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Association of Year-to-Year Lipid Variability With Risk of Cognitive Decline and Dementia in Community-Dwelling Older Adults

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Abstract

Background and Objectives

Lipid metabolism in older adults is affected by various factors including biological aging, functional decline, reduced physiologic reserve, and nutrient intake. The dysregulation of lipid metabolism could adversely affect brain health. This study investigated the association between year-to-year intraindividual lipid variability and subsequent risk of cognitive decline and dementia in community-dwelling older adults.

Methods

ASPirin in Reducing Events in the Elderly (ASPREE) was a randomized trial of aspirin, involving 19,114 participants aged 65 years and older from Australia and the United States who were free of dementia and major cognitive impairment. ASPREE-eXTension is the post-trial observational follow-up of participants, currently to a maximum of 11 years. This post hoc analysis included participants who had lipid levels measured at baseline and in years 1, 2, and 3. Year-to-year variability in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides over the first 3 years was quantified using variability independent of the mean. Individuals who initiated or discontinued lipid-lowering therapy during this period were excluded. Multivariable Cox proportional hazards regression was used to analyze associations with incident dementia, adjudicated by expert panels, and cognitive impairment with no dementia (CIND) confirmed by a battery of cognitive tests, occurring after year 3. A linear mixed model was used for assessing the association with changes in 4 cognitive function domains, including global, memory, processing speed, verbal fluency, and a composite score from baseline to the end of follow-up.

Results

The analysis included 9,846 individuals (median [interquartile range] age: 73.9 [71.7–77.3] years, 54.9% female). 509 incident dementia and 1,760 CIND events were recorded over a median follow-up of 5.8 and 5.4 years after variability assessment. The hazard ratios (95% CI) comparing the highest and lowest quartiles of TC and LDL-c variability were 1.60 (1.23–2.08) and 1.48 (1.15–1.91) for dementia and 1.23 (1.08–1.41) and 1.27 (1.11–1.46) for CIND. Higher TC and LDL-c variability was also associated with a faster decline in global cognition, episodic memory, psychomotor speed, and the composite score (all $p < 0.001$). No strong evidence was found for an association of HDL-c and triglyceride variability with dementia and cognitive change.

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Glossary

3MS = Modified Mini-Mental State; **AD** = Alzheimer disease; **ADRD** = AD-related dementia; **ASPREE** = ASPirin in Reducing Events in the Elderly; **ASPREE-XT** = ASPREE-eXTension; **BMI** = body mass index; **CIND** = cognitive impairment with no dementia; **CVD** = cardiovascular disease; **DBP** = diastolic blood pressure; **HDL-c** = high-density lipoprotein cholesterol; **HR** = hazard ratio; **IQR** = interquartile range; **LDL-c** = low-density lipoprotein cholesterol; **SBP** = systolic blood pressure; **TC** = total cholesterol; **VIM** = variability independent of the mean.

Discussion

Tracking variability of TC and LDL-c may serve as a novel biomarker of incident dementia and cognitive decline in older adults.

Introduction

Dementia and cognitive decline are major health issues disproportionately affecting older adults and have an insidious onset. Early detection and treatment can slow disease progression. Dyslipidemia at midlife has been identified as a risk factor of cognitive decline and dementia later in life.[1-4] However, the impact of lipid levels measured in older age on neurocognitive outcomes is less defined. Previous research yielded mixed results, with many suggesting no significant association,[5-7] while others found that low cholesterol may increase the dementia risk.[8,9] Most studies used cholesterol values measured at a single time point, which fails to account for what the level was in the past and fluctuations over time. Lipid levels in older individuals are more dynamic, influenced not only by factors such as physical activity and diet but also by reduced physiologic reserve, morbidities, functional decline and sarcopenia, and more frequent use of lipid-lowering medications.[10] Consequently, lipid measurements taken in later life may reflect transient rather than enduring values, potentially under/overestimating their long-term impact and cumulative risk exposure from midlife onward.

Monitoring cholesterol fluctuations through repeated measurements could provide complementary risk information on dementia and cognitive decline, particularly in older people.[11] Despite such potential, the clinical value of monitoring lipid changes measured in late life for identifying high-risk individuals for dementia and cognitive decline has been largely understudied. Few studies investigating this relationship have often been limited by short follow-up periods, inclusion of younger adults, small sample sizes, and lack of administration of cognitive tests.[12-17] This study leveraging the extensive data from a large-scale randomized trial—the ASPirin in Reducing Events in the Elderly (ASPREE), with its post-trial observational phase, ASPREE-eXTension (ASPREE-XT)—addressed these limitations and examined the association between the change (measured by year-to-year variability) in various lipid metrics and subsequent risk of cognitive impairment and incident dementia (robustly adjudicated by an international expert panel rather than relying on hospital records) in an older cohort.

Methods

Study Design

The ASPREE and ASPREE-XT studies have been described previously.[18-21] In brief, ASPREE (NCT01038583) was a double-blinded, randomized, placebo-controlled trial of low-dose aspirin. A total of 19,114 community-dwelling individuals aged 70 years and older (≥65 for US ethnic minorities) were recruited from Australia (87%) and the United States (13%). Participants had no history of cardiovascular disease (CVD) events, diagnosed dementia, independence-limiting physical disability, or significant cognitive decline (Modified Mini-Mental State [3MS] Examination score ≥78) at trial entry. Participants were not excluded based on their cognitive scores on other domains. The intervention phase of the ASPREE trial ended in June 2017. ASPREE-XT is an ongoing post-trial observational study following those (>80%) who consented to be followed for further 5 years. For this analysis, we used data from both ASPREE and ASPREE-XT (data cut until 2021) with a maximum follow-up of 11 years. No informed consent was required for this post hoc analysis.

Setting and Participants

At baseline and each annual visit, participants were required to fast overnight and their blood samples were collected in a local clinic or pathology center the following day for lipid and glucose measurements. Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation in most cases and only measured directly if triglyceride is too high.[22] Participants who had cholesterol values measured at baseline and year 1, 2, and 3 annual visits were included in this analysis. Because we aimed to study change in lipid levels unrelated to changes in lipid-lowering treatment (commencement or cessation per se), those who initiated or discontinued the medication during the measurement period were excluded. Because doses of lipid-lowering therapy were unknown, the effect of dose changes on lipid variability could not be investigated. Participants were asked to bring all currently used prescription medications or a list of these to their baseline and annual visits. When this was not possible, medication use was ascertained by self-report and subsequently

confirmed by review of primary care practice records, where possible.

Lipid Variability

The main exposure of interest is year-to-year intraindividual variability of total cholesterol (TC), which represents the fluctuations in TC annually within a single individual over time. Analyses were also conducted for the intraindividual variability of other lipid metrics including LDL-c, high-density lipoprotein cholesterol (HDL-c), and triglycerides. Lipid variability was quantified using 4 consecutive measurements at baseline and at year 1 through year 3. Different indices were considered[12,23,24]: (1) SD; (2) coefficient of variation; (3) average real variability, defined as the average absolute difference between consecutive measurements; and (4) variability independent of the mean (VIM). Spearman correlation analysis was used to describe the pairwise associations between different indices of TC variability and average mean TC values. Because there was a high correlation between these indices, we chose to use VIM to define variability in our analysis because it is least correlated with the mean cholesterol values (eFigure 1). VIM was calculated as $\text{VIM} = k \times \frac{\text{SD (lipid)}}{\text{mean (lipid)}^m}$, where m is computed from fitting a power model $\text{SD(lipid)} = \text{constant} \times \text{mean(lipid)}^m$ and k is the mean value of $(\text{mean(lipid)})^m$.[12] Mean(lipid) and SD (lipid) are the mean value and its SD of 4 lipid measurements at baseline and at year 1, 2, and 3 annual visits. Formulas for other variability indices can be found in eMethods 1.

Outcomes and Follow-Up

The main end point was incident all-cause dementia, a prespecified component of the primary outcome in ASPREE. The diagnosis of dementia was adjudicated by an expert panel who were blinded to the randomized study drug assignment according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (details in eMethods 2).[25] Other end points included cognitive impairment with no dementia (CIND) and changes in domain-specific cognition. The latter include global cognitive function measured by the 3MS Examination,[26] episodic memory by the Hopkins Verbal Learning Test–Revised[27] Delayed Recall task, psychomotor speed by the Symbol Digit Modalities Test,[28] and language and executive function by the single-letter (F) Controlled Oral Word Association Test.[29] The cognitive test battery was administered at baseline and at years 1, 3, and 5, followed by a final visit (which could have been a given participant's third, fourth, fifth, sixth, or seventh annual visit depending on the year of their recruitment), and at 4 subsequent ASPREE-XT annual visits (at the first-year follow-up of ASPREE-XT, only 3MS Examination was measured). A composite *z* score for cognition was computed to integrate these domains, as described previously, to reduce ceiling and floor effects.[30,31] For all cognitive domains, a higher score denotes better function. CIND was defined as a >1.5-SD individual decline in the cognitive score of any domain, in the absence of a dementia diagnosis. Participants whose baseline cognitive score was lower than 1.5 SD were excluded from the CIND analysis.

For dementia and CIND, the follow-up started from year 3. Those who had dementia (or CIND) or reached the end of follow-up during the lipid variability measurement period were excluded from the analysis for dementia (or CIND). Participants were censored if they experienced the event of interest (dementia for the dementia analysis and CIND for the CIND analysis), reached the end of follow-up, or died, whichever occurred first. For cognitive change, the follow-up started from baseline by assuming a bidirectional relationship between cholesterol fluctuation and cognitive change.

Statistical Analysis

Baseline descriptive statistics are presented as medians (interquartile range; IQR) for continuous variables and frequency (percentage) for categorical variables. To better show the cumulative magnitude of lipid fluctuations, we calculated the total year-over-year absolute change in lipid levels during the variability measurement period (|year 1 lipid level – baseline lipid level | + | year 2 lipid level – year 1 lipid level | + | year 3 lipid level – year 2 lipid level|) and the absolute change between the fourth and the first measurement, stratified by each lipid metric quartile and use of lipid-lowering medications.

We used Cox proportional hazards regression models to assess the association with subsequent incident dementia and CIND: model 1 was adjusted for baseline sex and age; model 2 was adjusted for sex, age, baseline race/country, body mass index (BMI) categories, smoking status and alcohol consumption, years of education, systolic and diastolic blood pressure (SBP/DBP), use of antihypertensive and lipid-lowering medication, diabetes, chronic kidney disease, family history of dementia, Fried frailty criteria,[32] randomized treatment assignment (aspirin/placebo), and 3MS Examination score, as well as mean values of TC, HDL-c, and triglycerides from baseline through year 3. For brevity, we only report model 2 results in the following text. Lipid variability was modeled as either a categorical (by quartiles) or a continuous (per 1-SD increase) variable. For the primary analysis of dementia, cumulative incidence curves were plotted by the quartiles of each individual lipid variability. Subgroup analysis was performed by age, sex, BMI categories, smoking status, alcohol consumption, education, hypertension, chronic kidney disease, lipid-lowering medication use, diabetes, randomized treatment (aspirin/placebo), family history of dementia, *APOE* ε4 carrier status, 3MS Examination score (below/above median), and frailty status (analysis was not performed for race and country because of <20 dementia events in US and non-Caucasian participants). Restricted cubic splines with 3 prespecified knots based on Harrell recommended percentiles (10th, 50th, 90th) were plotted to visualize the potentially nonlinear association between lipid variability and incident dementia. To aid in interpretation, we also assessed whether the association with dementia was moderated by the overall trend of lipid fluctuation (ascending/descending) and

the baseline values (low, medium, high by tertile). The ascending (descending) trend was defined as a higher (lower) lipid level at year 3 than at the baseline.

To assess the association between lipid variability and cognitive change over time, we used a linear mixed-effect model for repeated measures over time including random effect for participants and fixed effects of time (visit), lipid variability, the interaction between lipid variability and visit, and covariates.

Two ancillary analyses were performed. First, we repeated all analyses in participants who initiated or discontinued their lipid-lowering treatment during the time of lipid variability measurements, so as to compare the impact of drug-induced and no drug-induced changes in lipid values on risks of neurocognitive outcomes. Second, we replaced the lipid variability with mean value of each lipid metric measured from baseline through year 3, to investigate whether the mean values also associate with risk of our study end points.

Four sensitivity analyses were conducted. First, we further adjusted for SBP and DBP variability from baseline to year 3 in the outcome models to explore the existence of indication bias (e.g., hemodynamic disturbance caused by progression of morbidities or declined physiologic reserve). Second, we further adjusted for BMI change from baseline to year 3 to explore whether the association between lipid variability and dementia risk is a result of reverse causality. Early-stage dementia commonly leads to unintentional weight loss due to changes in dietary habits that could potentially influence lipid levels. Third, we further adjusted for *APOE* ε4 carrier status in the model (data available in 83% of participants), the strongest genetic risk factor of Alzheimer disease (AD), to examine the robustness of findings from our main analysis. Last, we repeated the outcome analyses excluding 35 participants who developed stroke before year 3 because this group was at a higher risk of dementia.

All analyses were performed using Stata/SE version 17.0 (StataCorp., College Station, TX) and were 2-sided. *p* Values less than 0.05 were considered statistically significant for main analyses of associations with dementia and CIND. An adjustment for multiple comparisons was made for the cognition analysis and subgroup analyses to reduce type I error in which case a *p* value less than 0.01 (0.05/5) and 0.003 (0.05/15) was considered statistically significant, respectively.

Data Availability

Requests for data access can be made through the ASPREE Principal Investigators with details for applications provided online.[33,34]

Results

Baseline Characteristics

Of the 19,114 ASPREE participants, we excluded 2,630 who started/ceased lipid-lowering medications, 3,402 who stopped follow-up before year 3, and 3,236 with missing data on lipids. The remaining 9,846 participants were included in the analytic cohort (median [IQR] age: 73.9 [71.7–77.3] years, 54.9% female). Participant selection flowchart is presented in eFigure 2. Table 1 presents the baseline characteristics of the entire cohort and subgroups based on TC variability. Participants in the lower TC variability quartiles were more likely to have a higher education level, lower baseline TC and triglyceride levels, and fewer diabetes and frailty and less likely to use lipid-lowering medications. Baseline characteristics including lipids and cognition were comparable between the included participants and those who were excluded because of missing data on lipids (eTable 1).

The cumulative annual absolute change in each lipid metric and the absolute change between the first and last measurements are presented in eTable 2. In the highest quartile, the total absolute change in TC, LDL-c, HDL-c, and triglycerides was 2.36, 2.07, 0.81, and 1.46 mmol/L, respectively, and the absolute change between the first and last measurement was 1.02, 0.92, 0.35, and 0.57 mmol/L, respectively.

Risk of Incident Dementia

For dementia analysis, 140 participants who had diagnosed dementia, ended follow-up, or died before year 3 were further excluded. After year 3, 509 participants (5%) developed incident dementia during a median (IQR) follow-up of 5.8 (4.5–7.1) years.

Participants in the higher quartile of TC variability had a higher incidence rate of dementia (Q4 vs Q1: 11.3 vs 7.1 cases per 1,000 person-years). Compared with the lowest quartile of TC variability, the risk of dementia in the Q2, Q3, and Q4 was increased by 37%, 44%, and 60%, respectively (p for linear trend = 0.001). Similar to TC variability, there was a stepwise increase in dementia risk with higher quartiles of LDL-c variability, with hazard ratios (HRs) of 1.17, 1.26, and 1.48 for the Q2, Q3, and Q4, respectively (p for linear trend = 0.002) (Table 2). The cumulative incidence curves by the quartiles of TC and LDL-c variability are presented in Figure 1.

Every 1-SD increase in TC and LDL-c variability was associated with a 13% and 12% increased risk of dementia, respectively (p = 0.002 and p = 0.004). Restricted cubic splines revealed a consistently positive relationship between TC and LDL-c variability and dementia risk but no evident association for HDL-c and triglycerides (Figure 2).

When further stratifying the variability groups by the overall trend of lipid fluctuation (descending/ascending trends) and by baseline values (low/medium/high), the results showed that higher TC or LDL-c variability was associated with a greater risk of dementia, regardless of the trend and the baseline values. The risk of dementia seemed to be highest in participants with high TC/LDL-c variability with an ascending trend and a high baseline value over time (Figures 3 and 4). No significant modification by covariates was found (eTable 3).

Table 1 Baseline Characteristics of the Entire Study Cohort and by the Quartiles of Total Cholesterol Variability

	Total (n = 9,846)	Q1 (n = 2,463)	Q2 (n = 2,460)	Q3 (n = 2,463)	Q4 (n = 2,460)
Age, y, median (IQR)	73.9 (71.7–77.3)	73.9 (71.7–77.6)	73.9 (71.7–77.2)	73.9 (71.7–77.1)	74.0 (71.7–77.1)
Female, n (%)	5,409 (54.9)	1,374 (55.8)	1,369 (55.7)	1,296 (52.6)	1,370 (55.7)
Country/race, n (%)					
Australia-White	9,350 (95.0)	2,336 (94.8)	2,336 (95.0)	2,365 (96.0)	2,313 (94.0)
United States-White	118 (1.2)	27 (1.1)	33 (1.3)	24 (1.0)	34 (1.4)
Others	378 (3.8)	100 (4.1)	91 (3.7)	74 (3.0)	113 (4.6)
Smoking status, n (%)					
Never	5,684 (57.7)	1,463 (59.4)	1,451 (59.0)	1,370 (55.6)	1,400 (56.9)
Past	3,901 (39.6)	935 (38.0)	947 (38.5)	1,033 (41.9)	986 (40.1)
Current	261 (2.7)	65 (2.6)	62 (2.5)	60 (2.4)	74 (3.0)
Drinking status, n (%)					
Never	1,646 (16.7)	412 (16.7)	408 (16.6)	408 (16.6)	418 (17.0)
Past	453 (4.6)	97 (3.9)	108 (4.4)	112 (4.6)	136 (5.5)
Current	7,747 (78.7)	1,954 (79.3)	1,944 (79.0)	1,943 (78.9)	1,906 (77.5)
Education, ≥12 y, n (%)	4,986 (50.6)	1,294 (52.5)	1,246 (50.7)	1,239 (50.3)	1,207 (49.1)
Family history of dementia, n (%)	2,454 (24.9)	606 (24.6)	616 (25.0)	622 (25.3)	610 (24.8)
BMI categories, n (%)					
Underweight (<18.5 kg/m^2)	165 (1.7)	41 (1.7)	50 (2.0)	37 (1.5)	37 (1.5)
Normal (18.5–24.9 kg/m^2)	2,433 (24.7)	617 (25.1)	625 (25.4)	622 (25.3)	569 (23.1)
Overweight (25–29.9 kg/m^2)	4,465 (45.4)	1,104 (44.8)	1,132 (46.0)	1,124 (45.6)	1,105 (44.9)
Obese (≥30 kg/m^2)	2,742 (27.9)	691 (28.1)	640 (26.0)	665 (27.0)	746 (30.3)
Diabetes, n (%)	887 (9.0)	183 (7.4)	195 (7.9)	194 (7.9)	315 (12.8)
CKD, n (%)	2,216 (24.0)	506 (21.8)	540 (23.5)	536 (23.2)	634 (27.4)
SBP, mean ± SD	139.5 ± 16.4	139.4 ± 16.4	139.7 ± 16.5	139.1 ± 16.2	139.7 ± 16.3
DBP, mean ± SD	77.5 ± 9.9	77.5 ± 10.0	77.6 ± 9.9	77.3 ± 9.8	77.3 ± 9.9
TC, median (IQR)	5.2 (4.6–5.9)	5.1 (4.6–5.8)	5.2 (4.6–5.8)	5.3 (4.6–5.9)	5.3 (4.6–6.1)
LDL-c, median (IQR)	3.0 (2.5–3.6)	3.0 (2.5–3.5)	3.0 (2.5–3.5)	3.0 (2.5–3.6)	3.1 (2.5–3.8)
HDL-c, median (IQR)	1.5 (1.3–1.8)	1.6 (1.3–1.9)	1.5 (1.3–1.9)	1.5 (1.3–1.8)	1.5 (1.2–1.9)
Triglycerides, median (IQR)	1.2 (0.9–1.6)	1.1 (0.8–1.5)	1.1 (0.9–1.5)	1.2 (0.9–1.6)	1.3 (0.9–1.7)
Antihypertensives, n (%)	5,023 (51.0)	1,218 (49.5)	1,243 (50.5)	1,231 (50.0)	1,331 (54.1)
Lipid-lowering medications, n (%)	3,152 (32.0)	683 (27.7)	722 (29.4)	731 (29.7)	1,016 (41.3)
Frailty status, n (%)					
No frail	6,250 (63.5)	1,566 (63.6)	1,583 (64.4)	1,605 (65.2)	1,496 (60.8)
Prefrail	3,441 (35.0)	867 (35.2)	835 (33.9)	823 (33.4)	916 (37.2)
Frail	155 (1.6)	30 (1.2)	42 (1.7)	35 (1.4)	48 (2.0)
Randomized aspirin, n (%)	4,901 (49.8)	1,226 (49.8)	1,194 (48.5)	1,241 (50.4)	1,240 (50.4)
3MS Examination score, mean ± SD	93.7 (4.4)	93.8 (4.4)	93.7 (4.4)	93.7 (4.5)	93.5 (4.5)

Abbreviations: 3MS = Modified Mini-Mental State; BMI = body mass index; DBP = diastolic blood pressure; HDL-c = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-c = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol.
Quartile 1 (Q1) through quartile 4 (Q4) indicate ascending quartiles of TC variability. CKD[24] was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 or urinary albumin-to-creatinine ratio ≥3 mg/mmol. "Prefrail" included anyone with 1 or 2 criteria, and "Frail" included anyone with 3 or more criteria of the adapted Fried frailty criteria,[32] including body weight, strength, exhaustion, walking speed, and physical activity.

Table 2 Association Between Lipid Variability and Risk of Incident Dementia and CIND

	Dementia			CIND		
		HR (95% CI)			HR (95% CI)	
	Events/total (IR)	Model 1	Model 2	Events/total (IR)	Model 1	Model 2
TC variability (mean = 0.39)						
Categorical by quartiles						
Q1 (<0.22)	98/2,437 (7.1)	1 ref	1 ref	440/1,794 (47.1)	1 ref	1 ref
Q2 (0.22–<0.33)	128/2,430 (9.3)	1.35 (1.03–1.75)	1.37 (1.05–1.78)	435/1,789 (47.0)	1.02 (0.90–1.17)	1.01 (0.89–1.16)
Q3 (0.33–<0.46)	136/2,431 (9.8)	1.44 (1.11–1.87)	1.44 (1.11–1.87)	425/1,784 (45.6)	1.01 (0.88–1.15)	0.99 (0.86–1.13)
Q4 (≥0.46)	147/2,408 (11.3)	1.67 (1.30–2.16)	1.60 (1.23–2.08)	460/1,685 (54.4)	1.27 (1.11–1.45)	1.23 (1.08–1.41)
***p* for linear trend**		<0.001	0.001		0.001	0.007
Continuous						
Per 1-SD (0.26) increase		1.15 (1.07–1.24), $p < 0.001$	1.13 (1.05–1.23), $p = 0.002$		1.08 (1.04–1.13), $p < 0.001$	1.07 (1.02–1.12), $p = 0.005$
LDL-c variability (mean = 0.34)						
Categorical by quartiles						
Q1 (<0.20)	109/2,437 (7.9)	1 ref	1 ref	410/1,794 (43.8)	1 ref	1 ref
Q2 (0.20–<0.29)	123/2,430 (8.9)	1.16 (0.90–1.50)	1.17 (0.90–1.52)	464/1,789 (50.8)	1.21 (1.06–1.38)	1.22 (1.06–1.39)
Q3 (0.29–<0.41)	124/2,431 (9.2)	1.22 (0.95–1.58)	1.26 (0.97–1.63)	416/1,784 (45.5)	1.11 (0.96–1.27)	1.10 (0.96–1.26)
Q4 (≥0.41)	153/2,408 (11.5)	1.53 (1.20–1.96)	1.48 (1.15–1.91)	470/1,685 (53.7)	1.31 (1.15–1.50)	1.27 (1.11–1.46)
***p* for linear trend**		0.001	0.002		0.001	0.004
Continuous						
Per 1-SD (0.24) increase		1.13 (1.05–1.22), $p = 0.001$	1.12 (1.04–1.22), $p = 0.004$		1.09 (1.04–1.13), $p < 0.001$	1.07 (1.03–1.12), $p = 0.002$
HDL-c variability (mean = 0.14)						
Categorical by quartiles						
Q1 (<0.09)	135/2,437 (9.7)	1 ref	1 ref	444/1,794 (46.5)	1 ref	1 ref
Q2 (0.09–<0.13)	127/2,430 (9.1)	0.95 (0.75–1.21)	0.95 (0.74–1.21)	426/1,789 (45.7)	0.99 (0.87–1.13)	0.98 (0.86–1.12)
Q3 (0.13–<0.17)	118/2,431 (8.8)	0.90 (0.70–1.15)	0.88 (0.69–1.13)	444/1,784 (50.0)	1.06 (0.93–1.21)	1.04 (0.91–1.18)
Q4 (≥0.17)	129/2,408 (9.8)	1.04 (0.82–1.32)	1.03 (0.80–1.31)	446/1,685 (51.6)	1.12 (0.98–1.28)	1.07 (0.94–1.22)

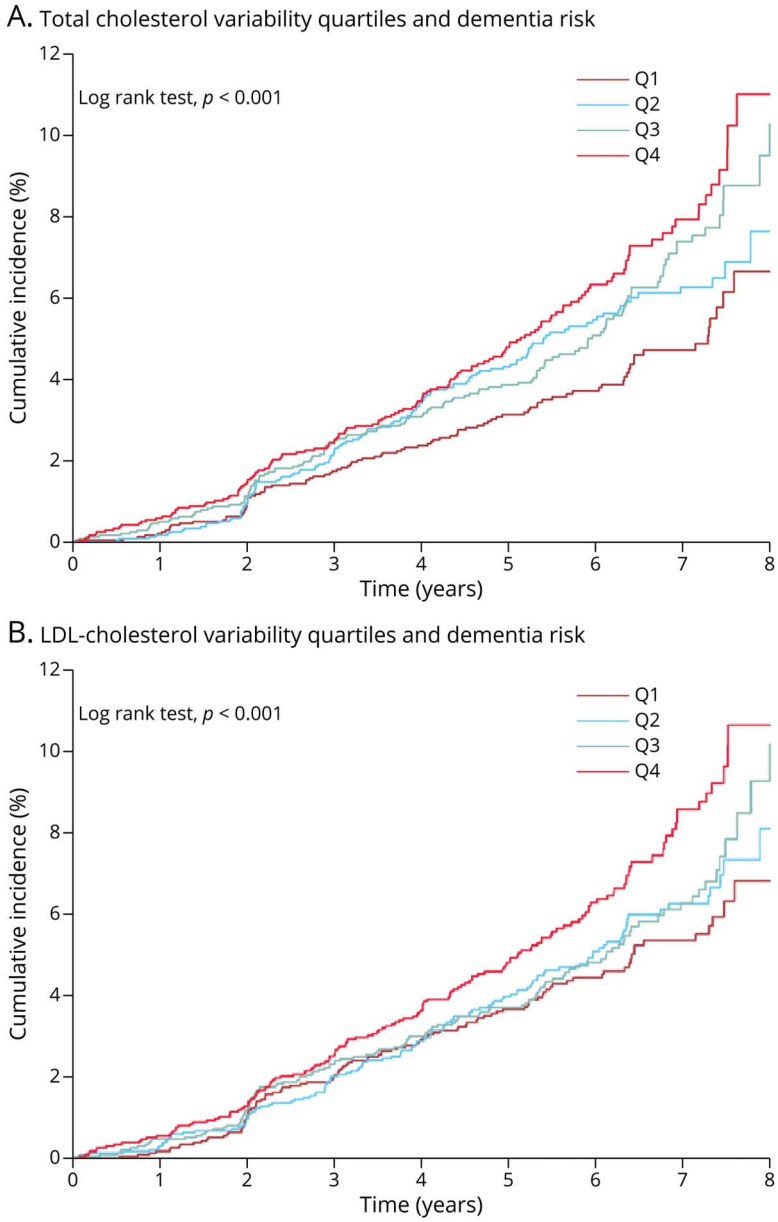
Continued

Table 2 Association Between Lipid Variability and Risk of Incident Dementia and CIND *(continued)*

	Dementia			CIND		
		HR (95% CI)			HR (95% CI)	
	Events/total (IR)	Model 1	Model 2	Events/total (IR)	Model 1	Model 2
***p* for linear trend**		0.90	0.99		0.06	0.23
Continuous						
Per 1-SD (0.08) increase		1.01 (0.92–1.10), $p = 0.84$	1.01 (0.92–1.10), $p = 0.91$		1.05 (0.999–1.10), $p = 0.06$	1.03 (0.98–1.08), $p = 0.18$
Triglyceride variability (mean = 0.25)						
Categorical by quartiles						
Q1 (<0.16)	128/2,437 (9.2)	1 ref	1 ref	430/1,794 (45.8)	1 ref	1 ref
Q2 (0.16–<0.24)	115/2,430 (8.4)	0.92 (0.72–1.19)	0.95 (0.74–1.23)	431/1,789 (47.1)	1.07 (0.94–1.22)	1.07 (0.94–1.23)
Q3 (0.24–<0.32)	138/2,431 (10.2)	1.14 (0.90–1.45)	1.14 (0.89–1.45)	445/1,784 (50.1)	1.16 (1.01–1.32)	1.15 (1.01–1.32)
Q4 (≥0.32)	128/2,408 (9.5)	1.11 (0.87–1.42)	1.14 (0.89–1.46)	454/1,685 (50.7)	1.21 (1.06–1.38)	1.19 (1.04–1.36)
***p* for linear trend**		0.19	0.15		0.002	0.005
Continuous						
Per 1-SD (0.12) increase		1.05 (0.96–1.15), $p = 0.27$	1.06 (0.97–1.15), $p = 0.21$		1.08 (1.03–1.13), $p = 0.001$	1.08 (1.03–1.13), $p = 0.003$

Abbreviations: 3MS = Modified Mini-Mental State; CIND = cognitive impairment with no dementia; HDL-c = high-density lipoprotein cholesterol; HR = hazard ratio; IR = incidence rate; LDL-c = low-density lipoprotein cholesterol; TC = total cholesterol.
Quartile 1 (Q1) through quartile 4 (Q4) indicate ascending quartiles of each lipid variability independent of the mean. IR was incident events per 1,000 person-years. Model 1: adjusting for age and sex; model 2: adjusting for age, sex, race/country, body mass index categories, smoking status and alcohol consumption, years of education, systolic and diastolic blood pressure, use of antihypertensive and lipid-lowering medication, diabetes, chronic kidney disease, family history of dementia, Fried frailty, randomized treatment assignment (aspirin/placebo), and 3MS Examination score, as well as mean values of TC, HDL-c, and triglycerides through baseline to year 3. *p* Values for linear trend were calculated with each lipid variability quartile modeled as a continuous variable.

Figure 1 Cumulative Incidence Curves for Incident Dementia by the Quartiles of Total Cholesterol and LDL Cholesterol



(A and B) The cumulative incidence rate of dementia event occurring after the variability measurement period (from year 3) by quartile groups of total cholesterol and LDL cholesterol variability. Participants in the higher quartile groups (greater variability) had a higher rate of incident dementia events over a maximum of 8-year follow-up. LDL = low-density lipoprotein.

No significant association with incident dementia was observed for HDL-c and triglycerides (Table 2, Figures 1 and 2).

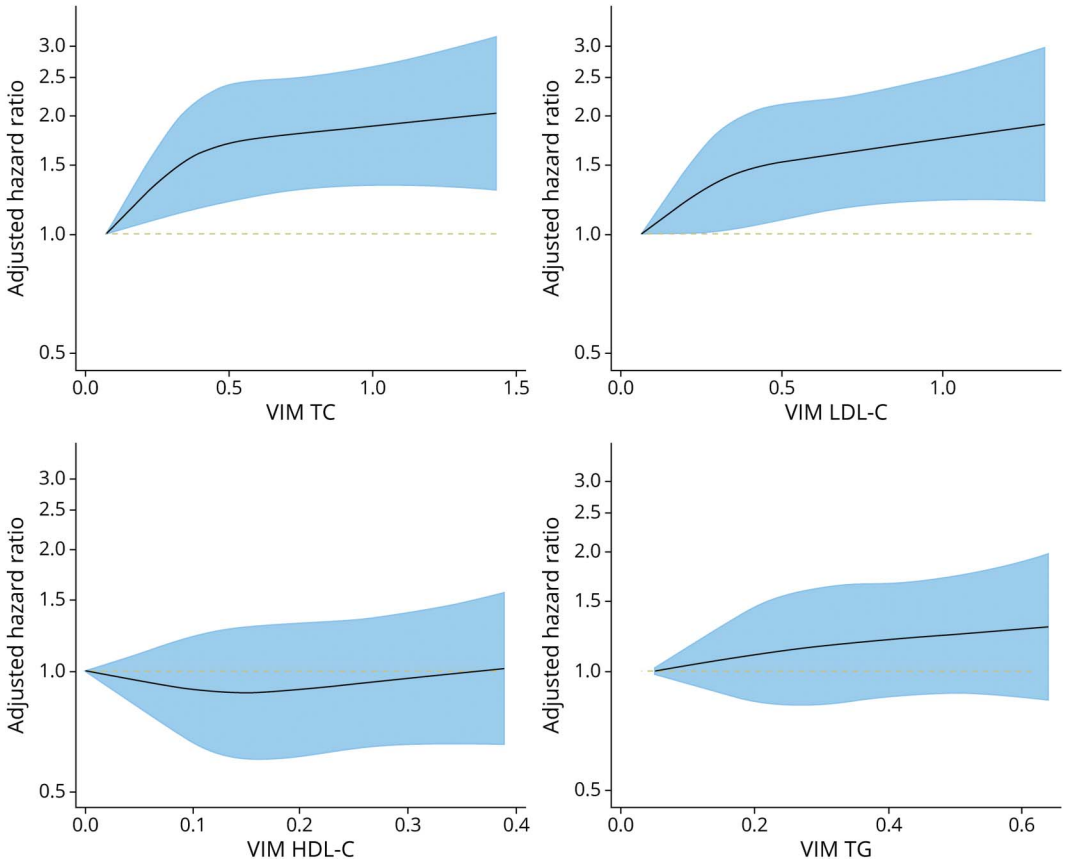
Risk of Incident CIND

After excluding 2,794 who developed CIND, ended follow-up, or died before year 3 or had a baseline cognitive score lower than 1.5 SD compared with the overall population, 7,052 were included in the CIND analysis. 1,760 incident CIND cases (25%) were identified from year 3 during a median (IQR) follow-up of 5.4 (4.1–6.5) years. Participants in the highest quartile of TC and LDL-c variability had the greatest risk of CIND, with HRs of 1.23 (95% CI 1.08–1.41) and 1.27 (1.11–1.46) when compared with the lowest quartile. Higher quartiles of triglyceride variability were also associated with a greater risk of CIND. Per 1-SD increase in the variability of TC, LDL-c, and triglycerides was associated with a respective 7%, 7%, and 8% increased risk of CIND. There was no association between HDL-c variability and CIND (Table 2).

Cognitive Change Over Time

Table 3 lists the results of the association between lipid variability and change in each cognitive domain and their composite over time with a maximum follow-up of 11 years (mean measurement times: 5–7 times across domains). Compared with the lowest quartile, higher quartiles of TC and LDL-c variability were associated with a more rapid decline in global cognition, episodic memory, and psychomotor speed as well as the composite cognition ($p < 0.001$), but not in language and executive function. No significant association with cognitive change was found for HDL-c variability or triglyceride variability, except for

Figure 2 Restricted Cubic Splines for Dementia Associated With Individual Lipid Variability



Restricted cubic splines with 3 prespecified knots based on Harrell recommended percentiles (10th, 50th, 90th) were plotted to visualize the potentially nonlinear association between lipid variability and incident dementia. HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VIM = variability independent of the mean.

a negative association between quartiles of HDL-c variability and composite cognition (p for linear trend = 0.009). However, when analyzing HDL-c variability on a continuous scale, the risk estimate became nonsignificant (p = 0.01).

Ancillary Analysis

Analysis limiting to participants who initiated or ceased their lipid-lowering medications found no significant association between lipid variability, dementia, CIND, and cognitive change over time, suggesting a differentiated role between natural and artificial fluctuation of TC and LDL-c in neurocognition and dementia risk (eTables 4 and 5). The variability in TC and LDL-c in participants who switched lipid-lowering medication was almost doubled than in the included participants (Table 2). The mean value of lipids from baseline through year 3 was not associated with risk of any outcome, except for the association of mean TC and HDL-c with change in the composite cognitive score over time (eTables 6 and 7).

Sensitivity Analysis

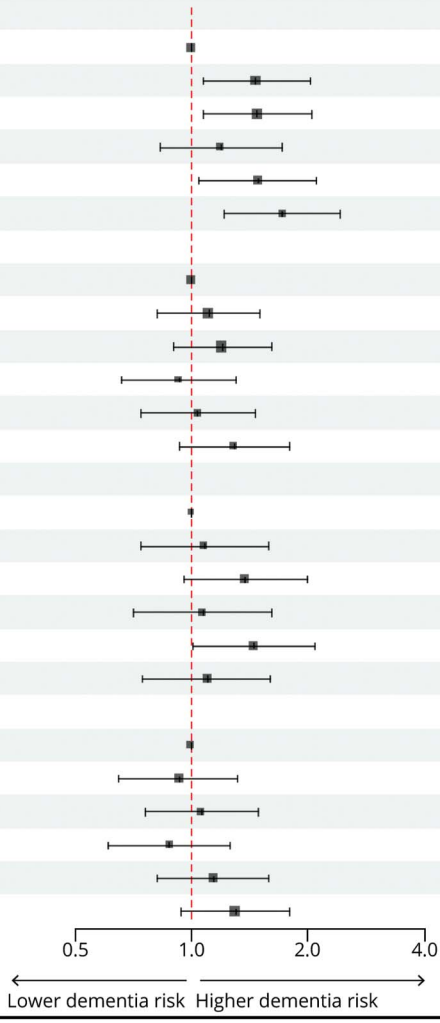
Repeating the analysis by further adjusting for SBP and DBP variability or BMI change from baseline through year 3 yielded results similar to the main analysis, suggesting a low probability that our finding is affected by indication bias or reverse causality (eTables 8 and 9). Adjusting for *APOE* ε4 carrier status and excluding participants with the stroke events before year 3 also yielded similar results as our main analysis (eTables 10 and 11).

Discussion

In this post hoc analysis of 9,846 initially healthy older adults free of dementia and major cognitive impairment, higher TC and LDL-c variability was associated with a greater risk of dementia (median follow-up: 5.8 years), CIND (median follow-up: 5.4 years), and faster cognitive decline over time (mean measurement times: 5–7 times across domains). The associations were independent of the overall trend of cholesterol fluctuation and baseline levels and were not modified by study covariates. No significant association was found between variability in HDL-c and triglycerides, dementia, and cognitive change over time. However, higher triglyceride variability seemed to be associated with increased risk of CIND. No association with any outcome was found for possibly drug-induced variations in lipids and the mean value of lipids during the variability measurement period. Our study suggests that cholesterol variability may represent a novel

Figure 3 Association Between Lipid Variability and Dementia, Stratified by Trend of Lipid Change Between Baseline and Year 3

Lipid metric	N	Event number (incidence rate)	Adjusted HR (95% CI)
Total cholesterol			
Descending trend/low variability (Ref)	1,531	60 (6.9)	1.00 (1.00 – 1.00)
Descending trend/medium variability	1,729	102 (10.0)	1.47 (1.07 – 2.03)
Descending trend/high variability	1,865	106 (10.2)	1.48 (1.07 – 2.04)
Ascending trend/low variability	1,278	58 (8.0)	1.19 (0.83 – 1.71)
Ascending trend/medium variability	1,269	69 (9.6)	1.49 (1.05 – 2.11)
Ascending trend/high variability	1,269	76 (11.0)	1.72 (1.22 – 2.43)
LDL cholesterol			
Descending trend/low variability (Ref)	1,571	80 (9.0)	1.00 (1.00 – 1.00)
Descending trend/medium variability	1,769	93 (9.2)	1.11 (0.82 – 1.50)
Descending trend/high variability	1,972	116 (10.6)	1.20 (0.90 – 1.61)
Ascending trend/low variability	1,202	54 (7.9)	0.93 (0.66 – 1.31)
Ascending trend/medium variability	1,209	57 (8.4)	1.04 (0.74 – 1.47)
Ascending trend/high variability	1,155	70 (11.1)	1.29 (0.93 – 1.79)
HDL cholesterol			
Descending trend/low variability (Ref)	1,011	45 (7.8)	1.00 (1.00 – 1.00)
Descending trend/medium variability	1,323	65 (8.6)	1.08 (0.74 – 1.58)
Descending trend/high variability	1,429	85 (10.9)	1.38 (0.96 – 1.99)
Ascending trend/low variability	1,058	49 (8.1)	1.07 (0.71 – 1.61)
Ascending trend/medium variability	1,405	87 (11.1)	1.45 (1.01 – 2.09)
Ascending trend/high variability	1,518	70 (8.2)	1.10 (0.75 – 1.60)
Triglycerides			
Descending trend/low variability (Ref)	1,228	61 (8.8)	1.00 (1.00 – 1.00)
Descending trend/medium variability	1,398	63 (8.0)	0.93 (0.65 – 1.32)
Descending trend/high variability	1,461	75 (9.1)	1.06 (0.76 – 1.49)
Ascending trend/low variability	1,301	58 (8.0)	0.88 (0.61 – 1.26)
Ascending trend/medium variability	1,502	87 (10.3)	1.14 (0.82 – 1.59)
Ascending trend/high variability	1,586	96 (10.9)	1.30 (0.94 – 1.79)



A total of 705, 828, 1,962, and 1,230 participants with identical total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride values at baseline and year 3 were excluded from their respective analyses. HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein.

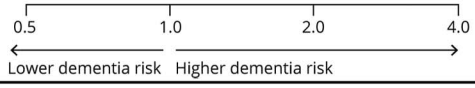
biomarker or risk factor for identifying older individuals at risk of dementia, outperforming the actual lipid values.

Previous studies mainly focused on the relationship between visit-to-visit (time intervals varied between visits ranging from several months to years) cholesterol variability and risk of major adverse cardiovascular events and death.[35-37] Only a handful of studies have investigated the relationship between lipid variability and neurocognitive outcomes.[12-17] None of them has distinguished the change in lipids with and without drug-induced alternation, which are expected to have a distinct role in dementia risk. Other limitations of historical studies include a short follow-up, inclusion of younger adults, using 3 measurements to construct variability index, small sample sizes, lack of administrating cognitive assessments, and ascertainment of dementia outcomes.

By analyzing data from 4,428 dementia-free participants older than 70 years with high CVD risk, a post hoc analysis of the PROSPER trial (PROspective Study of Pravastatin in the Elderly at Risk) reported that higher visit-to-visit variability in LDL-c was associated with worsened attention, processing speed, and memory over a 2.5-year follow-up, independent of mean LDL-c levels and use of statins.[13] Its subcohort analysis on 535 participants with brain MRI data found that higher LDL-c variability was associated with a slower cerebral blood flow and greater white matter hyperintensity volume. More recently, a cohort study including 11,571 individuals aged 60 years or older who were free of AD and AD-related dementia (ADRD) found that the highest quintile of variability for TC and triglycerides was associated with the greatest risk of incident AD/ADRD over 10 years.[12] However, this study used linkage data and International Classification of Diseases

Figure 4 Association Between Lipid Variability and Dementia, Stratified by Tertile of Baseline Values

Lipid metric	N	Event number (incidence rate)	Adjusted HR (95% CI)
Total cholesterol			
Low baseline value/low variability (Ref)	1,173	54 (8.2)	1.00 (1.00 – 1.00)
Low baseline value/medium variability	1,088	64 (10.5)	1.38 (0.96 – 1.99)
Low baseline value/high variability	1,099	69 (11.6)	1.40 (0.98 – 2.01)
Medium baseline value/low variability	1,144	50 (7.7)	1.02 (0.67 – 1.55)
Medium baseline value/medium variability	1,110	59 (9.3)	1.16 (0.78 – 1.73)
Medium baseline value/high variability	947	46 (8.9)	1.15 (0.76 – 1.75)
High baseline value/low variability	930	36 (6.7)	0.86 (0.51 – 1.46)
High baseline value/medium variability	1,039	58 (9.8)	1.33 (0.82 – 2.15)
High baseline value/high variability	1,176	73 (11.1)	1.51 (0.97 – 2.37)
LDL cholesterol			
Low baseline value/low variability (Ref)	1,267	59 (8.3)	1.00 (1.00 – 1.00)
Low baseline value/medium variability	1,171	68 (10.5)	1.41 (0.99 – 2.01)
Low baseline value/high variability	1,153	73 (11.6)	1.42 (1.00 – 2.02)
Medium baseline value/low variability	1,100	47 (7.5)	0.98 (0.65 – 1.49)
Medium baseline value/medium variability	1,048	45 (7.6)	1.04 (0.68 – 1.59)
Medium baseline value/high variability	894	48 (9.8)	1.29 (0.85 – 1.94)
High baseline value/low variability	884	48 (9.5)	1.28 (0.78 – 2.10)
High baseline value/medium variability	1,012	52 (8.9)	1.30 (0.80 – 2.12)
High baseline value/high variability	1,177	69 (10.5)	1.46 (0.93 – 2.27)
HDL cholesterol			
Low baseline value/low variability (Ref)	1,391	68 (8.6)	1.00 (1.00 – 1.00)
Low baseline value/medium variability	1,386	69 (8.9)	0.98 (0.70 – 1.37)
Low baseline value/high variability	1,324	69 (9.4)	1.05 (0.75 – 1.47)
Medium baseline value/low variability	945	47 (8.7)	0.98 (0.65 – 1.46)
Medium baseline value/medium variability	852	45 (9.3)	1.02 (0.68 – 1.54)
Medium baseline value/high variability	778	44 (10.3)	1.13 (0.75 – 1.70)
High baseline value/low variability	928	53 (10.2)	0.92 (0.56 – 1.50)
High baseline value/medium variability	994	61 (10.7)	0.99 (0.62 – 1.59)
High baseline value/high variability	1,108	53 (8.7)	0.88 (0.55 – 1.41)
Triglycerides			
Low baseline value/low variability (Ref)	1,318	74 (10.0)	1.00 (1.00 – 1.00)
Low baseline value/medium variability	1,295	67 (9.2)	0.96 (0.96 – 1.34)
Low baseline value/high variability	1,353	79 (10.5)	1.16 (0.84 – 1.60)
Medium baseline value/low variability	953	50 (9.4)	1.04 (0.71 – 1.53)
Medium baseline value/medium variability	952	52 (10.0)	1.16 (0.79 – 1.71)
Medium baseline value/high variability	839	44 (9.3)	1.11 (0.74 – 1.68)
High baseline value/low variability	980	40 (7.2)	0.91 (0.56 – 1.49)
High baseline value/medium variability	1,013	44 (7.7)	0.97 (0.60 – 1.56)
High baseline value/high variability	1,029	59 (10.2)	1.28 (0.83 – 1.98)



The mean (SD, range) of low, medium, and high baseline values for total cholesterol was 4.3 (0.5, 2.2–4.8), 5.2 (0.2, 4.9–5.6), and 6.3 (0.6, 5.7–10.3) mmol/L; for LDL cholesterol was 2.2 (0.4, 0.6–2.7), 3.1 (0.2, 2.8–3.4), and 4.0 (0.5, 3.5–7.5) mmol/L; for HDL cholesterol was 1.2 (0.2, 0.1–1.4), 1.6 (0.1, 1.5–1.7), and 2.1 (0.3, 1.8–5.6) mmol/L; and for triglyceride was 0.8 (0.2, 0.1–1.0), 1.2 (0.1, 1.1–1.4), and 2.0 (0.5, 1.5–4.5) mmol/L. HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein.

codes to ascertain dementia cases, which may lead to underdiagnosis. The time interval between each lipid measurement is not fixed (could vary from days to years) that might influence the results. Because AD/ADRD progresses along a continuum from subclinical disease to mild cognitive impairment to clinically manifested AD, our results support this study and extend the findings to include an association between lipid variability and cognitive changes that may precede the development of dementia.

The mechanisms underlying the association between cholesterol variability and dementia are uncertain. Several hypotheses are proposed. One proposed hypothesis is that fluctuations in cholesterol levels might be an epiphenomenon accompanying chronic diseases linking to an increased risk of dementia, potentially due to disrupted homeostasis.[37] This hypothesis was supported by our subgroup analysis observing the stronger association between TC variability and incident dementia in prefrail/frail participants. Variation

Table 3 Association Between Lipid Variability and Cognitive Change Over Time

Cognitive test	Model	Coefficient (95% CI) for time × quartile			*p* Value for linear trend	Coefficient (95% CI) for time × continuous lipid variability metric	*p* Value
		Second quartile	Third quartile	Fourth quartile			
Total cholesterol variability							
Global cognition	Age/sex	0.008 (−0.019 to 0.035)	−0.023 (−0.050 to 0.004)	−0.044 (−0.071 to −0.016)	<0.001**	−0.079 (−0.117 to −0.041)	<0.001**
	Full	0.008 (−0.019 to 0.035)	−0.022 (−0.049 to 0.005)	−0.044 (−0.071 to −0.016)	<0.001**	−0.078 (−0.116 to −0.040)	<0.001**
Language and execution function	Age/sex	0.011 (−0.012 to 0.034)	0.008 (−0.015 to 0.031)	−0.024 (−0.047 to −0.000)	0.06	−0.019 (−0.052 to 0.013)	0.24
	Full	0.010 (−0.013 to 0.033)	0.009 (−0.014 to 0.032)	−0.024 (−0.047 to −0.0002)	0.07	−0.019 (−0.051 to 0.013)	0.25
Psychomotor speed	Age/sex	−0.011 (−0.054 to 0.032)	−0.018 (−0.061 to 0.025)	−0.045 (−0.089 to −0.001)	0.05	−0.114 (−0.174 to −0.053)	<0.001**
	Full	−0.011 (−0.055 to 0.032)	−0.016 (−0.059 to 0.027)	−0.044 (−0.087 to 0.000)	0.06	−0.111 (−0.171 to −0.051)	<0.001**
Episodic memory	Age/sex	−0.007 (−0.020 to 0.007)	−0.006 (−0.020 to 0.007)	−0.030 (−0.044 to −0.016)	<0.001**	−0.038 (−0.057 to −0.019)	<0.001**
	Full	−0.007 (−0.020 to 0.007)	−0.006 (−0.019 to 0.008)	−0.030 (−0.044 to −0.016)	<0.001**	−0.038 (−0.057 to −0.019)	<0.001**
Composite	Age/sex	−0.0002 (−0.003 to 0.003)	−0.001 (−0.004 to 0.002)	−0.007 (−0.010 to −0.005)	<0.001**	−0.010 (−0.014 to −0.006)	<0.001**
	Full	−0.0002 (−0.003 to 0.003)	−0.001 (−0.004 to 0.002)	−0.007 (−0.010 to −0.004)	<0.001**	−0.009 (−0.013 to −0.006)	<0.001**
LDL-c variability							
Global cognition	Age/sex	−0.005 (−0.033 to 0.022)	−0.032 (−0.060 to −0.005)	−0.045 (−0.073 to −0.018)	<0.001**	−0.090 (−0.132 to −0.049)	<0.001**
	Full	−0.005 (−0.032 to 0.022)	−0.032 (−0.059 to −0.005)	−0.045 (−0.072 to −0.017)	<0.001**	−0.089 (−0.131 to −0.047)	<0.001**
Language and execution function	Age/sex	0.003 (−0.020 to 0.025)	−0.003 (−0.026 to 0.020)	−0.016 (−0.039 to 0.008)	0.17	−0.006 (−0.041 to 0.030)	0.76
	Full	0.003 (−0.020 to 0.025)	−0.002 (−0.025 to 0.021)	−0.015 (−0.038 to 0.008)	0.20	−0.005 (−0.040 to 0.030)	0.78
Psychomotor speed	Age/sex	−0.037 (−0.080 to 0.006)	−0.011 (−0.054 to 0.033)	−0.066 (−0.109 to −0.022)	0.02	−0.138 (−0.204 to −0.072)	<0.001**
	Full	−0.037 (−0.080 to 0.006)	−0.009 (−0.052 to 0.034)	−0.064 (−0.108 to −0.021)	0.02	−0.135 (−0.201 to −0.069)	<0.001**
Episodic memory	Age/sex	−0.001 (−0.014 to 0.013)	0.002 (−0.011 to 0.016)	−0.028 (−0.042 to −0.014)	<0.001**	−0.047 (−0.068 to −0.026)	<0.001**
	Full	−0.001 (−0.014 to 0.013)	0.003 (−0.011 to 0.016)	−0.028 (−0.042 to −0.014)	<0.001**	−0.047 (−0.068 to −0.026)	<0.001**
Composite	Age/sex	−0.0002 (−0.003 to 0.003)	−0.001 (−0.004 to 0.002)	−0.007 (−0.010 to −0.005)	<0.001**	−0.011 (−0.016 to −0.007)	<0.001**
	Full	−0.001 (−0.004 to 0.001)	−0.001 (−0.003 to 0.002)	−0.007 (−0.010 to −0.005)	<0.001**	−0.011 (−0.015 to −0.007)	<0.001**
HDL-c variability							
Global cognition	Age/sex	−0.007 (−0.035 to 0.020)	0.023 (−0.005 to 0.050)	0.002 (−0.026 to 0.030)	0.40	0.027 (−0.100 to 0.155)	0.67
	Full	−0.008 (−0.035 to 0.019)	0.022 (−0.005 to 0.050)	0.003 (−0.024 to 0.031)	0.35	0.034 (−0.093 to 0.161)	0.60

Continued

Table 3 Association Between Lipid Variability and Cognitive Change Over Time *(continued)*

Cognitive test	Model	Coefficient (95% CI) for time × quartile			*p* Value for linear trend	Coefficient (95% CI) for time × continuous lipid variability metric	*p* Value
		Second quartile	Third quartile	Fourth quartile			
Language and execution function	Age/sex	−0.028 (−0.051 to −0.005)	−0.018 (−0.041 to 0.006)	−0.031 (−0.054 to −0.008)	0.03	−0.134 (−0.241 to −0.027)	0.01
	Full	−0.028 (−0.051 to −0.006)	−0.018 (−0.041 to 0.005)	−0.030 (−0.053 to −0.007)	0.03	−0.132 (−0.239 to −0.025)	0.02
Psychomotor speed	Age/sex	0.036 (−0.007 to 0.079)	0.0003 (−0.043 to 0.043)	−0.035 (−0.078 to 0.009)	0.05	−0.178 (−0.380 to 0.025)	0.09
	Full	0.035 (−0.007 to 0.078)	−0.0004 (−0.044 to 0.043)	−0.034 (−0.077 to 0.010)	0.06	−0.171 (−0.374 to 0.031)	0.10
Episodic memory	Age/sex	−0.008 (−0.021 to 0.006)	−0.016 (−0.296 to −0.002)	−0.016 (−0.030 to −0.002)	0.01	−0.062 (−0.125 to 0.001)	0.05
	Full	−0.008 (−0.022 to 0.005)	−0.016 (−0.296 to −0.002)	−0.015 (−0.029 to −0.002)	0.01	−0.060 (−0.123 to 0.003)	0.06
Composite	Age/sex	−0.001 (−0.004 to 0.001)	−0.002 (−0.005 to 0.001)	−0.004 (−0.007 to −0.001)	0.008*	−0.017 (−0.029 to −0.004)	0.01
	Full	−0.001 (−0.004 to 0.001)	−0.002 (−0.005 to 0.001)	−0.004 (−0.007 to −0.001)	0.009*	−0.016 (−0.029 to −0.003)	0.01
Triglyceride variability							
Global cognition	Age/sex	0.018 (−0.010 to 0.045)	0.001 (−0.027 to 0.028)	0.006 (−0.021 to 0.034)	0.96	0.013 (−0.065 to 0.092)	0.74
	Full	0.018 (−0.010 to 0.045)	0.001 (−0.027 to 0.028)	0.007 (−0.021 to 0.034)	0.94	0.015 (−0.063 to 0.093)	0.70
Language and execution function	Age/sex	−0.010 (−0.033 to 0.013)	−0.005 (−0.028 to 0.018)	−0.003 (−0.026 to 0.020)	0.91	0.0001 (−0.066 to 0.066)	0.996
	Full	−0.010 (−0.033 to 0.013)	−0.005 (−0.028 to 0.018)	−0.002 (−0.025 to 0.021)	0.96	0.003 (−0.062 to 0.069)	0.92
Psychomotor speed	Age/sex	0.010 (−0.033 to 0.053)	−0.028 (−0.072 to 0.015)	−0.015 (−0.059 to 0.028)	0.23	−0.067 (−0.191 to 0.057)	0.29
	Full	0.010 (−0.033 to 0.053)	−0.029 (−0.072 to 0.015)	−0.015 (−0.058 to 0.029)	0.24	−0.063 (−0.187 to 0.060)	0.31
Episodic memory	Age/sex	−0.001 (−0.014 to 0.013)	−0.008 (−0.022 to 0.005)	−0.011 (−0.025 to 0.002)	0.06	−0.027 (−0.066 to 0.012)	0.18
	Full	−0.001 (−0.014 to 0.013)	−0.009 (−0.022 to 0.005)	−0.011 (−0.025 to 0.003)	0.06	−0.026 (−0.065 to 0.013)	0.19
Composite	Age/sex	−0.0001 (−0.003 to 0.003)	−0.002 (−0.004 to 0.001)	−0.0003 (−0.003 to 0.002)	0.55	−0.001 (−0.009 to 0.007)	0.78
	Full	−0.0001 (−0.003 to 0.003)	−0.002 (−0.005 to 0.001)	−0.0003 (−0.003 to 0.002)	0.58	−0.001 (−0.009 to 0.007)	0.83

Abbreviations: HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol.
A Bonferroni-adjusted *p* value was used to account for the multiple testing of 4 cognitive domains and 1 composite cognitive score. $^{**}p < 0.001$, $^{*}p < 0.01$.

in cholesterol levels may serve as a surrogate of body's inability to maintain homeostasis with advancing age and increasing disease burden and, hence, a higher risk of dementia. Adjusting for blood pressure variability and BMI change did not alter our results, suggesting that the cholesterol variability is less likely caused by changes in dietary patterns and hemodynamic disturbance, but other factors such as neuropathologic factors, genetic factors, and physical disability might be at play.

Another possibility is that the association of lipid variability with dementia was moderated by frailty (although not statistically significant), rather than lipid variability being directly influenced or accompanied by it. Previous studies have found that individuals living with frailty and prefrailty had an increased risk of dementia,[38] which means that they are also more likely to be influenced by cholesterol fluctuation on dementia risk. A stronger association between TC variability and dementia risk was also seen in those with family history and who are *APOE* ε4 carriers, the subgroup of participants who are more susceptible to dementia.

Furthermore, our analysis revealed no significant association between mean cholesterol values during the variability measurement period and any of our study end points, which is in line with many previous studies investigating cholesterol measured in late life and dementia risk.[6,7,39] This finding suggests that the instability of cholesterol performs better than actual values in providing insights into individuals' risk of dementia development. Fluctuations in cholesterol levels have been suggested to induce damage on brain vasculature by destabilizing atherosclerotic plaques (primarily composed of LDL-c), altering their composition, and increasing the likelihood of rupture and growth. Consequently, this process could lead to the narrowing or obstruction of cerebral blood vessels.[12,35,40] Epidemiologic evidence supporting this hypothesis comes from studies demonstrating reduced cerebral blood flow in individuals with high LDL-c variability[13] and a significant association between high LDL-c variability and accelerated coronary atheroma progression in patients with atherosclerotic CVD undergoing serial intravascular ultrasonography.[41] These findings might also explain the lack of association between HDL-c and triglyceride variability and dementia. Moreover, cholesterol variation might contribute to cognitive impairment by inducing vascular endothelial dysfunction and a proinflammatory and high oxidative stress milieu that are implicated in the pathologic process of dementia development.[42-44]

Routine screening of lipids in older adults is common in most high-income countries such as Australia and the United States, with the data easily accessible through the electronic medical record system. The feasibility of calculating lipid variability using electronic health records to predict adverse events has been demonstrated.[45] Monitoring cholesterol change over time of older people can help clinicians to identify asymptomatic at-risk individuals who are likely to benefit from the early detection and treatment. Because the causes of cholesterol variability can vary and coexist, it is crucial for clinicians to discern any pathologic factors that contribute to this variation. Our stratified analysis by cholesterol fluctuation and baseline levels, despite reduced statistical power, revealed a dose-dependent relationship between higher cholesterol variability and increased dementia risk, regardless of the trend or baseline values. Individuals with an ascending cholesterol trend and high baseline levels exhibited the highest risk, suggesting that those with suboptimal cholesterol control over time may benefit most from interventions. Such interventions could include lifestyle change and persistent statin use to prevent further cholesterol elevation and potentially reduce dementia risk.

Like variability in other biomarkers, a major limitation of cholesterol variability is its nonstandardized assessment methods. It remains unclear which variability index, measurement frequency, and thresholds would provide best predictability. This might not matter if lipid variability was used as a harbinger of impending adverse neurocognitive outcomes, particularly in high-risk dementia groups, rather than for risk prediction. Future studies may also need to ascertain whether reducing cholesterol variation could translate into neurocognitive benefits.

This study has several limitations. First, although we intentionally excluded participants who initiated or discontinued lipid-lowering agents during the measurement period of lipid variability, it is possible that the variation was caused by nonadherence to lipid-lowering medication or change in dosage.[46] However, because all participants who reported statin use at baseline were likely prevalent users rather than new users, we would expect that dose changes and nonadherence would be less likely to explain lipid variability. Furthermore, owing to our exclusive focus on lipid variability independent of medication effects, our findings are not applicable to individuals who discontinue or initiate statin therapy for whatever reason. Second, clinical trials such as ASPREE are likely to enroll healthier participants compared with the general population regarding burden of frailty, morbidity, and polypharmacy. Whether our study findings are generalizable to broad, unselected groups of older population is unknown. The reasons for lipid fluctuation can vary and coexist, and some may not necessarily contribute to dementia risk. It is also unknown whether the predictive value of lipid variability changes when the underlying reasons differ. Third, the study did not adjust for dietary patterns, physical activity, and other potential confounders that may influence lipid variability and dementia risk. In addition, subgroup analyses and some analyses by lipid quartile may have reduced study power and wide CIs, in which they were unable to rule out clinically meaningful HRs. Last, there remains the potential for reverse causation. However, we have adopted robust analytical approaches to minimize this.

Despite these limitations, our study has several strengths. First, to enhance data accuracy, our study used lipid data from 4 time points to better identify trends and patterns of lipid fluctuations over time while minimizing the impact of random and diurnal variations. Our study investigating year-to-year variability of different lipid metrics over a fixed period of 3 years has made study participants more comparable between each other. This study also benefited from the utilization of high-quality prospective data derived from a large-scale, contemporary randomized trial and its post-trial follow-up phase. The data collection process was executed rigorously and systematically, encompassing fasting lipid levels and other covariates. A lack of dementia history signed off by participants' GP or primary care physician and administering 3MS Examination to every participant at enrollment excluded individuals with possible dementia at baseline, hence minimizing the possibility of reverse causality. Serial neurocognitive testing at baseline and throughout the follow-up period was protocol-driven, and the dementia outcomes were meticulously adjudicated by expert panels.

Greater variability in TC and LDL-c was associated with higher risk of dementia, CIND, and faster cognitive decline in community-dwelling older adults, independent of average mean lipid levels. Further large, well-designed, prospective cohort studies in older adults are needed to verify our results and explore whether lipid variability identifies a high-risk group or directly contributes to cognition and dementia risk in this age group.

Author Contributions

Z. Zhou: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C. Moran: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. A.M. Murray: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. S. Zoungas: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. C. Magnussen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. T.T.-J. Chong: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. R.C. Shah: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. K.M. Sheets: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M. Nelson: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. C. Zhu: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. A.M. Tonkin: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. S. Talic: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M.E. Ernst: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. S.G. Orchard: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. J.J. McNeil: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. R. Wolfe: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. R.L. Woods: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. J.T. Neumann: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. P. Qiu: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. J. Ryan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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