the 5 years before survey instead of a binary statin use indicator.

Bias Assessment: Alternate Outcomes

As a positive control to confirm our models had adequate confounder control, we included models for alternate outcomes of known associations with cholesterol measures using 2 comparison outcomes: incident myocardial infarction and stroke (ischemic and hemorrhagic). We also checked for the observed associations in the subset of our sample with no history of myocardial infarction or stroke at baseline (n = 164,121).

Standard Protocol Approvals, Registrations, and Patient Consents

This analysis was approved by the Institutional Review Boards at the University of California San Francisco and the Kaiser Permanente Northern California and Mid-Atlantic States boards. The requirement for patient informed consent was waived because analyses were conducted on preexisting data.

Data Availability

Data are available to qualified researchers by application to the KP Research Bank, contingent upon project approval by the KP Research Bank Access Review Committee (ARC), IRB approval, and execution of a Materials and Data Transfer Agreement (MDTA).

Results

Our analytic sample included 184,367 participants (mean [SD] age at survey, 69.5 years [8.46]; 55.1% female, 72.6% White) (Table 1). In the 2 years after survey completion, lipids were measured an average of 2.51 [1.66] times per participant. Over an average follow-up of 8.77 years [4.12], 25,214 incident cases of dementia were observed.

Models with flexible splines indicated significant nonlinear relationships between HDL-C and hazard of dementia, such that both low and high values of HDL-C were associated with slightly elevated risk of dementia (Figure 1A). In the fully adjusted model categorizing HDL-C, HDL-C in the lowest quintile (11–41 mg/dL) was associated with a 7% increase in hazard of dementia (HR = 1.07, 95% CI 1.03–1.11) compared with the middle quintile, whereas the highest quintile of HDL-C (>65 mg/dL) was associated with a 15% elevation in risk (HR = 1.15, 95% CI 1.11–1.20) compared with the middle quintile (Table 2).

In fully adjusted models, there was little association between LDL-C and dementia (Figure 1B), and HRs were close to the null in all quintiles (Table 2).

Dropping missing values did not alter results for either HDL-C or LDL-C analysis (eFigure 4, links.lww.com/WNL/D135). Adjustment for clinical covariates, compared with survey covariates alone, did not alter findings for HDL-C and moved estimates even closer to the null for LDL-C (eTable 2, links.lww.com/WNL/D136). Additional adjustment for BMI did not substantially change results for HDL-C or LDL-C (eTable 3). In post hoc analyses, Black individuals tended to have higher dementia risk compared with White individuals in the lowest quintile of LDL-C compared with the middle

Table 1 Baseline Characteristics of the Analytic Cohort

Characteristics	Younger than 65 y (N = 66,048) n (%) or mean (SD)	Older than 65 y (N = 118,319) n (%) or mean (SD)	Total analytic cohort (N = 184,367) n (%) or mean (SD)
Age at survey	60.8 (2.5)	74.3 (6.47)	69.5 (8.46)
Female	35,157 (53.2)	66,518 (56.2)	101,675 (55.1)
Race/ethnicity			
Asian	6,599 (10.0)	9,371 (7.9)	15,970 (8.7)
Black	2,951 (4.5)	4,417 (3.7)	7,368 (4.0)
Hispanic	5,341 (8.1)	9,786 (8.3)	15,127 (8.2)
Other	4,002 (6.1)	7,128 (6.0)	11,130 (6.0)
White	46,688 (70.7)	87,181 (73.7)	133,869 (72.6)
Unknown	467 (0.7)	436 (0.4)	903 (0.5)
Characteristics obtained from survey			
Income			
$100k+	20,889 (31.6)	13,181 (11.1)	34,070 (18.5)
$60k–$99k	19,521 (29.6)	22,898 (19.4)	42,419 (23.0)
$40k–$59k	10,592 (16.0)	22,229 (18.8)	32,821 (17.8)
$20k–$39k	6,816 (10.3)	25,386 (21.5)	32,202 (17.5)
<$20k	2,656 (4.0)	15,460 (13.1)	18,116 (9.8)
Missing	5,574 (8.4)	19,165 (16.2)	24,739 (13.4)
Education			
Greater than HS Diploma	33,112 (50.1)	42,507 (35.9)	75,619 (41.0)
High School Diploma	26,142 (39.6)	53,378 (45.1)	79,520 (43.1)
Less than HS Diploma	2,467 (3.7)	10,955 (9.3)	13,422 (7.3)
Other	375 (0.6)	773 (0.7)	1,148 (0.6)
Missing	3,952 (6.0)	10,706 (9.0)	14,658 (8.0)
Smoking history			
Never	33,334 (50.5)	54,372 (46.0)	87,706 (47.6)
Current or former	29,631 (44.9)	54,197 (45.8)	83,828 (45.5)
Missing	3,083 (4.7)	9,750 (8.2)	12,833 (7.0)
Marital status			
Never married	3,497 (5.3)	3,873 (3.3)	7,340 (4.0)
Married	48,577 (73.5)	73,193 (61.9)	121,770 (66.0)
Separated	9,767 (14.8)	13,779 (11.6)	23,546 (12.8)
Widowed	2,737 (4.1)	24,097 (20.4)	26,834 (14.6)
Missing	1,470 (2.2)	3,377 (2.9)	4,847 (2.6)
Alcohol class			
None	21,818 (33.0)	34,901 (29.5)	56,719 (30.8)
Light to moderate	23,914 (36.2)	38,886 (32.9)	62,800 (34.1)
Heavy	10,700 (16.2)	13,987 (11.8)	24,687 (13.4)

Continued

Table 1 Baseline Characteristics of the Analytic Cohort *(continued)*

Characteristics	Younger than 65 y (N = 66,048) n (%) or mean (SD)	Older than 65 y (N = 118,319) n (%) or mean (SD)	Total analytic cohort (N = 184,367) n (%) or mean (SD)
Missing	9,616 (14.6)	30,545 (25.8)	40,161 (21.8)
US nativity			
Yes	52,341 (79.2)	92,264 (78.0)	144,605 (78.4)
No	11,379 (17.2)	20,308 (17.2)	31,687 (17.2)
Missing	2,328 (3.5)	5,747 (4.9)	8,075 (4.4)
General health			
Excellent	8,451 (12.8)	8,928 (7.5)	17,379 (9.4)
Very good	20,450 (31.0)	29,488 (24.9)	49,938 (27.1)
Good	23,523 (35.6)	50,644 (42.8)	74,167 (40.2)
Fair	7,749 (11.7)	20,928 (17.7)	28,677 (15.6)
Poor	1,241 (1.9)	2,941 (2.5)	4,182 (2.3)
Missing	4,634 (7.0)	5,390 (4.6)	10,024 (5.4)
Characteristics obtained from electronic health records			
Cardiovascular disease	5,440 (8.2)	24,336 (20.6)	29,776 (16.2)
Diabetes	10,493 (15.9)	23,638 (20.0)	34,131 (18.5)
Hypertension	33,697 (51.0)	87,821 (74.2)	121,518 (65.9)
Stroke	585 (0.9)	3,698 (3.1)	4,283 (2.3)
Head injury	425 (0.6)	1,196 (1.0)	1,621 (0.9)
Major depression	13,292 (20.1)	19,139 (16.2)	32,431 (17.6)
Previous or current statin use	27,069 (41.0)	70,198 (59.3)	97,267 (52.8)
Average systolic blood pressure	128 (11.8)	131 (11.4)	130 (11.6)
Average diastolic blood pressure	75.8 (7.43)	71.7 (7.36)	73.2 (7.65)
Cholesterol measures[a]			
Average LDL-C (mg/dL)	115 (30.6)	104 (30.0)	108 (30.6)
Average HDL-C (mg/dL)	53.7 (15.0)	53.7 (14.9)	53.7 (15.0)
Average cholesterol ratio	0.507 (0.195)	0.561 (0.210)	0.54 (0.21)
Average number of laboratory measurements	2.33 (1.66)	2.60 (1.65)	2.51 (1.66)

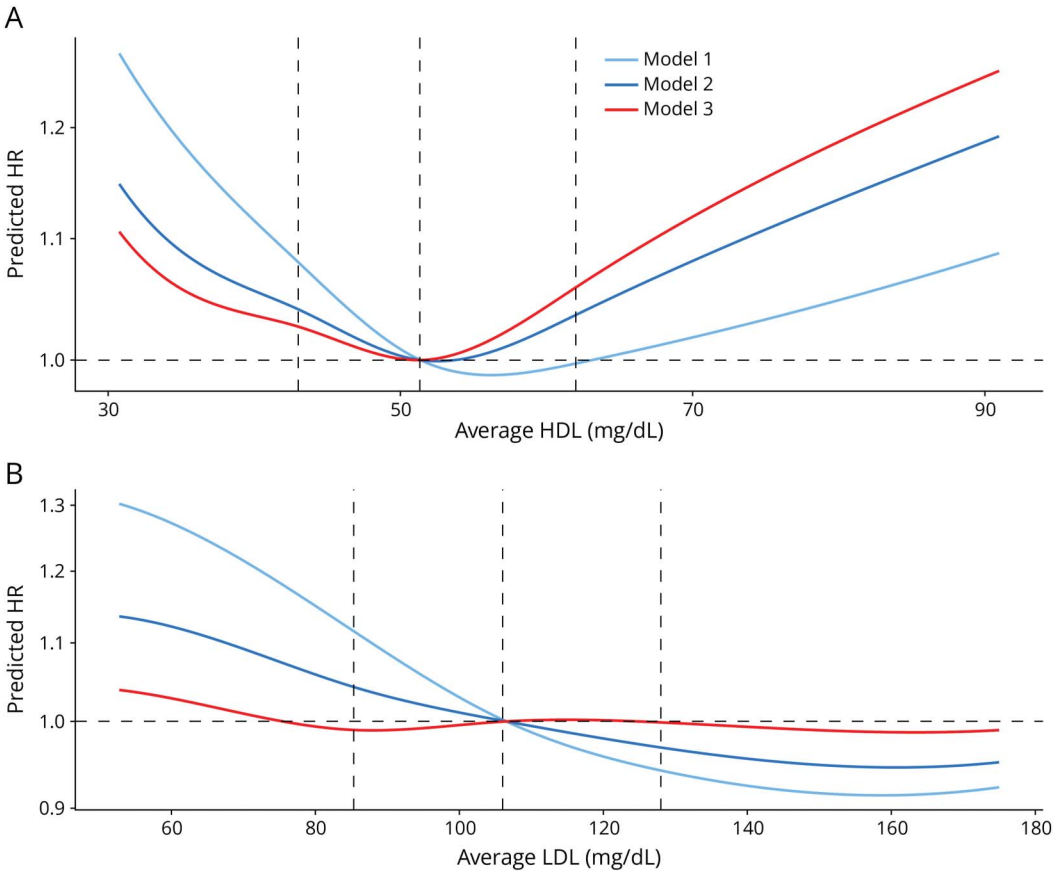
[a] Cholesterol was measured in the 2 years after survey completion, before follow-up began.

quintile (interaction term = 1.21, 95% CI 1.01–1.45) and in the highest quintile of LDL-C compared with the middle quintile (interaction term = 1.18, 95% CI 0.97–1.44; eTable 4). There was no statistically significant interaction between racial-ethnic group and cholesterol after adjusting for multiple comparisons.

The intraclass correlation of HDL-C measures was 0.97 (0.973–0.974) and that for LDL-C measures was 0.90 (0.895–0.913). Hazard ratio estimates using the first (single) measurement of cholesterol measure were similar to estimates using the 2-year averages for both HDL-C and LDL-C (Figure 2), and gains in precision were negligible (eTable 5, links.lww.com/WNL/D136).

In fully adjusted models using linear specifications of LDL-C and HDL-C (eTable 6, links.lww.com/WNL/D136), LDL-C was not associated with dementia (HR = 1.00, 95% CI 0.99–1.00), and a 10-mg/dL increase in HDL-C was associated with a 2.9% increase (95% CI 1.9%–3.9%) in dementia

Figure 1 Hazard Ratios for ADRD With B-Splines for Each Average Cholesterol Measure



Knots at the 25th, 50th, and 75th percentiles of: (A) average HDL-C (unscaled), (B) average LDL-C (unscaled). Range of predicted HRs shown for the 2nd to the 98th percentile of LDL-C (52.7–175 mg/dL) and HDL-C (30.7–91 mg/dL) observed in the analytic data. ADRD = Alzheimer disease–related dementia.

risk. Associations with the HDL-LDL ratio were close to the null and generally similar in pattern to associations of HDL alone (eTables 6 and 7, eFigure 5, links.lww.com/WNL/D135).

Participants with a history of statin use had an average LDL-C of 97.9 mg/dL [29.1] and nonusers had an average of 119 mg/dL [28.4]. Prior statin use was a qualitative modifier of the relationship between a linear term for LDL-C and incident ADRD (p value for interaction <0.001), with a 10-mg/dL difference in LDL-C associated with increased dementia risk in statin users (HR = 1.01, 95% CI 1.01–1.02) and decreased risk in nonusers (HR = 0.98; 95% CI 0.97–0.99). When categorizing LDL-C by quintile, there was statistically significant effect measure modification in the 1st and 2nd quintiles compared with that in the 3rd quintile (p value for interaction <0.001), which can also be visualized using splines (Figure 3).

The first-ever measure of LDL-C was on average 29 mg/dL higher compared with the 2-year postsurvey average (Pearson correlation = 0.330). HDL-C differed by less than 2 mg/dL (Pearson correlation = 0.764). At first-ever LDL-C measurement, 7.5% of the cohort had a history of statin use compared with 52.8% at survey. First-ever LDL-C measurement was not significantly associated with hazard of dementia in any model (eTable 8, links.lww.com/WNL/D136). First-ever measure of HDL-C was nonlinearly associated with hazard of ADRD.

When adjusting for number of prescription months on statins in the 5 years before survey completion (mean = 6.029, SD = 7.47), the results for the associations between quintiles of cholesterol and risk of ADRD were not different from primary analyses for either LDL-C or HDL-C (eTable 9, links.lww.com/WNL/D136).

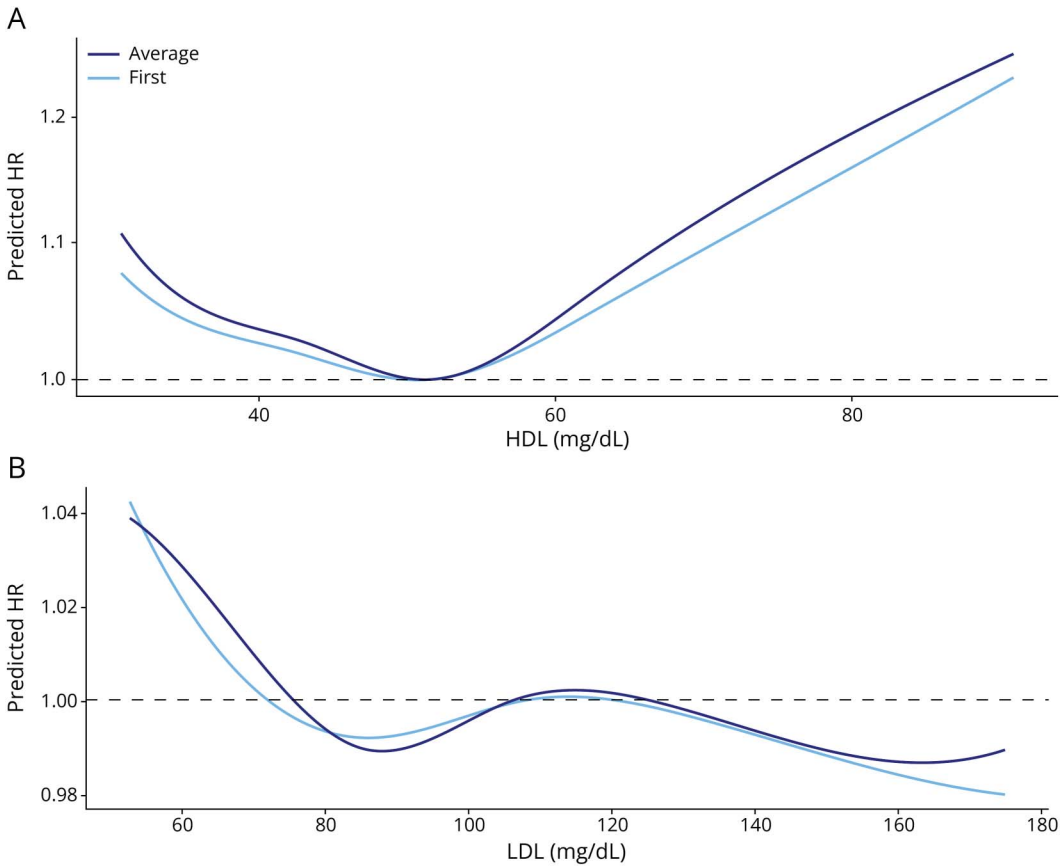
Higher LDL-C was associated with slightly lower dementia hazard in those younger than 65 years (HR = 0.99, 95% CI 0.98–1.00) and those older than 65 years (per 10 mg/dL difference: HR = 0.99, 95% CI 0.97–1.00), although this association was statistically significant only among those older than 65 years. There was no statistically significant interaction between LDL-C and dichotomized age when included linearly (p = 0.59) or categorized by quintile (p = 0.48). HDL-C was associated with dementia risk in those younger than 65 years (HR = 1.06, 95% CI 1.02–1.09) and older than 65 years

Table 2 Hazard Ratios for ADRD by Quintile of 2-Year Average HDL-C and LDL-C

	Quintile of cholesterol measure, HR (95% CI)				
Cholesterol measure	**Q1 lowest**	**Q2**	**Q3**	**Q4**	**Q5 highest**
HDL-C					
Model 1	1.18 (1.13–1.23)	1.05 (1.01–1.09)	ref	0.99 (0.95–1.03)	1.04 (1.00–1.08)
Model 2	1.10 (1.05–1.14)	1.02 (0.98–1.06)	ref	1.02 (0.98–1.06)	1.11 (1.07–1.16)
Model 3	1.07 (1.03–1.11)	1.01 (0.97–1.05)	ref	1.04 (1.00–1.08)	1.15 (1.11–1.20)
LDL-C					
Model 1	1.21 (1.16–1.25)	1.09 (1.05–1.13)	ref	0.94 (0.90–0.98)	0.92 (0.88–0.96)
Model 2	1.09 (1.05–1.13)	1.04 (1.0–1.08)	ref	0.97 (0.93–1.01)	0.96 (0.92–1.00)
Model 3	1.01 (0.97–1.05)	1.00 (0.96–1.04)	ref	0.99 (0.95–1.04)	1.00 (0.96–1.04)

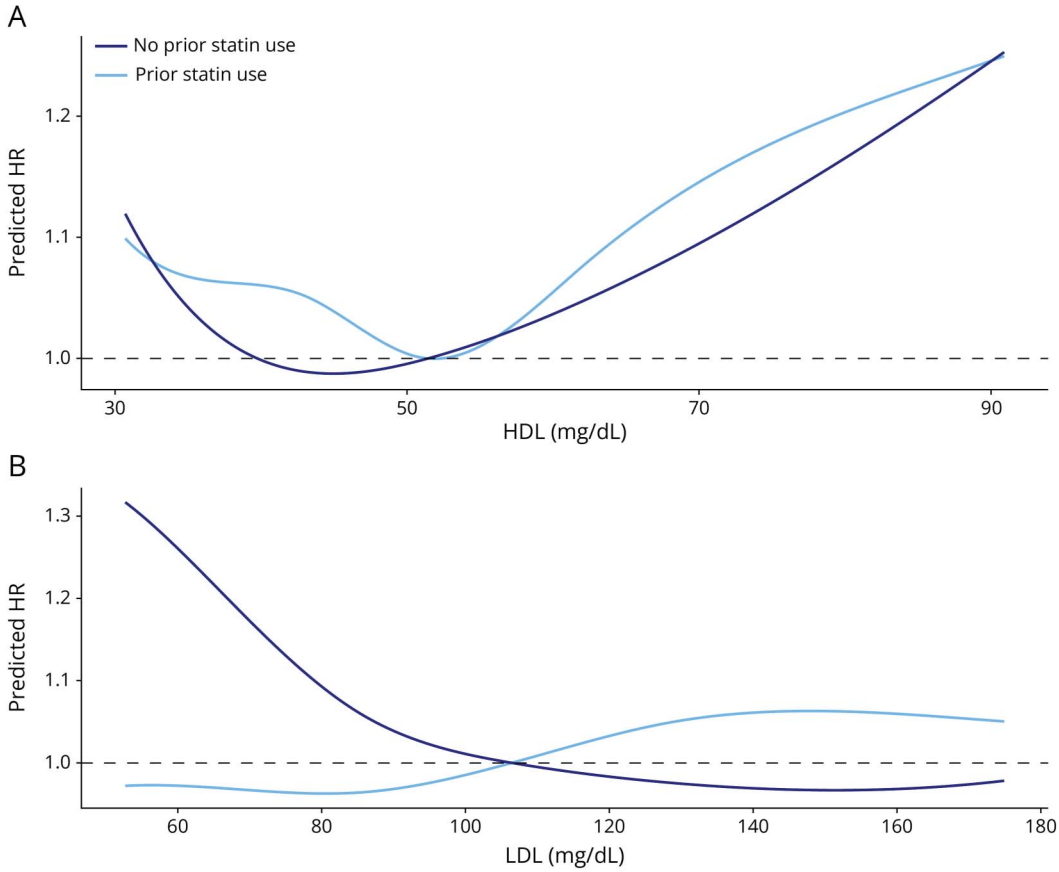
LDL-C and HDL-C are scaled by 10 mg/dL.
Covariate sets include the following: (1) basic demographics and known confounders (age at survey, sex, race/ethnicity, education, income, US nativity, and marital status); (2) model 1 covariates plus probable confounders (history of diabetes, major depression, head injury; systolic blood pressure, number of lipid measurements, current alcohol use, and current smoking status); (3) model 2 covariates plus confounders we identified as also being potential mediators (history of diagnosed cardiovascular disease, stroke, hypertension; any history of statin use; and general health measure). Nonresponders were retained by including "missing" indicators for all survey covariates.

Figure 2 Hazard Ratios for ADRD for First Cholesterol Measure vs 2-Year Average of Cholesterol Measures in Most Adjusted Model



All models include B-splines for cholesterol with knots at the 25th, 50th, and 75th percentiles. (A) HDL-C (unscaled). (B) LDL-C (unscaled). Range of predicted HRs shown for the 2nd to the 98th percentile of LDL-C (52.7–175 mg/dL) and HDL-C (30.7–91 mg/dL) observed in the analytic data. ADRD = Alzheimer disease–related dementia.

Figure 3 Hazard Ratios for ADRD for Linear Average Cholesterol Measure in Most Adjusted Covariate Set, Stratified by History of Statin Use at Survey Completion



All models include B-splines for cholesterol with knots at the 25th, 50th, and 75th percentiles. (A) HDL-C (unscaled). (B) LDL-C (unscaled). Range of predicted HRs shown for the 2nd to the 98th percentile of LDL-C (52.7–175 mg/dL) and HDL-C (30.7–91 mg/dL) observed in the analytic data. ADRD = Alzheimer disease–related dementia.

(HR = 1.06, 95% CI 1.05–1.07). There was statistically significant interaction between HDL-C and dichotomized age (younger and older than 65 years) when HDL-C was included linearly (p = 0.003) or categorized by quintile (p < 0.001) (Figure 4).

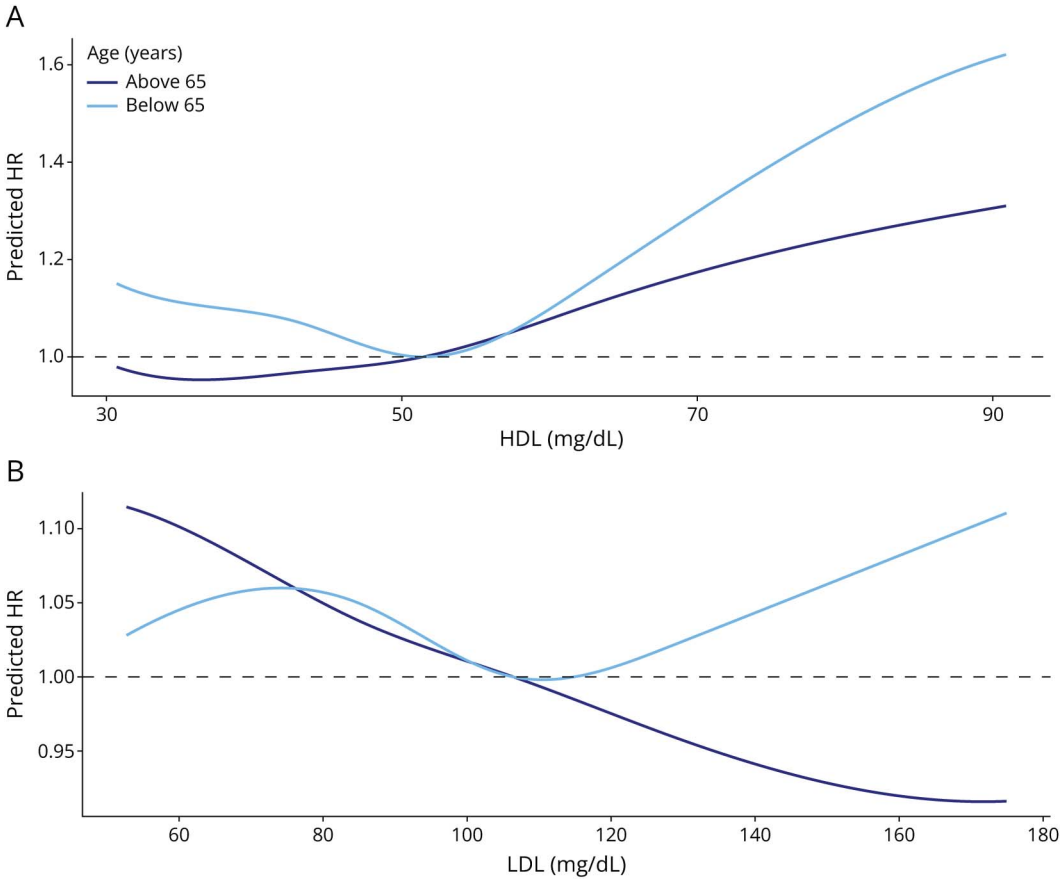
HDL-C was linearly associated with dementia risk in men (per 10 mg/dL difference: HR = 1.03, 95% CI 1.01–1.04) and women (per 10 mg/dL difference: HR = 1.03, 95% CI 1.02–1.04). There was no statistically significant interaction between HDL-C and sex when HDL-C was included linearly (p value for interaction = 0.729), categorized by quintile (p value for interaction = 0.232), or plotted with B-splines (eFigure 6, links.lww.com/WNL/D135). There was no significant increased risk of dementia for having an HDL-C level under the metabolic disease threshold (40 mg/dL for men and 50 mg/dL for women; HR: 1.02, 95% CI 0.97–1.07).

In positive control analyses, higher LDL-C was associated with a higher risk of MI (HR per 10 mg/dL = 1.03, 95% CI 1.02–1.04), but not with stroke (Table 3). Increases in HDL-C were associated with decreases in risk of MI and stroke.

Discussion

In a large and diverse cohort of KPNC patients, both the highest and lowest HDL-C quintiles were associated with small elevations in incidence of dementia. We found no clinically meaningful association between LDL-C and risk of ADRD in the overall sample. The association of HDL-C with increased risk of ADRD was identical for people younger and older than 65 years at baseline, though statistically significant only among individuals older than 65 years. Results for LDL-C were similar for people older or younger than 65 years at baseline. Prior statin use did not modify the association of HDL-C and ADRD incidence. For the 47% of participants with no history of statin use before cholesterol assessments, however, higher LDL-C was associated with lower ADRD incidence, whereas higher LDL-C was associated with slightly higher ADRD risk for individuals with a history of statin use. Using multiple measures of cholesterol instead of a single measurement did not alter the results. Control for covariates

Figure 4 Hazard Ratios for ADRD for Linear Average Cholesterol Measure in Most Adjusted Covariate Set, Stratified by a Dichotomous Indicator of Age (Younger and Older than 65 Years) at Survey Completion



All models include B-splines for cholesterol with knots at the 25th, 50th, and 75th percentiles. (A) HDL-C (unscaled). (B) LDL-C (unscaled). Range of predicted HRs shown for the 2nd to the 98th percentile of LDL-C (52.7–175 mg/dL) and HDL-C (30.7–91 mg/dL) observed in the analytic data. ADRD = Alzheimer disease–related dementia.

strengthened adverse estimated effects of high HDL-C but attenuated estimated effects of LDL-C and the HDL-LDL ratio. The pattern of associations of cholesterol measures with stroke and MI was consistent with prior evidence, strengthening interpretation of results for dementia. While we observed no significant association between LDL-C and stroke risk, this is consistent with some previous literature showing weak or no association between LDL-C and stroke.[33-35]

Table 3 Hazard Ratios for Myocardial Infarction and Stroke (n = 164,121) by Linear Average Cholesterol Measure

	Alternative outcome	
Cholesterol measure	**Myocardial function HR (CI)**	**Stroke HR (CI)**
HDL-C (per 10 mg/dL)	0.901 (0.885–0.917)	0.967 (0.952–0.981)
LDL-C (per 10 mg/dL)	1.030 (1.021–1.038)	1.000 (0.993–1.008)

LDL-C and HDL-C are scaled by 10 mg/dL.
Includes adjustment for the following: age at survey, sex, race/ethnicity, education, income, US nativity, and marital status, history of diagnosed medical conditions (diabetes, major depression, head injury, cardiovascular disease [excluding MI], and hypertension), any history of statin use, systolic blood pressure, number of lipid measurements, current alcohol use, current smoking status, and general health measure.

Several studies have investigated the relationship between LDL-C, HDL-C, and ADRD risk.[6,9,12,17,20,36-38] Our finding of a U-shaped association between HDL-C and dementia is consistent with a recent study reporting an association between genetically determined high HDL-C and risk of AD using Mendelian randomization (OR per 1 SD increase = 1.10, 95% CI 1.05–1.16).[39] Together, our results additionally support recent literature suggesting complex effects of HDL-C on many diseases and mortality.[14,40] Because HDL-C is nonlinearly associated with risk of cardiovascular disease,[14] HDL-C may be nonlinearly associated with dementia through this increased risk of cardiovascular disease. Alternatively, this nonlinear relationship may be explained by physiologic changes in HDL-C (i.e., trajectories of increase or decrease) due to incipient dementia. For example, stable BMI and systolic blood pressure, other cardiovascular risk factors, are

associated with better cognitive outcomes.[41-43] There is inconsistency in the small body of prior literature on the association between lipid trajectories and dementia.[9,44,45] Future studies with large diverse samples should investigate the association between trajectories in HDL-C and risk of dementia to give more context to our nonlinear finding.

Our results are inconsistent with some prior studies showing a significant harmful effect of elevated LDL-C[6,11,12,19,36,46] or no effect of HDL-C[10,11,19,20] on dementia risk. Many prior studies of HDL-C were likely too small to detect the effects of a magnitude we reported.[10,11] For example, the 3C study, with 7,470 participants, reported a 95% CI for HDL-C HR ranging from 0.91 to 1.09.[11] Even a large recent UK Biobank study,[12] which reported no association with HDL-C (HR = 1.04, 95% CI 0.92–1.17), had substantial uncertainty due to the relatively small number of accrued cases with dementia in its relatively young cohort with an average age of 57 years (5,334 cases compared with 25,214 in our sample). The UK Biobank study reported LDL-C as protective against dementia (HR 0.92, 95% CI 0.872–0.965) and did not find evidence for nonlinearity in the effect of HDL-C. This may be attributable to omission of important clinical covariates (i.e., history of diabetes, cardiovascular disease, hypertension, statin use, etc.) in the UK Biobank analysis because we found controlling for certain covariates increased the estimated adverse effect of high HDL-C. Differences between our findings and UK Biobank results may also be due to differences in context or cohort characteristics. The KPNC cohort includes more racial/ethnic diversity than the UK Biobank and those used in some previous studies.[6,12] Although we were limited by sample size and multiple comparisons, our results suggest there may be clinically significant interaction between racial-ethnic identity and LDL-C on dementia risk, where Black individuals tended to have higher dementia risk compared with White individuals in the highest and lowest quintiles of LDL-C. This interaction may be clinically meaningful and should be investigated in future analyses with a larger representation of Black individuals.

Previous studies have reported differences in the effect of LDL-C on dementia risk by age. The largest study to date in a cohort of UK patients found a significant effect of LDL-C in those younger than 65 years (rate ratio 1.07, 95% CI 1.03–1.13).[6] Our results are inconsistent with this finding and the UK Biobank study because we found no association between LDL-C and dementia in participants younger than 65 years. That cohort was much larger than that in this study, but notably less diverse and in a different population. Our results are also inconsistent with that of the 3C study, which found a harmful association between LDL-C and dementia in patients older than 65 years.[11] Differences in medical management of elevated LDL-C may also contribute to our findings.

We interpret the apparent effect modification of LDL-C by prior statin use very cautiously. Because a harmful effect is only seen in previous statin users, it is possible that this is due to residual confounding. Measured LDL in statin users is likely confounded by statin use and dose. This effect should be evaluated in future independent studies from models considering time-varying statin use and modeling the dynamic relationship between LDL-C and statin use over time. LDL-C cholesterol earlier in life may nonetheless be relevant for dementia risk.[9,27,47] We also evaluated the ratio between HDL-C and LDL-C on prior evidence suggesting the ratio was more strongly predictive of cardiovascular outcome than either measure alone.[48] In our analyses, the HDL/LDL ratio predicted ADRD incidence, though this was largely driven by the association with HDL-C.

This study has some limitations. The dataset comprised KPNC members who volunteered for survey participation. Selection bias could have influenced our results, with our survey cohort having more frequent interactions with the Kaiser health care system, compared with their patient base or the larger population in Northern California. In addition, we did not adjust for *APOE* status, as in some previous analyses.[6,10] Although we had an unusually large range of control variables, the possibility of unmeasured confounding cannot be definitively ruled out.

Our study also has important strengths compared with prior work, including a large sample with nearly a decade of follow-up, which allowed more precise estimation of nonlinear associations and permitted us to detect even fairly small effect sizes. The sample is also unusually diverse and the comprehensive clinical data provided multiple cholesterol measures on most participants. By using averages across multiple measurements, we could rigorously evaluate and rule out concerns about measurement error contributing to our findings. Sensitivity analyses using MI and stroke as outcomes were consistent with previous literature showing that LDL-C is associated with an increased risk of MI and HDL-C is associated with a decreased risk of MI.[2-4] The consistency of our alternative outcomes analyses with previous research adds merit to our analyses of dementia, regarding the direction of the effect.

In conclusion, this large diverse cohort study with ubiquitous access to health care is an important addition to understanding the effects of cholesterol on dementia risk. We found that in this cohort of older KPNC patients, HDL-C was nonlinearly associated with dementia risk, with both low and high levels corresponding to higher risk. LDL-C had little association with incident dementia. These results support the conclusion that some lipoproteins may be modifiable risk factors of dementia, even in late life. Future studies should investigate the presence of a causal relationship of HDL-C variation and dementia risk using an HDL polygenic risk score.

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Appendix Authors

Name	Location	Contribution
Erin L. Ferguson, MPH	Department of Epidemiology and Biostatistics, University of California, San Francisco	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Scott C. Zimmerman, MPH	Department of Epidemiology and Biostatistics, University of California, San Francisco	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data; code review
Chen Jiang, PhD	Kaiser Permanente Division of Research, Oakland, CA	Study concept or design; analysis or interpretation of data
Minhyuk Choi, MPH	Department of Epidemiology and Biostatistics, University of California, San Francisco	Analysis or interpretation of data
Kaitlin Swinnerton, MIDS	Department of Epidemiology and Biostatistics, University of California, San Francisco	Analysis or interpretation of data
Vidhu Choudhary, MA	Kaiser Permanente Division of Research, Oakland, CA	Major role in the acquisition of data
Travis J. Meyers, PhD, MPH	Kaiser Permanente Division of Research, Oakland, CA	Drafting/revision of the article for content, including medical writing for content
Thomas J. Hoffmann, PhD	Department of Epidemiology and Biostatistics, University of California, San Francisco	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Paola Gilsanz, ScD	Kaiser Permanente Division of Research, Oakland, CA	Drafting/revision of the article for content, including medical writing for content; study concept or design
Akinyemi Oni-Orisan, PharmD, PhD	Institute for Human Genetics; Department of Clinical Pharmacy, University of California, San Francisco	Drafting/revision of the article for content, including medical writing for content; study concept or design
Rachel A. Whitmer, PhD	Department of Public Health Sciences, University of California, Davis	Drafting/revision of the article for content, including medical writing for content; study concept or design
Neil Risch, PhD	Department of Epidemiology and Biostatistics; Institute for Human Genetics, University of California, San Francisco	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Ronald M. Krauss, MD	Departments of Pediatrics and Medicine, University of California, San Francisco	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Catherine A. Schaefer, PhD	Kaiser Permanente Division of Research, Oakland, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
M. Maria Glymour, ScD, MS	Department of Epidemiology and Biostatistics, University of California, San Francisco	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data

References

1. Kuklina EV, Carroll MD, Shaw KM, Hirsch R. Trends in high LDL cholesterol, cholesterol-lowering medication use, and dietary saturated-fat intake: United States, 1976-2010. *NCHS Data Brief*. 2013(117):1-8.
2. Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70-100 years: a contemporary primary prevention cohort. *Lancet*. 2020;396(10263):1644-1652. doi:10.1016/S0140-6736(20)32233-9
3. Prospective Studies Collaboration, Lewington S, Whitlock G, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370(9602):1829-1839. doi:10.1016/S0140-6736(07)61778-4
4. The Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302(18):1993-2000. doi:10.1001/jama.2009.1619
5. Peters R, Xu Y, Antikainen R, et al. Evaluation of high cholesterol and risk of dementia and cognitive decline in older adults using individual patient meta-analysis. *Dement Geriatr Cogn Disord*. 2021;50(4):318-325. doi:10.1159/000519452
6. Iwagami M, Qizilbash N, Gregson J, et al. Blood cholesterol and risk of dementia in more than 1·8 million people over two decades: a retrospective cohort study. *Lancet Healthy Longev*. 2021;2(8):e498–e506. doi:10.1016/S2666-7568(21)00150-1
7. Contois JH, Warnick GR, Sniderman AD. Reliability of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B measurement. *J Clin Lipidol*. 2011;5(4):264-272. doi:10.1016/j.jacl.2011.05.004
8. Glasziou PP, Irwig L, Heritier S, Simes RJ, Tonkin A. Monitoring cholesterol levels: measurement error or true change? *Ann Intern Med*. 2008;148(9):656-661. doi:10.7326/0003-4819-148-9-200805060-00005
9. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dement Geriatr Cogn Disord*. 2009;28(1):75-80. doi:10.1159/000231980
10. Svensson T, Sawada N, Mimura M, Nozaki S, Shikimoto R, Tsugane S. The association between midlife serum high-density lipoprotein and mild cognitive impairment and dementia after 19 years of follow-up. *Transl Psychiatry*. 2019;9(1):1-9. doi:10.1038/s41398-018-0336-y
11. Schilling S, Tzourio C, Soumaré A, et al. Differential associations of plasma lipids with incident dementia and dementia subtypes in the 3C Study: a longitudinal, population-based prospective cohort study. *PLoS Med*. 2017;14(3):e1002265. doi:10.1371/journal.pmed.1002265
12. He XY, Kuo K, Yang L, et al. Serum clinical laboratory tests and risk of incident dementia: a prospective cohort study of 407,190 individuals. *Transl Psychiatry*. 2022;12(1):1-8. doi:10.1038/s41398-022-02082-x
13. Martin SS, Khokhar AA, May HT, et al. HDL cholesterol subclasses, myocardial infarction, and mortality in secondary prevention: the lipoprotein investigators collaborative. *Eur Heart J*. 2015;36(1):22-30. doi:10.1093/eurheartj/ehu264
14. Zhong GC, Huang SQ, Peng Y, et al. HDL-C is associated with mortality from all causes, cardiovascular disease and cancer in a J-shaped dose-response fashion: a pooled analysis of 37 prospective cohort studies. *Eur J Prev Cardiol*. 2020;27(11):1187-1203. doi:10.1177/2047487320914756

15. Imano H, Noda H, Kitamura A, et al. Low-density lipoprotein cholesterol and risk of coronary heart disease among Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Prev Med.* 2011;52(5):381-386. doi:10.1016/j.ypmed.2011.02.019
16. Ancelin ML, Ripoche E, Dupuy AM, et al. Sex differences in the associations between lipid levels and incident dementia. *J Alzheimers Dis.* 2013;34(2):519-528. doi:10.3233/JAD-121228
17. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to alzheimer disease and vascular dementia. *Arch Neurol.* 2004;61(5):705-714. doi:10.1001/archneur.61.5.705
18. Zingel R, Bohlken J, Riedel-Heller S, Barth S, Kostev K. Association between low-density lipoprotein cholesterol levels, statin use, and dementia in patients followed in German general practices. *J Alzheimers Dis.* 2021;79(1):37-46. doi:10.3233/JAD-201176
19. Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. *J Alzheimers Dis.* 2017;56(1):215-228. doi:10.3233/JAD-160826
20. Mielke MM, Bandaru VVR, Haughey NJ, et al. Serum ceramides increase the risk of alzheimer disease: the Women's Health and Aging Study II. *Neurology*. 2012;79(7):633-641. doi:10.1212/WNL.0b013e318264e380
21. Gordon NP. Similarity of the Kaiser Permanente senior member population in northern California to the non-Kaiser Permanente covered and general population of seniors in northern California: Statistics from the 2009 California Health Interview Survey. *Oakl CA Kais Perm North Calif Div Res.* 2012.
22. Enger SM, Van Den Eeden SK, Sternfeld B, et al. California Men's Health Study (CMHS): a multiethnic cohort in a managed care setting. *BMC Public Health* 2006;6:172. doi:10.1186/1471-2458-6-172
23. Schaefer C. C-A3-04: the Kaiser Permanente Research Program on Genes, Environment and Health: a resource for genetic epidemiology in adult health and aging. *Clin Med Res.* 2011;9(3-4):177-178. doi:10.3121/cmr.2011.1020.c-a3-04
24. Hoffmann TJ, Theusch E, Haldar T, et al. A large electronic-health-record-based genome-wide study of serum lipids. *Nat Genet.* 2018;50(3):401-413. doi:10.1038/s41588-018-0064-5
25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18(6):499-502.
26. *Drinking Levels Defined*. National Institute on Alcohol Abuse and Alcoholism (NIAAA). Accessed October 7, 2022. niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking.
27. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64(2):277-281. doi:10.1212/01.WNL.0000149519.47454.F2
28. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143. doi:10.1161/CIR.0000000000000625
29. Fernandez ML, Webb D. The LDL to HDL Cholesterol ratio as a valuable tool to evaluate coronary heart disease risk. *J Am Coll Nutr.* 2008;27(1):1-5. doi:10.1080/07315724.2008.10719668
30. Enomoto M, Adachi H, Hirai Y, et al. LDL-C/HDL-C ratio predicts carotid intima-media thickness progression better than HDL-C or LDL-C alone. *J Lipids*. 2011;2011:549137. doi:10.1155/2011/549137
31. Gosse MA. How accurate is self-reported BMI? *Nutr Bull.* 2014;39(1):105-114. doi:10.1111/nbu.12075
32. Rhee TG, Kumar M, Ross JS, Coll PP. Age-related trajectories of cardiovascular risk and use of aspirin and statin among U.S. adults aged 50 or older, 2011-2018. *J Am Geriatr Soc.* 2021;69(5):1272-1282. doi:10.1111/jgs.17038
33. Shahar E, Chambless LE, Rosamond WD, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2003;34(3):623-631. doi:10.1161/01.STR.0000057812.51734.FF
34. Oliver MF. Cholesterol and strokes. *BMJ*. 2000;320(7233):459-460.
35. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol.* 2009;8(5):453-463. doi:10.1016/S1474-4422(09)70058-4
36. Reitz C. Dyslipidemia and dementia: current epidemiology, genetic evidence, and mechanisms behind the associations. *J Alzheimers Dis.* 2012;30(s2):S127-S145. doi:10.3233/JAD-2011-110599
37. Koch M, Jensen MK. HDL-cholesterol and apolipoproteins in relation to dementia. *Curr Opin Lipidol.* 2016;27(1):76-87. doi:10.1097/MOL.0000000000000257
38. Malik R, Georgakis MK, Neitzel J, et al. Midlife vascular risk factors and risk of incident dementia: longitudinal cohort and mendelian randomization analyses in the UK Biobank. *Alzheimers Dement.* 2021;17(9):1422-1431. doi:10.1002/alz.12320
39. European Alzheimer's & Dementia Biobank Mendelian Randomization (EADB-MR) Collaboration. Genetic associations between modifiable risk factors and Alzheimer disease. *JAMA Netw Open.* 2023;6(5):e2313734. doi:10.1001/jamanetworkopen.2023.13734
40. Martinez LO, Ingueneau C, Genoux A. Is it time to reconcile HDL with cardiovascular diseases and beyond? An update on a paradigm shift. *Curr Opin Lipidol.* 2020;31(5):302-304. doi:10.1097/MOL.0000000000000705
41. Beeri MS, Tirosh A, Lin HM, et al. Stability in BMI over time is associated with a better cognitive trajectory in older adults. *Alzheimers Dement.* 2022;18(11):2131-2139. doi:10.1002/alz.12525
42. Lee ATC, Fung AWT, Richards M, et al. Late-life longitudinal blood pressure trajectories as predictor of dementia. *Sci Rep.* 2022;12(1):1630. doi:10.1038/s41598-022-05680-3
43. Stewart R, Xue QL, Masaki K, et al. Change in blood pressure and incident dementia. *Hypertension.* 2009;54(2):233-240. doi:10.1161/HYPERTENSIONAHA.109.128744
44. Wagner M, Helmer C, Tzourio C, Berr C, Proust-Lima C, Samieri C. Evaluation of the concurrent trajectories of cardiometabolic risk factors in the 14 years before dementia. *JAMA Psychiatry*. 2018;75(10):1033-1042. doi:10.1001/jamapsychiatry.2018.2004
45. Bruce DG, Davis WA, Davis TME. Low serum HDL-cholesterol concentrations in mid-life predict late-life cognitive impairment in type 2 diabetes: the Fremantle diabetes study. *J Diabetes Complications*. 2017;31(6):945-947. doi:10.1016/j.jdiacomp.2016.12.009
46. Moroney JT, Tang MX, Berglund L, et al. Low-density lipoprotein cholesterol and the risk of dementia with stroke. *JAMA*. 1999;282(3):254-260. doi:10.1001/jama.282.3.254
47. George KM, Gilsanz P, Peterson RL, et al. Impact of cardiovascular risk factors in adolescence, young adulthood, and midlife on late-life cognition: study of healthy aging in African Americans. *J Gerontol Ser A*. 2021;76(9):1692-1698. doi:10.1093/gerona/glab143
48. Millán J, Pintó X, Muñoz A, et al. Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag.* 2009;5:757-765.