RESEARCH ARTICLE

Association Between Triglycerides and Risk of Dementia in Community-Dwelling Older Adults

A Prospective Cohort Study

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Abstract

Background and Objectives

It has been suggested that higher triglyceride levels were associated with a lower risk of Alzheimer disease. This study aimed to examine the association of triglycerides with dementia and cognition change in community-dwelling older adults.

Methods

This prospective longitudinal study used data from the Aspirin in Reducing Events in the Elderly (ASPREE) randomized trial of adults aged 65 years or older without dementia or previous cardiovascular events at enrollment. The main outcome was incident dementia. Other outcomes included changes in composite cognition and domain-specific cognition (global cognition, memory, language and executive function, and psychomotor speed). The association between baseline triglycerides and dementia risk was estimated using Cox proportional hazard models adjusting for relevant risk factors. Linear mixed models were used to investigate cognitive change. The analysis was repeated in a subcohort of participants with available *APOE*-ε4 genetic data with additional adjustment for *APOE*-ε4 carrier status and an external cohort (UK Biobank) with similar selection criteria applied.

Results

This study included 18,294 ASPREE participants and 68,200 UK Biobank participants (mean age: 75.1 and 66.9 years; female: 56.3% and 52.7%; median [interquartile range] triglyceride: 106 [80–142] mg/dL and 139 [101–193] mg/dL), with dementia recorded in 823 and 2,778 individuals over a median follow-up of 6.4 and 12.5 years, respectively. Higher triglyceride levels were associated with lower dementia risk in the entire ASPREE cohort (hazard ratio [HR] with doubling of triglyceride: 0.82, 95% CI 0.72–0.94). Findings were similar in the subcohort of participants with APOE-ε4 genetic data (n = 13,976) and in the UK Biobank cohort (HR was 0.82 and 0.83, respectively, all $p \leq 0.01$). Higher triglycerides were also associated with slower decline in composite cognition and memory over time ($p \leq 0.05$).

Discussion

Older adults with higher triglyceride levels within the normal to high-normal range had a lower dementia risk and slower cognitive decline over time compared with individuals with lower triglyceride levels. Higher triglyceride levels may be reflective of better overall health and/or lifestyle behaviors that would protect against dementia development. Future studies are warranted to investigate whether specific components within the total circulating pool of plasma triglycerides may promote better cognitive function, with the hope of informing the development of new preventive strategies.

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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

3MS = Modified Mini-Mental State Examination; **AD** = Alzheimer disease; **ASPREE** = Aspirin in Reducing Events in the Elderly; **ASPREE-XT** = ASPREE-eXTension; **CVD** = cardiovascular disease; **HDL-c** = high-density lipoprotein cholesterol; **HR** = hazard ratio; **IQR** = interquartile range; **LDL-c** = low-density lipoprotein cholesterol; **PUTG** = polyunsaturated fatty acid containing triglyceride.

Introduction

Dementia imposes a substantial personal and public health burden.[1] There have been ongoing concerns that aggressive lipid control in older people may be linked to accelerated cognitive decline and increased risk of dementia.[2,3] However, evidence from historical studies on the relationship between dyslipidemia and neurocognitive outcomes has been inconsistent.[4] A recent study using data of more than 500,000 participants from the UK Biobank cohort who were aged between 40 and 69 years (mean age: 56.5 years) reported a U-shaped relationship between low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), total cholesterol levels, and dementia risk, but an inverse relationship between triglyceride levels and dementia risk over 12 years of follow-up.[5] Triglyceride levels were proposed to be less affected by wasting diseases (sarcopenia and other end-stage diseases) and aging processes that are known to cause cholesterol decline in late life (explaining the observed U-shaped relationship of cholesterol metrics with dementia risk in previous studies).[6] Thus, triglyceride levels may be a more stable biomarker of dementia risk in older populations.

Yet, previous studies examining triglycerides have generated mixed findings, with some reporting a positive association and others reporting a neutral or negative association.[7-16] To provide robust evidence, we analyzed data from a large prospective study of community-based older people who did not have dementia or major cognitive impairment at recruitment and examined the relationship between triglyceride levels, incident dementia risk, and cognitive change over time.

Methods

Study Population

The study population consisted of individuals recruited into the Aspirin in Reducing Events in the Elderly (ASPREE), a double-blinded, placebo-controlled, randomized trial of daily low-dose aspirin in older people.[17-20] ASPREE recruited 19,114 community-dwelling adults from Australia (87.4%) and the United States (12.6%), who were aged 70 years or older (≥65 for US minorities), without diagnosed dementia, a history of diagnosed cardiovascular disease (CVD) events, or major life-limiting (<5 years) illness at trial enrollment. All participants had to score ≥78/100 for the Modified Mini-Mental State Examination (3MS), used to ascertain global cognitive status at enrollment.[21] The ASPREE trial ended in June 2017 after which participants were continued to be followed in the ongoing observational phase, the ASPREE-eXTension (XT) cohort study. The present analysis followed participants from trial enrollment to the second ASPREE-XT annual study visit (last visit completed in August 2019). Using a complete case approach because of a small amount of missing data (n = 820), this analysis included all ASPREE participants who did not have missing data on baseline triglycerides and other covariates.

External Validation Cohort

To check the reliability of our study results, we repeated our main analyses in an external cohort, the UK Biobank, using similar selection criteria and analytic approach applied. The UK Biobank recruited more than 500,000 participants from the general population across the United Kingdom.[22] In this study, we included those aged 65 years or older and who had no diagnosed dementia or previous CVD events at enrollment.

Exposure Measurement

The exposure was fasting plasma/serum triglyceride levels measured at baseline. In ASPREE, participants' fasting total cholesterol, HDL-c, LDL-c, and triglycerides were measured in a clinic or local pathology center (Australia) or the study trial center (the United States). In UK Biobank, lipid traits were measured in the nonfasting blood sample collected at baseline recruitment. Details on serum sample handling and assays in the UK Biobank have been described previously.[23]

Study Outcomes

The main outcome measure was incident dementia. In ASPREE, dementia was defined according to the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition*, American Psychiatric Association criteria,[24] and adjudicated as a primary trial end point by an expert committee masked to ASPREE study treatment assignment.[25] To meet the diagnosis, participants must have developed memory impairment and impairment in at least 1 additional cognitive domain (aphasia, apraxia, agnosia, or disturbance of executive functions) that caused incident impairment in social and independent living functioning.

Dementia outcome in UK Biobank was defined by *International Classification of Diseases, 10th Revision* codes, from the health records of UK Biobank.[26] Outcome adjudication for incident dementia was conducted by the UK Biobank Outcome Adjudication Group. More details are available in eMethods (links.lww.com/WNL/D180).

Other outcomes included changes in composite cognitive function and domain-specific cognition. During the ASPREE clinical trial, cognitive function was assessed at baseline and at years 1, 3, and 5 and/or at final visit, which was precipitated by early cessation of the trial in June 2017. During the ASPREE-XT period, cognition was assessed with the 3MS only, in the first year and then annually with all cognitive tests. The full battery of cognitive tests was administered, including the 3-MS[21] to measure global cognition, the Symbol Digit Modalities Test[27] to measure psychomotor speed, the Hopkins Verbal Learning Test-Revised[28] Delayed Recall task to measure episodic memory, and the single letter (F) Controlled Oral Word Association Test[29] to measure language and executive function. To reduce floor and ceiling effects, a composite cognitive *z*-score was computed by standardizing the raw score for each individual cognitive domain to a *z*-score and then estimating the mean of the *z*-scores for the 4 cognitive tests.[30]

Baseline Covariates

Potential baseline confounders were selected a priori according to their plausible associations with either triglycerides or dementia or both. These included age, sex (male, female), race and ethnicity (White, Black, Hispanic/Latino, others), country (Australia, the United States), smoking (never, past, current), alcohol consumption (never, past, current), formal years of education (<12 years, ≥12 years), family history (father/mother/sibling) of dementia, diabetes, hypertension, waist circumference, LDL-c (mg/dL), HDL-c (mg/dL), statin use, other lipid-lowering medication use (omega-3-fatty acid, fenofibrate, ezetimibe, gemfibrozil, nicotinic acid), baseline composite cognitive *z*-score (for dementia analysis only), and randomized ASPREE treatment (aspirin/placebo). Secondary analyses were adjusted for the *APOE* ε4 allele carrier status (available for 76% of ASPREE participants).

For the analysis in the UK Biobank cohort, covariates included age, sex, race, smoking (never, past, current), alcohol consumption (never, past, current), LDL-c, HDL-c, waist circumference, systolic and diastolic blood pressure, diabetes, medications for lowering lipids, blood pressure, and glucose.

Statistical Analysis

The associations between baseline triglyceride levels with incident dementia were analyzed with Cox models, including all baseline covariates. Our main analysis modeled triglycerides as a continuous variable and logarithmically transformed using base 2 due to its skewed distribution. Restricted cubic splines with 3 prespecified knots placed at 10th, 50th, and 90th percentiles of the distribution of triglycerides were plotted to visualize the potentially nonlinear relationship between triglycerides and dementia. We also modeled triglycerides as a categorical variable using 2 sets of classification modes: (1) <10th, 10th–50th, 50th–90th, and >90th to assess the potential impact of very low and high triglyceride levels and (2) <89 mg/dL (<1 mmol/L), 89–176 mg/dL (1–2 mmol/L), 177–256 mg/dL (2–3 mmol/L), and >256 mg/dL (>3 mmol/L) for the convenience of interpreting results in clinical practice. Subgroup analyses were performed according to age, sex, *APOE*-ε4 carrier status, family history of dementia, diabetes, hypertension, waist circumference, LDL-c, HDL-c, and use of any lipid-lowering medication. The main analysis was repeated in the subcohort of participants with available genotype data with further adjustment made for carrier status of *APOE*-ε4 allele and the UK Biobank cohort.

Linear mixed effects models were used to examine the associations of triglycerides with changes in the global cognitive function (composite *z*-score) and 4 individual cognitive domains. The data were fitted using linear mixed models to calculate the change in cognitive function scores over time with increasing triglyceride levels. The models were constructed by entering baseline triglycerides (log-transformed with a base of 2), annual visit, log2 (triglycerides) × annual visit interaction, baseline covariates, random intercept, and random slope on time.

Sensitivity Analyses

Different sensitivity analyses were used to test the robustness of study findings. To detect possible indication/selection bias and reverse causality, we first compared the risk of incident dementia at different levels of triglycerides and LDL-c. We presumed that if there was indication bias introduced by the presence of preexisting diseases (e.g., wasting diseases) that increase the risk of dementia and also affect lipid metabolism, the association with triglycerides and with LDL-c would likely be comparable. We also performed a set of landmark analyses restricted to incident dementia that occurred 1, 2, 3, and 4 years after baseline (to exclude early dementia events that might be caused by preexisting conditions that also affected the triglyceride levels). In addition, we restricted the analysis for dementia in a subcohort of participants with stable waist circumference over time (defined as waist circumference during the first 3 years maintained within 10% of baseline values given that the majority had the data). Furthermore, presuming that individuals who had low triglyceride levels had a long-term survival advantage predisposing them to a higher risk of dementia, we complemented our main cause-specific hazard ratio (HR) analysis by analyzing subdistribution HRs for dementia with Fine-Gray competing risk models that consider death as a competing event.

Random measurement error of baseline triglycerides and fluctuations of triglyceride levels over time may bias its true association with dementia toward the null or "regression dilution bias."[31] We used a nonparametric method to correct for this bias.[32] An adjusted regression dilution ratio was calculated using fasting triglyceride values at baseline and at the second annual visit from 14,466 individuals to quantify the extent to which single measurements of the markers reflect their long-term average levels. A regression dilution ratio of 0.61 was used for triglycerides in the calibrated Cox models. We also repeated the main analyses by replacing the baseline triglyceride values with the mean values measured at baseline

and at all annual visits with available records. As HDL-c was negatively correlated with triglycerides (r = 0.46) and adjusting for diabetes and waist circumference may offset the potential negative impact of triglycerides on dementia, we repeated our main analysis without adjusting for these variables. To remove the impact of outliers, we repeated analysis in which participants with extreme triglyceride values (<1%, >99%) were excluded. Last, we repeated our main analysis of incident dementia in the ASPREE intervention group (randomized to aspirin) and control group (randomized to placebo) separately.

Standard Protocol Approvals, Registrations, and Patient Consents

The ASPREE and ASPREE-XT study were approved by the Human Research Ethics Committees at Monash University and Alfred Hospital in Australia and site-specific Institutional Review Boards in the United States. The UK Biobank was approved by the NHS National Research Ethics Service (21/NW/0157). All participants provided written informed consent.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator. Requests for data access will be available through the ASPREE Principal Investigators with details for applications provided through aspree.org/aus/for-researchers/ or aspree.org/usa/for-researchers/.

Results

Baseline Characteristics

A total of 18,294 (median [interquartile range (IQR)] age 74 [72–78] years; female: 56.3%) ASPREE participants were included in this study with a median follow-up of 6.4 (IQR 5.3–7.7) years; their median triglycerides level was 106 mg/dL (IQR 80–142 mg/dL, range: 9–1,081 mg/dL). Participants with higher triglyceride levels were less likely to be current drinkers, had lower education levels, and had a higher prevalence of diabetes and hypertension (Table 1). They were also more likely to report the use of lipid-lowering medications and had higher levels of waist circumference and lower HDL-c. Analysis using data from the UK Biobank cohort included 68,200 participants (mean age: 66.9 years; female: 52.7%; median [IQR] nonfasting triglyceride: 139 [101–193] mg/dL), with a median (IQR) follow-up of 12.5 (11.7–13.2) years. The baseline characteristics of UK Biobank participants are presented in eTable 1 (links.lww.com/WNL/D180).

Baseline Triglyceride Levels and Incident Dementia

When analyzing triglycerides on a continuous scale, a significant and similar inverse association was found between triglycerides and incident dementia in the entire study cohort, the subcohort of participants with genotypic data (total: n = 13,976; dementia: n = 583), and external UK Biobank cohort (total: n = 62,800, dementia: n = 2,778), with adjusted HR *per* doubling triglycerides of 0.82, 0.82, and 0.83, respectively (all p values ≤0.01) (Figure 1). The restricted cubic splines revealed that the risks of dementia decreased with higher triglyceride values, with no apparent threshold (Figure 1).

Analysis of triglyceride as a categorical variable demonstrated a graded inverse association between higher triglyceride levels and lower dementia risk in the entire study cohort and the subcohort of participants with genotypic data. Compared with those with triglycerides below the 10th percentile as a reference group (<62 mg/dL), the HRs for dementia in the 10–50th percentile category (63–106 mg/dL), 50–90th percentile category (107–186 mg/dL), and above 90th percentile category (>187 mg/dL) were 0.85, 0.76, and 0.64 in the entire cohort and were 0.72, 0.66, and 0.58 in the subcohort of participants with genotypic data (p for trend <0.05) (Figure 2). Similar trend of association was seen in the external UK Biobank cohort and when categorizing triglycerides by per 1 mmol/L increase (Figure 2).

Subgroup analysis found that the direction and magnitude of the inverse association between triglycerides and dementia risk was highly consistent across all subgroups, and not modified by age, sex, or risk factors related to triglycerides or dementia (all p values for interaction >0.15) (Figure 3).

Baseline Triglyceride Levels and Cognition Change Over Time

In the entire study cohort, higher triglyceride levels were significantly associated with slower decline in composite cognition (p = 0.02) and a borderline significantly slower decline in episodic memory (p = 0.05). There was a similar trend in the association with these domains in the subcohort with genotypic data, although the statistical significance for composite cognition and memory was no longer maintained due to reduced sample size. No significant associations were found for other cognition domains (Table 2).

Sensitivity Analyses

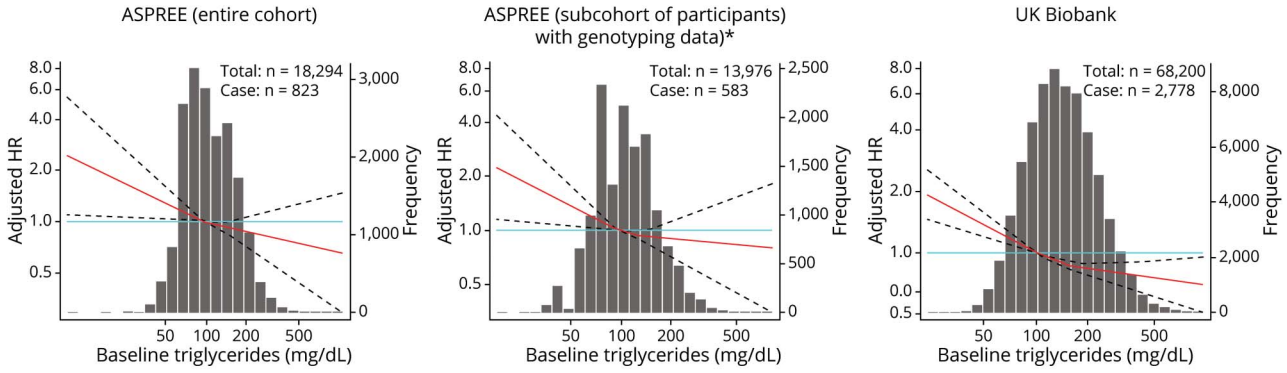
When grouping participants by the median values of baseline triglycerides and LDL-c of the study population, participants with a triglyceride level above the median (≥106 mg/dL) and a LDL-c level below the median (<116 mg/dL) had the lowest risk of dementia (HR 0.76, 95% CI 0.61–0.94), with the group of both triglycerides and LDL-c below the median as the reference group (eTable 2, links.lww.com/WNL/D180). This suggests that indication bias was unlikely. Repeating the analysis for dementia by (1) only allowing participants to enter the Cox model at 1, 2, 3, or 4 years after the initial start of follow-up; (2) limiting to those with stable waist circumference between baseline and second annual visit; (3) replacing the baseline triglyceride values with the mean values of baseline and follow-up visits in the outcome analyses; (4) not adjusting for HDL-c, diabetes, and waist circumference in the model; and (5) removing the participants with extreme

Table 1 Baseline Characteristics of Participants by Triglyceride Levels in ASPREE

Characteristics	All	Baseline triglyceride levels (mg/dL)			
		<10th (<62)	10th–50th (62–106)	50th–90th (107–186)	>90th (>186)
Individuals, n	18,294	1,416	7,449	7,312	2,117
Age, y, median (IQR)	74 (72–78)	74 (72–78)	74 (72–78)	74 (72–78)	74 (71–77)
Female, n (%)	10,305 (56)	750 (53)	4,210 (57)	4,211 (58)	1,134 (54)
Race and ethnicity, n (%)					
White	16,685 (91)	1,242 (88)	6,758 (91)	6,748 (92)	1,937 (92)
Black	873 (5)	129 (9)	446 (6)	240 (3)	58 (3)
Hispanic/Latino	469 (3)	24 (2)	146 (2)	211 (3)	88 (4)
Others	267 (1)	21 (2)	99 (1)	113 (2)	34 (2)
Country, n (%)					
Australia	15,953 (87)	1,109 (78)	6,455 (87)	6,519 (89)	1,870 (88)
USA	2,341 (13)	307 (22)	994 (13)	793 (11)	247 (12)
Smoking, n (%)					
Never	10,144 (55)	792 (56)	4,190 (56)	4,056 (55)	1,106 (52)
Former	7,450 (41)	576 (41)	2,998 (40)	2,975 (41)	901 (43)
Current	700 (4)	48 (3)	261 (4)	281 (4)	110 (5)
Alcohol, n (%)					
Never	3,181 (17)	204 (14)	1,160 (16)	1,401 (19)	416 (20)
Former	1,092 (6)	91 (6)	415 (6)	445 (6)	141 (7)
Current	14,021 (77)	1,121 (79)	5,874 (79)	5,466 (75)	1,560 (74)
Education (>12 y), n (%)	10,038 (55)	910 (64)	4,328 (58)	3,822 (52)	978 (46)
FH (father/mother/sibling) of dementia, n (%)	4,599 (25)	373 (26)	1,921 (26)	1,845 (25)	460 (22)
Diabetes, n (%)	1,946 (11)	93 (7)	612 (8)	828 (11)	413 (20)
Hypertension, n (%)	13,587 (74)	944 (67)	5,264 (71)	5,626 (77)	1,753 (83)
Statin use, n (%)	5,728 (31)	295 (21)	2,055 (28)	2,545 (35)	833 (39)
Other lipid-modifying medications, n (%)	826 (5)	73 (5)	272 (4)	328 (4)	153 (7)
Waist circumference, n (%)					
Normal (women: <80 cm; men: <94 cm)	3,550 (19)	539 (38)	1,919 (26)	946 (13)	146 (7)
High (women: 80–<88 cm; men 94–<102 cm)	4,687 (26)	418 (30)	2,126 (29)	1,750 (24)	393 (19)
Very high (women: ≥88 cm; men ≥102 cm)	10,057 (55)	459 (32)	3,404 (46)	4,616 (63)	1,578 (75)
LDL-c, mg/dL, mean (SD)	118 (34)	106 (29)	117 (32)	122 (35)	118 (40)
HDL-c, mg/dL, mean (SD)	61 (18)	76 (21)	66 (17)	57 (15)	48 (12)
Composite cognitive score, mean (SD)	0 (0.71)	0.06 (0.72)	0.03 (0.71)	−0.02 (0.70)	−0.09 (0.71)
***APOE*-ε4 carrier (n = 13,976)**	3,613 (26)	283 (26)	1,519 (26)	1,392 (25)	419 (27)

Abbreviations: ASPREE = Aspirin in Reducing Events in the Elderly; FH = family history; HDL-c = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-c = low-density lipoprotein cholesterol.
Other races/ethnicities including Australian aborigine/Torres Strait islander, native American, more than 1 race, native Hawaiian/Pacific Islander, and those who were not Hispanic and who did not state their ethnicity/race. Diabetes mellitus is defined from self-report or fasting glucose ≥126 mg/dL or on glucose-lowering medications. Hypertension is defined as blood pressure ≥140/90 mm Hg or on antihypertensive medications. Other lipid-lowering medication use included omega-3-fatty acid, fenofibrate, ezetimibe, gemfibrozil, and nicotinic acid. To convert cholesterol to mmol/L, multiply by 0.0259, and to convert triglycerides to mmol/L, multiply by 0.0113.

Figure 1 Association Between Baseline TG Levels and Risk of Incident Dementia in the ASPREE and UK Biobank



The figure shows restricted cubic splines for the association between TG levels and risk of incident dementia in ASPREE and UK Biobank. The scale of the primary Y-axis (left hand) reflects the values for the adjusted HRs for incident dementia (reference: TG = 100 mg/dL). The scale of the secondary Y-axis (right hand) shows the number of participants at different levels of TG. The solid red line shows multivariable HR with black dash lines denoting corresponding 95% CIs derived from restricted cubic splines regression with 3 knots. The light blue solid line was the reference line for HR of 1.0. The gray bar denotes population distribution based on TG. Cubic splines were adjusted for age, sex, race, country, smoking, alcohol consumption, education level, family history of dementia, diabetes, hypertension, waist circumference, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, statin use, other lipid-lowering medication use, and composite cognitive score at baseline and randomized aspirin in the ASPREE cohorts and adjusted for age, sex, race, smoking, alcohol consumption, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, waist circumference, systolic and diastolic blood pressure, diabetes, and medications for lipid-lowering, blood pressure-lowering, and glucose-lowering in the UK Biobank cohort. *Analysis further adjusted for the carrier status of APOE-ε4 allele. ASPREE = Aspirin in Reducing Events in the Elderly; HR = hazard ratio; TG = triglyceride.

values of triglycerides did not change the results (eTables 3–7). Subdistribution HRs estimated with a Fine-Gray model were similar to the cause-specific HRs presented in the main analysis (eTable 8). Using calibrated Cox proportional hazards models with correction for triglycerides with regression dilution ratio, the strength of the inverse associations between triglycerides and dementia was modestly enhanced (eTable 9). When repeating the dementia analysis in the ASPREE intervention group and control group separately, the results were shown to be similar in the entire cohort and the subcohort with *APOE*-ε4 data, with the *p* value for interaction between triglycerides and randomized groups of 0.82 and 0.73, respectively (eTable 10).

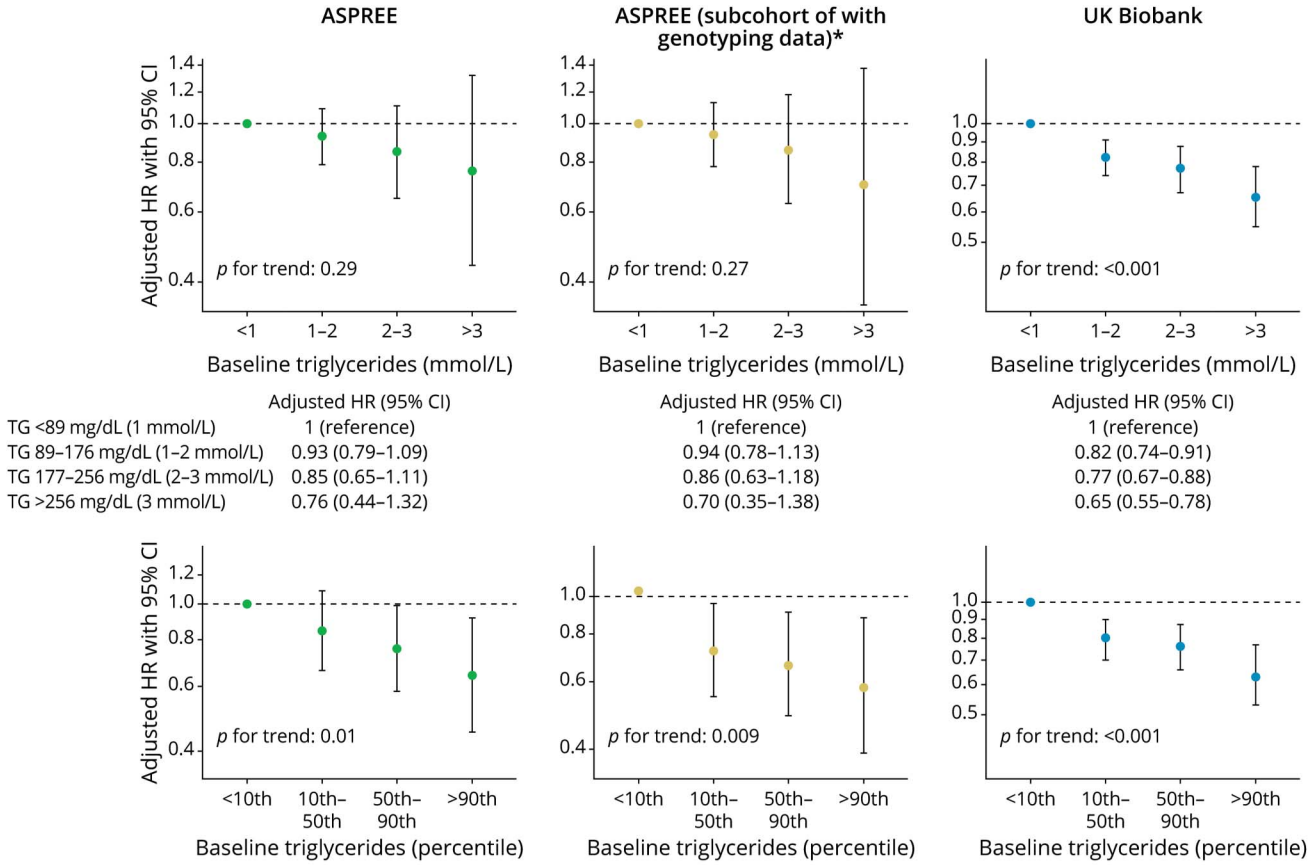
Discussion

This study found an inverse association between fasting serum/plasma triglyceride levels and risk of incident dementia in a large prospective cohort of community-dwelling older adults, with higher triglyceride levels associated with lower risk of dementia. The relationship was robust after adjusting for potential confounding factors and observed independently of other lipid measures, and not modified by age, sex, metabolic, and dementia risk factors, including carrier status for the *APOE*-ε4 allele. Similar findings were seen when repeating the analysis in the UK Biobank cohort using nonfasting triglyceride levels. Additional analysis revealed that participants with higher triglyceride levels had a slower decline in composite cognition and memory over time. As only 8% of ASPREE participants had triglyceride concentrations between 200 and 500 mg/dL and 0.1% had triglycerides >500 mg/dL (defined as "moderate" and "severe" hypertriglyceridemia[33]), our findings should only be generalized to older individuals whose triglyceride levels are within the normal and high-normal range.

Existing evidence regarding the association between triglycerides and neurologic outcomes has been mixed, with some studies reporting a negative association and others reporting a positive or no association.[7-16,34-42] Notably, most studies reporting an inverse association involved older individuals, but these studies were limited by their cross-sectional design, small sample size, and/or lack of systematic follow-up and outcome assessment.[15,34-36,39,40] Triglycerides measured in late life are more likely to be influenced by contemporaneous lifestyle behaviors, nutrition, and health conditions. By contrast, studies reporting positive associations commonly involve individuals at midlife and may reflect longer-term exposure to hypertriglyceridemia.[9,37,38,41] The findings suggest that the prognostic implication of triglycerides on neurocognitive outcomes differs depending on whether they are measured during early life, midlife, or late life.[5,42]

Based on our assumption regarding the varying neurocognitive impacts of triglycerides measured at different time points in life, one plausible explanation for our study findings is that lower triglycerides in older people may be attributable to their poorer nutritional intake and absorption, which are known predictors of cognitive decline and dementia.[43,44] By contrast, higher

Figure 2 Risk of Incident Dementia by TG Categories



	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
TG <89 mg/dL (1 mmol/L)	1 (reference)	1 (reference)	1 (reference)
TG 89–176 mg/dL (1–2 mmol/L)	0.93 (0.79–1.09)	0.94 (0.78–1.13)	0.82 (0.74–0.91)
TG 177–256 mg/dL (2–3 mmol/L)	0.85 (0.65–1.11)	0.86 (0.63–1.18)	0.77 (0.67–0.88)
TG >256 mg/dL (3 mmol/L)	0.76 (0.44–1.32)	0.70 (0.35–1.38)	0.65 (0.55–0.78)

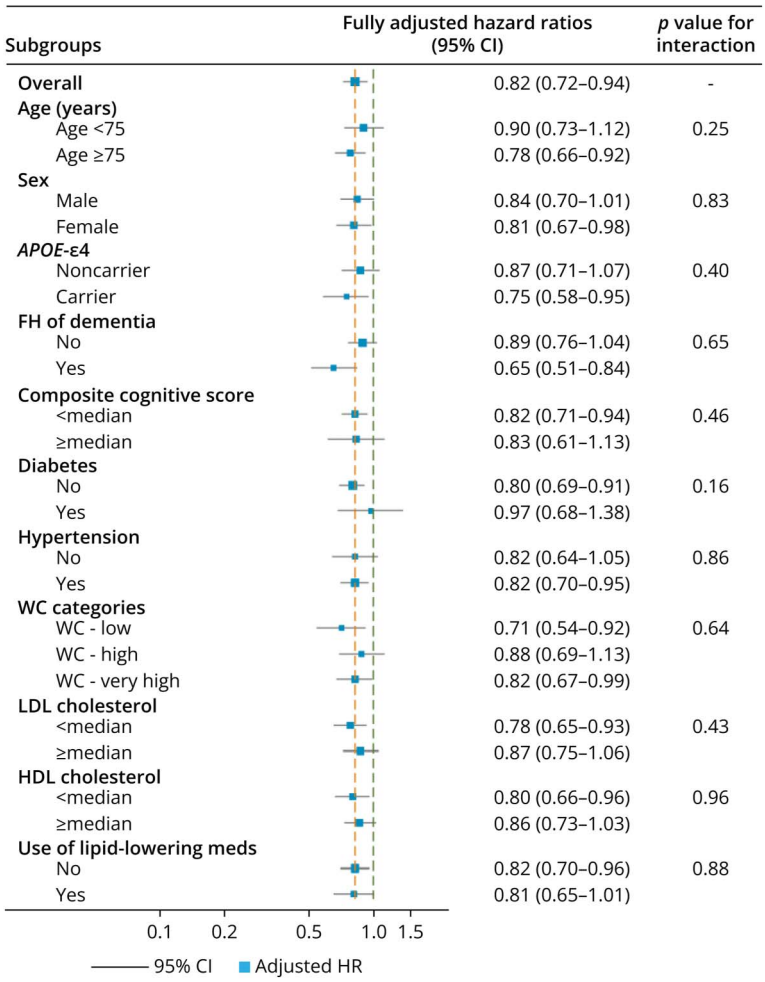
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
<10th percentile	1 (reference)	1 (reference)	1 (reference)
10th–50th percentile	0.85 (0.66–1.09)	0.72 (0.55–0.96)	0.80 (0.70–0.90)
50th–90th percentile	0.76 (0.58–0.99)	0.66 (0.49–0.91)	0.76 (0.66–0.87)
>90th percentile	0.64 (0.45–0.92)	0.58 (0.39–0.88)	0.63 (0.53–0.77)

Circles denote adjusted HRs for incident dementia, and error bars denote the corresponding 95% CIs. Adjustment was made for age, sex, race, country, smoking, alcohol consumption, education level, family history of dementia, diabetes, hypertension, waist circumference, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, statin use, other lipid-lowering medication use, and composite cognitive score at baseline and randomized aspirin in the ASPREE cohorts and adjusted for age, sex, race, smoking, alcohol consumption, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, waist circumference, systolic and diastolic blood pressure, diabetes, and medications for lipid-lowering, blood pressure-lowering, and glucose-lowering in the UK Biobank cohort. The TG values at 10th, 50th, and 90th percentile in the overall ASPREE cohort and the subcohort of participants with genotyped data were 62, 106, and 186 mg/dL and in the UK Biobank cohort were 78, 139, and 261 mg/dL. ASPREE = Aspirin in Reducing Events in the Elderly; HR = hazard ratio; TG = triglyceride.

triglycerides within the normal to normal-high range may indicate plentiful food sources and healthy lifestyle, therefore a lower dementia risk. Because better nutritional status is commonly associated with higher LDL-c and triglyceride levels, we assume that if better nutritional status is protective against the development of dementia, we may have expected to find the low risk of dementia among participants with both high triglycerides and LDL-c. However, our analysis in ASPREE does not support this hypothesis, as we have also shown that high LDL-c (reflective of better nutritional status) was associated with increased dementia risk. This result may point to other underlying factors that could help explain the observed relationship.

Triglycerides contribute up to 95% of dietary fats which are the main energy source of the brain. Yet, the biological mechanisms underpinning the potential relationship between low triglycerides and high risk of dementia and/or cognitive decline remain unknown. One explanation may lie in better understanding the specific plasma triglyceride components within the total circulating pool that could promote better cognitive function. A cross-sectional analysis by Bernath et al.[14] assessed the relationship between the 9 principal components of plasma triglycerides and cognition and found that the levels of 2 components consisting of long-chain polyunsaturated fatty acid–containing triglycerides (PUTGs) were significantly lower in patients with mild cognitive impairment and Alzheimer disease (AD) compared with those with normal cognition. Their neuroimaging analysis revealed that patients with lower PUTG levels had a greater atrophy of the hippocampus and entorhinal cortex, suggestive of early-stage AD. Future studies are warranted to

Figure 3 Subgroup Analysis of Dementia by Baseline Characteristics



HR for incident dementia with doubling triglycerides. The size of the squares representing the point estimates of the HRs is proportional to the inverse of the variance of the estimate. Analyses were adjusted for age, sex, race, country, smoking, alcohol consumption, education level, family history of dementia, diabetes, hypertension, waist circumference, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, statin, other lipid-lowering medications, and composite cognitive score at baseline and randomized aspirin, unless used as a stratifying variable. FH = family history; HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein; WC = waist circumference.

confirm their results and investigate which specific triglyceride component is neuroprotective.

The association between triglycerides and dementia risk could vary among older adults depending on their genetic vulnerability to both high triglycerides and neurocognitive disorders. However, current evidence supporting this genetic interplay is scant. One study found a significant association between high triglyceride levels and low incident AD risk, only in women carrying the apolipoprotein A5-1131C allele.[45] This variant is known to increase CVD risk by elevating plasma triglycerides levels, but its association with dementia risk remains unknown.[46] Future studies to identify genetic variants that were associated with increased levels of triglycerides and decreased risk of dementia are needed to fill the current evidence gap. One may also be interested in studying whether genetically elevated triglycerides measured using polygenic risk scores were associated with increased risk of dementia in later life. Our subgroup analyses did not reveal any significant modifying effect of family history of dementia and *APOE*-ε4, suggesting that the association between triglycerides and dementia risk is generally consistent between those who are genetically predisposed to high dementia risk and those who are not. Owing to the reduced statistical power of subgroup analysis, more studies are warranted to confirm this result.

Other explanations for our study findings include residual confounding and survival bias. For example, medications, such as thiazide diuretics and beta-blocker, which were shown to increase triglycerides, have been putatively associated with a lower risk of dementia.[47,48] Individuals in ASPREE were free of CVD events initially. Older people who had high triglyceride levels, yet remained free of CVD in their late life, may possess protective factors against CVD that might also predispose them to a lower risk of dementia. Knowing that patients with AD undergo structural brain atrophy and reduced brain energy metabolism,[49] a recent study of ketone diet with medium chain triglycerides found that the median chain fatty acid can quickly pass through the blood-brain barrier and provide energy for brain cells (neurons and astrocytes) beyond glucose. Specific dietary triglycerides supplementation may represent a promising preventive treatment for dementia and cognitive decline.[50] The correlation between dietary triglycerides and plasma triglycerides has yet to be determined.

Table 2 Association Between Baseline TG and Cognitive Score Changes Over Time

	Baseline			Follow-up		
	β	SE	*p* Value	β	SE	*p* Value
ASPREE (entire cohort)						
3-MS (Global function)	−0.172	0.057	0.002	0.017	0.014	0.23
SDMT (Psychomotor speed)	−0.190	0.118	0.11	−0.000	0.015	0.98
COWAT (Language, executive function)	−0.068	0.057	0.23	−0.014	0.008	0.09
HVLT-R Delayed Recall (Episodic memory)	−0.102	0.036	0.005	0.011	0.005	0.05
Composite *z*-score	−0.027	0.008	0.002	0.002	0.001	0.02
ASPREE (subcohort of participants with genotypic data)[a]						
3-MS (Global function)	−0.194	0.062	0.002	0.017	0.015	0.26
SDMT (Psychomotor speed)	−0.254	0.133	0.06	−0.007	0.016	0.67
COWAT (Language, executive function)	−0.088	0.066	0.18	−0.015	0.009	0.11
HVLT-R Delayed Recall (Episodic memory)	−0.113	0.041	0.006	0.009	0.006	0.11
Composite *z*-score	−0.033	0.010	0.001	0.002	0.001	0.06

Abbreviations: 3-MS = The Modified Mini-Mental State Examination; ASPREE = Aspirin in Reducing Events in the Elderly; COWAT = Controlled Oral Word Association Test; HVLT-R = Hopkins Verbal Learning Test-Revised Delayed Recall; SDMT = Symbol Digit Modalities Test; TG = triglyceride.
Cognitive data were taken from the annual visit at baseline (annual visit 0), 1, and 3–9 years. The data were fitted using linear mixed models to calculate the change in cognitive function scores over time with increasing TG levels. The annual visit of cognition measurement was treated as a continuous variable representing time. The models were constructed by entering baseline TG levels (log-transformed with a base of 2), annual visit, log2(TG) × annual visit interaction, baseline covariates, random intercept, and random slope on time. The presented β in baseline was the coefficient for baseline cognition in each domain (or composite) associated with baseline TG; β within follow-up was the coefficient for log2(TG) × annual visit interaction, which was interpreted as the mean difference in the annual rate of change in each domain (or composite) of cognitive score per doubling TG. In all models, covariate adjustment was made for age, sex, race, country, smoking, alcohol consumption, education level, family history of dementia, diabetes, hypertension, waist circumference, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, statin, other lipid-lowering medications, and randomized aspirin.
[a] Analysis further adjusted for the carrier status of APOE-ε4 allele.

This study has limitations. First, our study cannot establish a causal relationship between triglyceride levels and dementia. This is because of its post hoc, observational nature, and the possibilities of indication bias and residual confounding introduced by unmeasured and unobserved confounders remain. Although we have carefully attempted to exclude reverse causality, given the decades onset of dementia and cognitive decline, we cannot fully exclude this. Even so, the consistent results from the subgroup analysis and sensitivity analyses provide some evidence of the robustness of our findings. Second, most ASPREE participants had normal to high-normal triglyceride levels. Therefore, our results cannot be generalized to the population with severe hypertriglyceridemia, in whom pharmacologic treatments are indicated to prevent CVD events and other complications, such as acute pancreatitis.[51] Similarly, our findings are unique to the older population studied (older than 65 years) without CVD and are not generalizable to other populations.

Our study has some key strengths. To the best of our knowledge, this is the largest reported longitudinal follow-up study that has investigated the relationship between triglyceride levels and all-cause dementia in a demographically relevant older population. Other main strengths include the use of high-quality prospective data from a large-scale, contemporary randomized trial and post-trial long follow-up, rigorously and systematically collected data concerning fasting triglyceride levels and other covariates, protocol-driven serial neurocognitive testing at baseline and during follow-up, and the rigorous adjudication of end points. We assessed possible reverse causality in several exploratory analyses, and the findings did not change, suggesting that reverse causality was less likely.

In conclusion, among the older participants studied in ASPREE, those with higher triglyceride levels, albeit most within the normal to high-normal range, had lower risk of dementia and slower cognitive decline over time. Triglyceride levels may serve as a useful predictor for dementia risk and cognitive decline in older populations. Future studies should investigate whether specific triglyceride components within the total circulating pool if triglycerides may promote better cognitive function.

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Continued

Appendix *(continued)*

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