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RESEARCH ARTICLE

Independent associations of high-density lipoprotein cholesterol and triglyceride levels with Alzheimer's disease and related dementias

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Abstract

INTRODUCTION: We evaluated the independent associations between high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels with Alzheimer's disease and related dementias (ADRD).

METHODS: Among 177,680 members of Kaiser Permanente Northern California who completed a survey on health risks, we residualized TGs and HDL-C conditional on age, sex, and body mass index. We included these residuals individually and concurrently in Cox models predicting ADRD incidence.

RESULTS: Low (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.02–1.10) and high quintiles (HR 1.07, 95% CI 1.03–1.12) of HDL-C residuals were associated with an increased risk of ADRD compared to the middle quintile. Additional adjustment for TGs attenuated the association with high HDL-C (HR 1.03, 95% CI 0.99–1.08). Low TG residuals were associated with an increased ADRD risk (HR 1.10, 95% CI 1.06–1.15); high TG residuals were protective (HR 0.92, 95% CI 0.88–0.96). These estimates were unaffected by HDL-C adjustment.

DISCUSSION: Low HDL-C and TG levels are independently associated with increased ADRD risk. The correlation with low TG level explains the association of high HDL-C with ADRD.

KEYWORDS
Alzheimer's disease, cardiovascular risk factors, dementia, high-density lipoprotein cholesterol, lipids, modifiable risk factors, triglycerides, vascular risk factors

Highlights

- Strong correlations between lipid levels are important considerations when investigating lipids as late-life risk factors for Alzheimer's disease and related dementias (ADRD).
- Low levels of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) were independently associated with an increased risk of ADRD.
- We found no evidence for an association between high HDL-C and increased ADRD risk after adjustment for TGs.
- High levels of TGs were consistently associated with a decreased risk of ADRD.
- There may be interaction between TG and HDL-C levels, where both low HDL-C and TG levels increase the risk of ADRD compared to average levels of both.

1 | BACKGROUND

The evidence for lipids and lipoproteins as risk factors for Alzheimer's disease and related dementias (ADRD) is inconclusive, especially in late life.[1] As lipid levels are well-known risk factors for cardiovascular outcomes,[2–4] there is a plausible biological mechanism for how they could also increase dementia risk. In addition, dyslipidemia is common in the United States, with an estimated 53% of adults having abnormal lipid levels.[5] Therefore, lipids and lipoproteins may be important and common modifiable risk factors for dementia if their causal relationships with dementia can be established.

Recent work has suggested that high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) are associated with dementia risk. Prior evidence has found that high levels of HDL-C are associated with increased dementia risk,[6–8] with some evidence that low levels of HDL-C are also associated with increased dementia risk.[9,10] Recent studies have found that high levels of TGs are associated with decreased risk of dementia,[9,11,12] although prior work has also found harmful or null associations.[3,13–15]

HDL-C and TG levels are strongly inversely correlated,[11,16] due in part to shared metabolic factors and pleiotropic genetic variants.[17,18] Thus, studies not accounting for this relationship have not captured the independent associations of these lipids with dementia risk. The small body of work investigating mutually adjusted associations has been limited by sample size and inadequate covariate adjustment. One prior study reporting a U-shaped relationship between HDL-C level and dementia incidence was unable to adjust potentially important confounders including education and cardiovascular disease.[9] Another study investigating TG level and dementia did not report estimates for HDL-C levels.[11] Identifying the independent associations of HDL-C and TG levels with dementia risk is important because clinical treatment recommendations differ based on lipid type and level (low vs high).[19–21]

To rigorously evaluate the independent associations of HDL-C and TG levels with dementia incidence and extend our recently published work on late-life HDL-C level and dementia risk,[10] we analyzed data from a large and diverse survey cohort of older Kaiser Permanente Northern California (KPNC) members with repeated lipid measurements and longitudinal follow-up in electronic health records (EHRs) with up to 17 years of follow-up. Comprehensive laboratory measurements and detailed demographic and health behavior data allowed us to improve on the limitations of prior work and distinguish between the associations of TG and HDL-C levels with ADRD in late life.

2 | METHODS

2.1 | Study sample

We used data from two survey cohorts of KPNC members. KPNC is an integrated health care system that provides comprehensive care for its members, serving over 4.6 million members in Northern California. Older adults (≥65 years of age) in the KPNC system are similar to the greater population of older adults in California, except that the most advantaged and disadvantaged socioeconomic groups are underrepresented. With respect to other important characteristics, such as history of chronic diseases (cardiovascular disease, diabetes, hypertension) and lifestyle factors (smoking and body mass index [BMI]), the KPNC members are similar to other older adults in Northern California.[22]

This analysis uses data from the Kaiser Research Program on Genes, Environment, and Health (RPGEH) cohort and the California Men's Health Study (CMHS) cohort. RPGEH participants (male and female; age of 18 years or older) completed a demographics and health behavior survey in 2007.[23] CMHS included men between the ages of 45 and 69 in 2000, who completed a similar survey in 2002–2003.[24] For both survey cohorts, we linked KPNC EHR data including full

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed. Prior work has found U-shaped relationships between high-density lipoprotein cholesterol (HDL-C) and dementia. In addition, high triglyceride (TG) level may be associated with a decreased risk of dementia. Only two prior studies—which were limited by small sample size and poor covariate control—have considered the strong inverse correlations between lipids in their analyses.
2. **Interpretation**: Our findings have indicated that *low* levels of HDL-C and TGs were each independently associated with dementia risk. However, the previously reported association between *high* HDL-C level and dementia can be explained by the correlation of HDL-C with low TG level.
3. **Future directions**: Our article adds to a growing body of literature suggesting that there are important, independent relationships between low HDL-C level, low TG level, and dementia risk. Future studies should identify the appropriate clinical interventions based on these specific risk factors.

medical, laboratory, and pharmacy data, from 1996 through the end of the study period (i.e., December 2020). RPGEH participants made up 88.3% of the final sample.

2.2 | Inclusion and exclusion criteria

Of 265,224 participants, we excluded participants (Figure S1) who were under age 55 years at survey completion ($n = 5915$, 2.2%). This age restriction allowed for the surviving participants to be at least 68 years of age by the end of the study period by design, as dementia incidence is low prior to this age. In addition, we excluded individuals without at least one valid lipid panel (HDL-C and TG) within 2 years following survey completion ($n = 59{,}235$, 22.3%).

To minimize immortal time bias and define a consistent baseline across differing timelines of lipid measurement, we started follow-up for dementia 2 years after survey completion (Figure S2). We excluded 3849 individuals (1.5%) who had a diagnosis of dementia, Parkinson's disease, or amyotrophic lateral sclerosis and 14,159 participants (5.3%) who were lost to follow-up prior to this baseline.

We also excluded individuals missing covariate information for sex (11, 0.006%), BMI (1920, 0.7%), or systolic blood pressure (2455, 0.9%). As missing information on the survey was likely to be informative, especially for missing education (7.9%) and income (13.2%), we retained non-responders by adding a "missing" indicator for all survey covariates (discussed further below) except BMI (excluded, as aforementioned). Our final analytic sample included 177,680 participants.

2.3 | Measurement of lipids

We took the average of all serum, fasted measurements of HDL-C, TGs, and low-density lipoprotein cholesterol (LDL-C)[25] available in the EHRs in the 2 years following survey completion. We excluded 3656 individual measurements (0.4%) in this 2-year period for having values outside of plausible ranges for HDL-C (10–200 mg/dL; $n = 115$) or severe TG elevation (>500 mg/dL; $n = 3541$). Distributions of average HDL-C and TG levels were both right-skewed (Figures S3A and S4A). All analyses account for this non-normality by transforming HDL-C with a square root (Figure S3B) and TGs with a natural logarithm (Figure S4B).

2.4 | Measurement of ADRD

Incident ADRD was defined by the ninth and tenth revisions of the International Classification of Diseases (ICD-9 and ICD-10) diagnoses of Alzheimer's disease, vascular dementia, and nonspecific dementia (Table S1). We included diagnoses made during any type of clinical encounter (e.g., outpatient, inpatient, telehealth, and ambulatory care) except laboratory and radiology visits. Other types of dementia, such as Huntington's dementia or frontotemporal dementia, were included as censoring events.

2.5 | Measurement of BMI

We conceptualized baseline BMI (kg weight/m^2 height) as an important confounder, since it is known to be correlated with levels of HDL-C[26,27] and TG[28] and dementia.[1,29] BMI was calculated from self-reported weight and height on the survey. For the 8677 individuals (4.9%) with missing survey BMI, we calculated BMI from their most recent height and weight in the EHR prior to their survey data. BMI from the survey was our primary measure, as it was the measurement made closest to baseline. As we expected the relationship between BMI and dementia to be non-linear, we operationalized BMI as a categorical variable in our final models for dementia association (underweight, <18.5; average, 18.5–24.9; overweight, 25–29.9[25–30]; and obese, ≥30). Among 130,592 individuals who had both measures of BMI, 83.5% had perfect agreement (Cohen's kappa = 0.75, Table S2).

2.6 | Other covariates

We obtained demographics (age, sex, racial/ethnic identity), education level, income, U.S. nativity, marital status, current smoking status, alcohol use, and a measure of general health from the survey. We obtained history of comorbidities (cardiovascular disease, stroke,

hypertension, diabetes, major depression, and head injury), systolic blood pressure, history of statin use, number of HDL-C measurements, and number of TG measurements from the EHRs.

We adjusted for three groups of covariates, aiming to separate known confounders that temporally precede lipid levels, probable confounders that precede lipid levels, and potential mediators of the association between lipids and ADRD. Specifically, we compared estimates across the following adjustment sets: (1) demographics and known confounders (age at survey, sex [male, female], racial/ethnic identity [Asian, Black, Hispanic, White, other or unknown], education [less than high school, high school completion, more than high school, or missing], income [ordinal and reported in five categories, or missing], U.S. nativity, marital status [never married, married, separated, widowed, or missing], categorical BMI [as defined above], and an indicator of whether BMI was obtained from survey or EHR); (2) Model 1 covariates plus probable confounders (binary indicator for history of diabetes, hypertension, major depression, or head injury in her; systolic blood pressure [continuous; mean of systolic blood pressure (SBP) measurements in the 2 years after survey completion], alcohol use at time of survey based on the National Institute on Alcohol Abuse and Alcoholism [NIAAA] guidelines[30] [none, light to moderate, heavy, or missing], current smoking status [yes, no, or missing], number of HDL-C measurements in the 2 years after baseline [continuous; if HDL-C is in the model], and number of TG measurements [continuous; if TG is in the model]); and (3) Model 2 covariates plus variables that are potential mediators (binary indicators for EHR history of cardiovascular disease [myocardial infarction, ischemic heart disease, or revascularization procedures], stroke [either ischemic or hemorrhagic, pooled], any history of statin use, and general health measure self-reported on a 5-point scale [poor, fair, good, very good, excellent]).

2.7 | Calculation of residuals of lipids

Specifying lipids as quantiles in the primary outcome models may leave residual confounding by factors strongly associated with the continuous lipid measures. To account for such residual confounding, we residualized continuous lipid values against our strongest confounders as a first step and used residualized lipids in our primary models to predict onset of ADRD. We calculated residuals of HDL-C and TGs using linear regressions conditional on age at survey, sex, and restricted cubic splines of continuous BMI with knots at the 25th, 50th, and 75th percentiles. Residuals were calculated as the difference between the observed value of the lipid and the predicted value from this model. The residuals can be interpreted as deviations from average lipid levels given age, sex, and BMI.

2.8 | Statistical analysis

In our primary analysis, we estimated Cox proportional hazards models of time to incident dementia diagnosis associated with quintiles of residuals of HDL-C and TGs, to allow for relationships between lipids and dementia to be non-linear. Participants were censored at death, diagnosis of dementias other than ADRD, end of KPNC membership, or end of study period. Estimation of individual associations of HDL-C and TG residuals with incident dementia was based on models including both variables simultaneously. We additionally checked for evidence of interaction between quintiles of residuals of HDL-C and TGs.

To better visualize the differences in estimates for TGs and HDL-C across different sets of covariate adjustments, we plotted predicted hazard ratio (HR) by residual of HDL-C and TGs separately using restricted cubic splines for HDL-C and TGs, respectively, with knots at the 25th, 50th, and 75th percentiles. Prior work suggests that the relationship between lipids and ADRD differs between mid-life and late life.[10,31,32] As there may be heterogeneous effects by age, we checked for effect measure modification between each lipid (linear and using splines) with a binary measurement of age (years, above/below 65). Binary age was only used for this interaction analysis.

We included three secondary analyses. First, we used Cox proportional hazards models for incident dementia from raw values of quintiles of HDL-C and TGs individually and concurrently. Second, we repeated the primary analysis with adjustment for average linear LDL-C. Third, we repeated the primary analysis in a subset of healthy individuals without cardiovascular disease, stroke, or statin use at baseline (n = 80,109). All analyses were conducted using R (version 4.1.3).[33]

3 | RESULTS

Our final analytic sample included 177,680 KPNC members (mean [SD] age at survey, 69.4 years [8.41], 55.0% female, 77.2% White) (Table 1). Over an average of 8.80 years (4.11) years of follow-up, 24,105 incident cases of ADRD occurred.

In the 2 years after survey completion, HDL-C level was measured (n = 452,498) an average of 2.55 times [1.57] per individual, and TG level was measured (n = 441,527) an average of 2.43 times (1.62). HDL-C and TG levels were negatively correlated in this data set (Figure S5), with a Pearson's correlation coefficient of −0.44 without transformations, −0.48 when transformed, and −0.47 when in transformed residuals form.

3.1 | BMI and lipids

BMI was associated with both transformed HDL-C (correlation coefficient = −0.31) and transformed TG (correlation coefficient = 0.25) prior to residualizing, although scatterplots of HDL-C (Figure S6) and TGs (Figure S7) suggest that these relationships are non-linear.

3.2 | Calculation of residuals

Residuals given age, sex, and BMI are presented in Figure S8 (HDL-C) and Figure S9 (TG). Residuals of HDL-C (HDL.r) and TG (TG.r) values were approximately normally distributed (Figure S10) and

TABLE 1 Baseline characteristics of the analytic cohort: Two survey cohorts from KPNC.

Characteristic	Younger than 65 years (*N* = 63,744)	65 years of age or older (*N* = 113,936)	Total analytic cohort (*N* = 177,680)
Age at survey, years, mean (SD)	60.8 (2.50)	74.3 (6.42)	69.4 (8.41)
Female, *n* (%)	33,821 (53.1)	63,827 (56.0)	97,648 (55.0)
Race/ethnicity, *n* (%)			
Asian	7464 (11.7)	10,527 (9.2)	17,991 (10.1)
Black	3137 (4.9)	4722 (4.1)	7859 (4.4)
Hispanic	5112 (8.0)	8523 (7.5)	13,635 (7.7)
Other	358 (0.6)	595 (0.5)	953 (0.5)
White	47,639 (74.7)	89,532 (78.6)	13,7171 (77.2)
Unknown	34 (0.1)	37 (0.0)	71 (0.0)
Income, *n* (%)			
$100k+	20,248 (31.8)	12,803 (11.2)	33,051 (18.6)
$60k–$99k	18,907 (29.7)	22,246 (19.5)	41,153 (23.2)
$40k–$59k	10,233 (16.1)	21,538 (18.9)	31,771 (17.9)
$20k–$39k	6521 (10.2)	24,469 (21.5)	30,990 (17.4)
<$20k	2540 (4.0)	14,673 (12.9)	17,213 (9.7)
Missing	5295 (8.3)	18,207 (16.0)	23,502 (13.2)
Education, *n* (%)			
Greater than HS diploma	32,027 (50.2)	41,125 (36.1)	73,152 (41.2)
High school diploma	25,272 (39.6)	51,431 (45.1)	76,703 (43.2)
Less than HS diploma	2341 (3.7)	10,386 (9.1)	12,727 (7.2)
Other	360 (0.6)	745 (0.7)	1105 (0.6)
Missing	3744 (5.9)	10,249 (9.0)	13,993 (7.9)
BMI, *n* (%)			
Underweight (<18.5)	537 (0.8)	1690 (1.5)	2227 (1.3)
Healthy (18.5–24.9)	19,749 (31.0)	41,258 (36.2)	61,007 (34.3)
Overweight (25–29.9)	24,229 (38.0)	44,743 (39.3)	68,972 (38.8)
Obese (≥30)	19,229 (30.2)	26,245 (23.0)	45,474 (25.6)
Smoking history, *n* (%)			
Never	32,137 (50.4)	52,286 (45.9)	84,423 (47.5)
Current or former	28,640 (44.9)	52,337 (45.9)	80,977 (45.6)
Missing	2967 (4.7)	9313 (8.2)	12,280 (6.9)
Marital status, *n* (%)			
Never married	3358 (5.3)	3710 (3.3)	7068 (4.0)
Married	47,042 (73.8)	70,839 (62.2)	11,7881 (66.3)
Separated	9365 (14.7)	13,257 (11.6)	22,622 (12.7)
Widowed	2608 (4.1)	22,938 (20.1)	25,546 (14.4)
Missing	1371 (2.2)	3192 (2.8)	4563 (2.6)
Alcohol class, *n* (%)			
None	21,027 (33.0)	33,617 (29.5)	54,644 (30.8)
Light to moderate	23,175 (36.4)	37,654 (33.0)	60,829 (34.2)
Heavy	10,356 (16.2)	13,504 (11.9)	23,860 (13.4)
Missing	9186 (14.4)	29,161 (25.6)	38,347 (21.6)

(Continues)

TABLE 1 (Continued)

Characteristic	Younger than 65 years (*N* = 63,744)	65 years of age or older (*N* = 113,936)	Total analytic cohort (*N* = 177,680)
U.S. nativity, *n* (%)			
Yes	50,577 (79.3)	88,929 (78.1)	139,506 (78.5)
No	10,919 (17.1)	19,470 (17.1)	30,389 (17.1)
Missing	2248 (3.5)	5537 (4.9)	7785 (4.4)
General health, *n* (%)			
Excellent	8151 (12.8)	8591 (7.5)	16,742 (9.4)
Very good	19,784 (31.0)	28,532 (25.0)	48,316 (27.2)
Good	22,779 (35.7)	48,899 (42.9)	71,678 (40.3)
Fair	7439 (11.7)	20,087 (17.6)	27,526 (15.5)
Poor	1186 (1.9)	2801 (2.5)	3987 (2.2)
Missing	4405 (6.9)	5026 (4.4)	9431 (5.3)
Cardiovascular disease	5309 (8.3)	23,634 (20.7)	28,943 (16.3)
Diabetes	10,185 (16.0)	22,984 (20.2)	33,169 (18.7)
Hypertension	32,627 (51.2)	84,701 (74.3)	117,328 (66.0)
Stroke	571 (0.9)	3586 (3.1)	4157 (2.3)
Head injury	411 (0.6)	1146 (1.0)	1557 (0.9)
Major depression	12,795 (20.1)	18,392 (16.1)	31,187 (17.6)
Statin use	26,407 (41.4)	68,289 (59.9)	94,696 (53.3)
Average systolic blood pressure	128 (11.7)	131 (11.4)	130 (11.6)
Lipid measures[a]			
HDL-C level, mg/dL, mean (SD)	53.6 (15.0)	53.7 (14.9)	53.6 (14.9)
No. of HDL-C measurements, mean (SD)	2.31 (1.57)	2.59 (1.56)	2.49 (1.57)
TG level, mg/dL, mean (SD)	141 (71.0)	137 (64.4)	138 (66.9)
No. of TG measurements, mean (SD)	2.26 (1.65)	2.52 (1.59)	2.43 (1.62)

Abbreviation: ADRD, Alzheimer's disease and related dementias; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; KPNC, Kaiser Permanente Northern California; SD, standard deviation.
[a]Lipids were measured in the 2 years after survey completion, before follow-up began.

homoscedastic across BMI, age, and sex. When interpreting these residuals, negative residuals indicate a lower level of lipid than what is expected from an individual's BMI, sex, and age, whereas positive residuals indicate higher than expected levels of lipid.

3.3 | HDL-C and dementia

The relationship between HDL.r and hazard of dementia was nonlinear, with and without adjustment for TG.r, although the magnitude of the association for high HDL-C was notably attenuated with adjustment for TG (Figure 1).

Without adjustment for TG, individuals with HDL.r in the lowest quintile experienced a 6% elevation in hazard of dementia (HR 1.06, 95% confidence interval [CI] 1.02–1.10) compared to individuals with HDL.r in the middle quintile in models with full covariate adjustment (Model 3), whereas the highest quintile of HDL.r was associated with a 7% elevation in risk (HR 1.07, 95% CI 1.03–1.12) compared to the middle quintile (Table 2). This U-shaped relationship was altered by adjustment for TG.r, such that the association for low HDL-C level was strengthened (adjusted HR for lowest HDL.r vs middle quintile: = 1.12, 95% CI 1.08–1.17) but the association for high HDL.r was attenuated and no longer statistically significant (HR 1.03, 95% CI 0.99–1.08). The association between HDL.r in the highest quintile and dementia was similar in models only accounting for probable confounders (Model 2: HR 1.02, 95% CI 0.97–1.06).

In secondary analyses, results were consistent when using unresidualized HDL-C (Appendix 1, Table S3). Results were unchanged when additionally adjusting for LDL-C (Table S4). Among individuals without cardiovascular disease, stroke, or statin use, the lowest quintile of HDL.r was associated with a 9% increase in ADRD hazard (95% CI 1.01–1.17) and the highest quintile was not associated with ADRD (Table S5).

In the most-adjusted model adjusting for both HDL.r and TG.r, there was no statistically significant evidence of multiplicative interaction by binary age (global *p*-value for interaction = 0.413). In individuals 55–65 years of age, at survey completion, the highest quintile of HDL.r was associated with a 13% increase in ADRD hazard (95% CI 0.97–1.31;

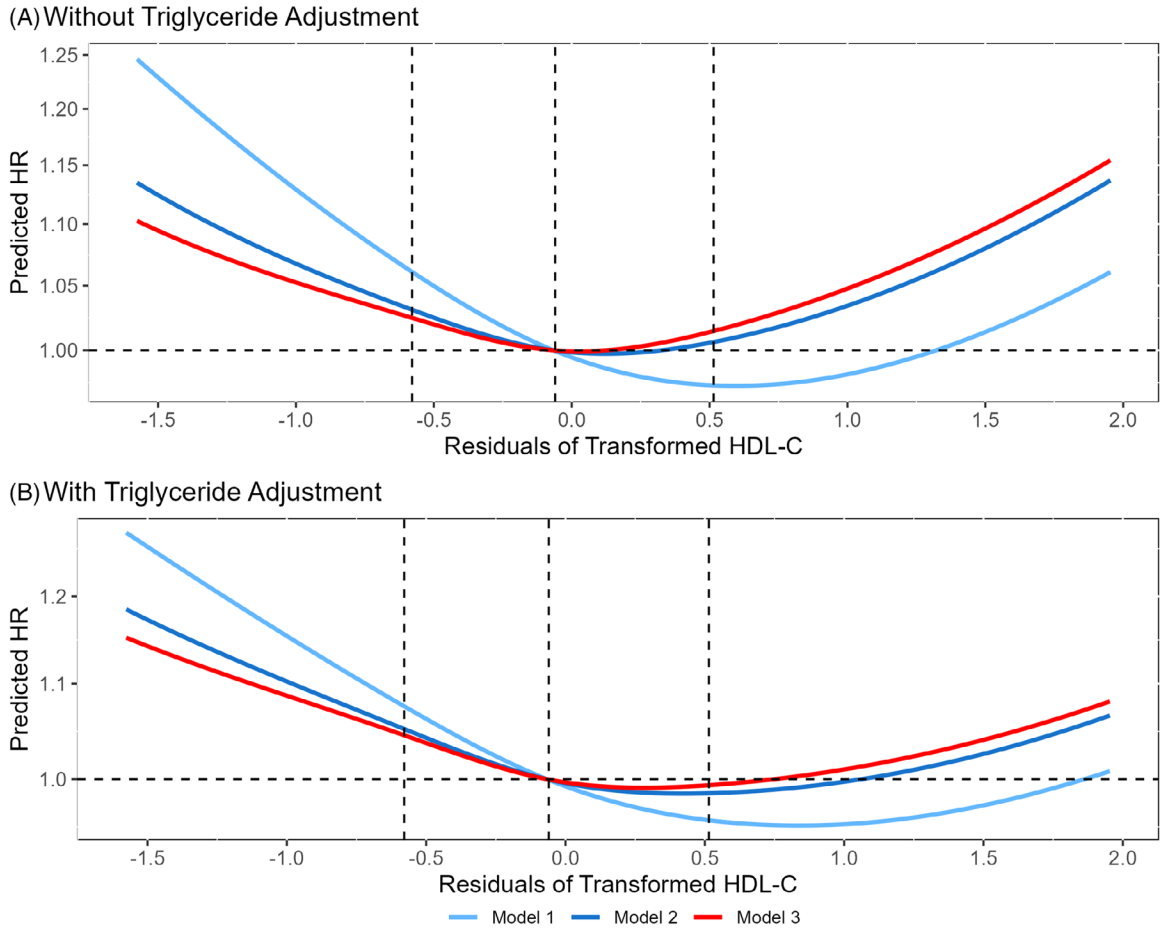

FIGURE 1 Hazard ratios for ADRD with b-splines for HDL-C residuals. Knots at the 25th, 50th, and 75th percentiles of residuals of square root–transformed HDL-C, without (A) and with (B) adjustment for residuals of TGs. ADRD, Alzheimer's disease and related dementias; HDL-C, high-density lipoprotein cholesterol; TGs, triglycerides.

TABLE 2 Hazard ratios for ADRD by quintile of HDL-C residuals, without and with adjustment for quintiles of TG residuals.[a]

	Quintile of HDL-C residuals, HR (95% CI)				
Model[b]	Q1 lowest	Q2	Q3	Q4	Q5 highest
HDL-C residuals, without adjustment for quintiles of TG residuals					
Model 1	1.15 (1.10–1.19)	1.03 (0.99–1.07)	ref	0.97 (0.93–1.00)	1.00 (0.96–1.04)
Model 2	1.08 (1.04–1.13)	1.01 (0.97–1.05)	ref	1.00 (0.96–1.04)	1.06 (1.02–1.10)
Model 3	1.06 (1.02–1.10)	1.06 (1.02–1.10)	ref	1.00 (0.96–1.04)	1.07 (1.03–1.12)
HDL-C residuals, with adjustment for quintiles of TG residuals					
Model 1	1.18 (1.13–1.23)	1.04 (1.00–1.09)	ref	0.96 (0.92–1.00)	0.98 (0.94–1.02)
Model 2	1.14 (1.09–1.19)	1.02 (0.98–1.07)	ref	0.98 (0.94–1.02)	1.02 (0.98–1.06)
Model 3	1.12 (1.08–1.17)	1.02 (0.98–1.06)	ref	0.99 (0.95–1.03)	1.03 (0.99–1.08)

Abbreviations: ADRD, Alzheimer's disease and related dementias; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

[a]HDL-C was transformed by square root and TG was transformed by natural logarithm.

[b]Covariate sets include: (1) basic demographics and known confounders (age at survey, sex, race/ethnicity, education, income, U.S. nativity, marital status, categorical BMI, and an indicator for source of BMI); (2) Model 1 covariates plus probable confounders (history of diabetes, hypertension, major depression, head injury; systolic blood pressure, number of lipid measurements, alcohol use, current smoking status); (3) Model 2 covariates plus confounders we identified as also being potential mediators (history of diagnosed cardiovascular disease or stroke; any history of statin use; and general health measure).

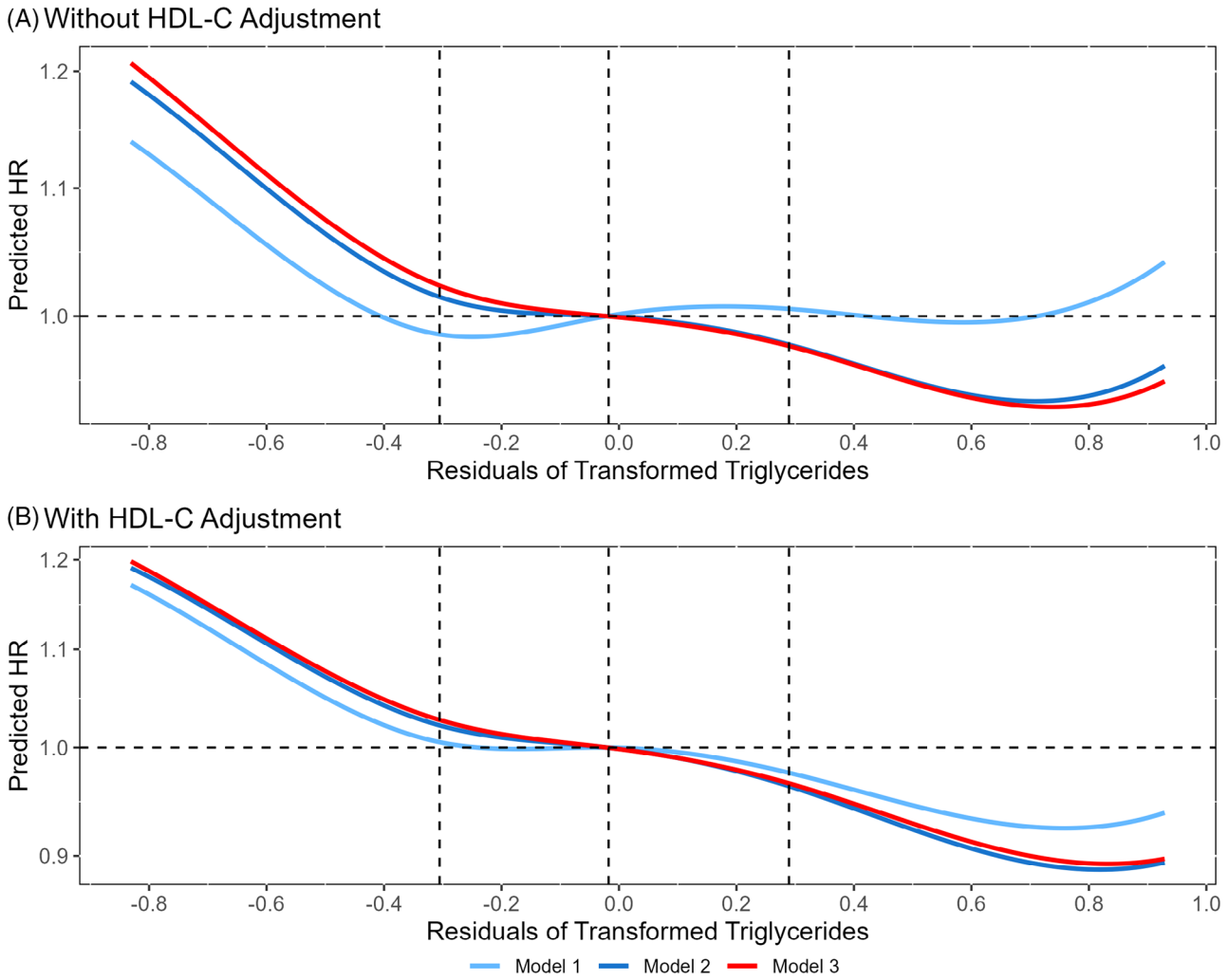

FIGURE 2 Hazard ratios for ADRD with b-splines for TG residuals. Knots at the 25th, 50th, and 75th percentiles of residuals of log-transformed TGs, without (A) and with (B) adjustment for residuals of HDL-C. ADRD, Alzheimer's disease and related dementias; HDL-C, high-density lipoprotein cholesterol; TGs, triglycerides.

Table S6). The CI for this estimate lacked precision and ranged from null to a clinically relevant harmful elevation in dementia risk.

3.4 | TG and dementia

The association between TG.r and dementia was linear (Figure 2), with lower TG.r residuals corresponding to higher dementia risk. Adjustment for HDL.r slightly attenuated the association between the lower TG.r and dementia, but it strengthened the protective association between higher TG.r and dementia hazard. In the most adjusted model (Model 3), the highest quintile of TG.r was associated with a 6% decrease in dementia hazard without adjustment for HDL.r (HR 0.94, 95% CI 0.91–0.98) compared to the middle quintile, and an 8% decrease (HR 0.92, 95% CI 0.88–0.96) when adjusting for HDL.r (Table 3). The associations remained significant in the model accounting only for likely confounders and adjusting for HDL.r (Model 2), for both the lowest (HR 1.09, 95% CI 1.05–1.14) and highest quintiles (HR 0.92, 95% CI 0.88–0.96) of TG.r.

Results were consistent when using unresidualized TG (Appendix 2, Table S7). Results were unchanged when adjusting for LDL-C (Table S4). Among the healthier participants, high TG.r was more strongly associated with a decreased ADRD hazard (HR 0.83, 95% CI 0.77–0.89; Table S5).

There was no statistically significant interaction between TG.r and binary age in the most adjusted model accounting for HDL.r (global *p*-value for interaction = 0.187). Although the lowest quintile of TG.r was no longer associated with ADRD in individuals 55–65 years of age (HR 1.01, 95% CI 0.87–1.17; Table S6), the CI is widely consistent with a decreased, null, and harmful associations.

3.5 | Interaction between HDL-C and TGs

There was evidence for multiplicative interaction between quintiles of HDL.r and TG.r (global *p*-value = 0.013). Having both low HDL.r and TG.r residuals (i.e., both in the first quintile) was associated with 1.32 times the hazard of ADRD (95% CI 1.16–1.51)

TABLE 3 Hazard ratios for ADRD by quintile of TG residuals, with and without adjustment for quintiles of HDL-C residuals.[a]

	Quintile of TG residuals, HR (95% CI)				
Model[b]	Q1 lowest	Q2	Q3	Q4	Q5 highest
TG residuals, without adjustment for quintiles of HDL-C residuals					
Model 1	1.05 (1.01–1.09)	0.98 (0.94–1.02)	ref	1.01 (0.97–1.05)	1.00 (0.96–1.04)
Model 2	1.09 (1.05–1.14)	1.00 (0.96–1.04)	ref	0.99 (0.95–1.03)	0.95 (0.91–0.99)
Model 3	1.11 (1.06–1.15)	1.01 (0.97–1.05)	ref	0.99 (0.95–1.03)	0.94 (0.91–0.98)
TG residuals, with adjustment for quintiles of HDL-C residuals					
Model 1	1.08 (1.04–1.13)	0.99 (0.95–1.03)	ref	0.99 (0.95–1.03)	0.94 (0.90–0.98)
Model 2	1.09 (1.05–1.14)	1.00 (0.96–1.04)	ref	0.97 (0.94–1.01)	0.91 (0.88–0.95)
Model 3	1.10 (1.06–1.15)	1.01 (0.97–1.05)	ref	0.98 (0.94–1.02)	0.92 (0.88–0.96)

Abbreviations: ADRD, Alzheimer's disease and related dementias; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.
[a]HDL-C was transformed by square root and TG was transformed by natural logarithm.
[b]Covariate sets include: (1) basic demographics and known confounders (age at survey, sex, race/ethnicity, education, income, US nativity, marital status, categorical BMI, and an indicator for source of BMI); (2) Model 1 covariates plus probable confounders (history of diabetes, hypertension, major depression, head injury; systolic blood pressure, number of lipid measurements, alcohol use, current smoking status); (3) Model 2 covariates plus confounders we identified as also being potential mediators (history of diagnosed cardiovascular disease or stroke; any history of statin use; and general health measure).

compared to being in the middle quintile for HDL.r and TG.r (Table S8).

4 | DISCUSSION

We found evidence that low levels of TG and HDL-C in late life are independently associated with an increased hazard of dementia. These associations were consistent in analyses using residuals and absolute plasma lipid concentrations, and across varying adjustment sets, indicative of a robust association. Compared to moderate levels, higher levels of TG were associated with a significantly lower hazard of dementia across adjustment sets and consideration of HDL-C. However, the observed association between high levels of HDL-C and dementia incidence was attenuated after adjustment for TG. Our results suggest that the association between high HDL-C and increased dementia incidence can be explained largely by the inverse relationship between HDL-C and TG, and elevated HDL-C per se does not increase dementia risk. We were unable to determine whether there is a significant interaction between HDL-C and TGs with age, as the smaller sample of individuals 55–64 years of age ($n = 63{,}744$) reduced our power.

These results suggest that low HDL-C and low TG levels have independent associations with dementia incidence, and that there is additional hazard of dementia for individuals with both low TG and low HDL-C levels. This is consistent with other studies that have reported relationships of low levels of HDL-C[34–37] or TGs[9,11,38,39] with dementia or cognitive decline. The mechanisms for these relationships are unknown, although low HDL-C is associated with an increased risk of stroke[40–42] and cardiovascular disease.[43,44] Prior work does not support vascular mechanisms for the association of low TG level with dementia, because high TG level is associated with cardiovascular disease risk,[45–47] also assuming a linear relationship between TG level and cardiovascular disease. The TG–dementia relationship may be driven by specific species of TG, such as highly unsaturated, long-chain TGs. Low levels of highly unsaturated, long-chain TGs have been linked to early imaging and laboratory (cerebrospinal fluid [CSF]) biomarkers of AD.[39] This mechanism may also explain why high TG level was protective for dementia risk in our sample, consistent with prior findings.[9,11] Although statins can lower TG levels by a modest amount,[21,48,49] we adjusted for baseline statin use to account for any confounding. Finally, these results cannot be generalized to individuals with hypertriglyceridemia, as we excluded TG measurements greater than 500 mg/dL.

High HDL-C level was no longer associated with dementia risk after adjusting for TG level and known and probable confounders. This result is inconsistent with prior reports of an association between high HDL-C level and dementia risk, including our own prior work and a Mendelian randomization (MR) study.[7,8,10] The findings based on MR may reflect pleiotropic effects of HDL-C genetic variants on TGs.[50]

This work has some notable strengths compared to prior work. In addition to considering independent associations, we were able to leverage a large sample of KPNC members. This sample is more diverse (10.1% Asian, 4.4% Black, and 7.7% Hispanic) than other cohorts investigating a similar research question, such as UK Biobank (6% non-White)[9] and Aspirin in Reducing Events in the Elderly trial (9% non-White).[11] The greater representation in this sample allows for better generalization of our results. In addition, the survey cohort with linked EHR data allowed us to account for many demographic, social,

and clinical factors that prior studies have not considered, such as income, history of stroke, and marital status.

This study also has several limitations. The sample was not representative with respect to some social factors, although the plausibility of substantial heterogeneity in the effects of TG and HDL-C levels across these factors is unclear.[22] In addition, the study cohort is susceptible to selection bias and health care utilization bias, as it consists of volunteers who may be more likely to engage with their health care network (especially with respect to receiving laboratory tests) compared to the full patient base of KPNC. Because these EHRs do not contain data from cognitive tests, our approach using ICD-defined ADRD likely underreported cases. In addition, although we were able to account for many known, probable, and possible confounders, we are unable to eliminate the possibility of unmeasured confounding. Our work does not rule out the possibility of reverse causation, where preclinical changes in neuropathology could affect lipid levels. Future work should prioritize identifying the directionality of these relationships. Finally, the associations of dementia risk with HDL-C and TG levels observed here cannot be considered causal without further studies aimed at testing this possibility. This work should be considered alongside the other literature to triangulate a causal effect before making individual- and population-level public health recommendations.

In conclusion, we found that low levels of HDL-C and TGs in late life are each independently associated with hazard of dementia in mutually adjusted models and that high levels of HDL-C are not associated with dementia risk after adjusting for TG level. If future studies find these associations to be causal, our findings suggest that the development of clinical interventions targeting low HDL-C and TG levels warrants investigation for mitigating dementia risk.

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CONFLICT OF INTEREST STATEMENT

The authors report no relevant conflicts of interest or disclosures. Author disclosures are available in the supporting information.

CONSENT STATEMENT

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

DIVERSITY, EQUITY, AND INCLUSION STATEMENT

Equitable representation of racial and ethnic groups is a priority in our approach to Alzheimer's disease and related dementias (ADRD) research. When developing our research plan and design, we decided to prioritize using a diverse, large data source to improve the generalizability of our results. The Kaiser Permanente Northern California membership base is exceptionally diverse and allows consistent data collection processes in a multi-racial sample. The present data source includes 17,991 (10.1%) individuals who identify as Asian, 7859 (4.4%) who identify as Black, and 13,635 (7.7%) who identify as Hispanic. We have not presented results stratified by racial and ethnic identity as there is no prior literature to suggest this interaction would be present.

DATA AVAILABILITY STATEMENT

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), institutional review board (IRB) approval, and execution of a Materials and Data Transfer Agreement (MDTA).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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