Higher Visit-to-Visit Low-Density Lipoprotein Cholesterol Variability Is Associated With Lower Cognitive Performance, Lower Cerebral Blood Flow, and Greater White Matter Hyperintensity Load in Older Subjects

BACKGROUND: Recently, it was shown that intraindividual variation in low-density lipoprotein cholesterol (LDL-C) predicts both cerebrovascular and cardiovascular events. We aimed to examine whether this extends to cognitive function and examined possible pathways using a magnetic resonance imaging substudy.

METHODS: We investigated the association between LDL-C variability and 4 cognitive domains at month 30 in 4428 participants of PROSPER (PROspective Study of Pravastatin in the Elderly at Risk). Additionally, we assessed the association of LDL-C variability with neuroimaging outcomes in a subset of 535 participants. LDL-C variability was defined as the intraindividual standard deviation over 4 postbaseline LDL-C measurements, and all analyses were adjusted for mean LDL-C levels and cardiovascular risk factors.

RESULTS: Higher LDL-C variability was associated with lower cognitive function in both the placebo and pravastatin treatment arms. Associations were present for selective attention (P=0.017 and P=0.11, respectively), processing speed (P=0.20 and P=0.029), and memory (immediate recall, P=0.002 and P=0.006; delayed recall, P=0.001 and P≤0.001). Furthermore, higher LDL-C variability was associated with lower cerebral blood flow in both trial arms (P=0.031 and P=0.050) and with greater white matter hyperintensity load in the pravastatin arm (P=0.046). No evidence was found for interaction between LDL-C variability and pravastatin treatment for both cognitive and magnetic resonance imaging outcomes.

CONCLUSIONS: We found that higher visit-to-visit variability in LDL-C, independently of mean LDL-C levels and statin treatment, is associated with lower cognitive performance, lower cerebral blood flow, and greater white matter hyperintensity load.

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Clinical Perspective

What Is New?

- This is the first study to provide observational evidence that lipid variability may be of importance to neurocognitive function because higher low-density lipoprotein cholesterol variability was associated with lower cognitive test performance for immediate and delayed memory-related tasks, selective attention and processing speed, lower cerebral blood flow, and greater white matter hyperintensity load in a magnetic resonance imaging substudy.
- In addition to being independent of mean low-density lipoprotein cholesterol levels and clinically overt cardiovascular diseases, the associations were present in both the placebo and pravastatin treatment arms, suggesting that the findings do not merely reflect pleiotropic effects of statins or nonadherence.

What Are the Clinical Implications?

- Consequently, these findings might contribute to the ongoing discussion on adverse neurocognitive events in proprotein convertase subtilisin-kexin type 9 trials.
- Moreover, they are in line with but independent of previously found associations between blood pressure variability and neurocognitive function, raising the question of whether loss of homeostasis could lead to neurocognitive decline through parallel pathophysiological pathways.

More than 85 years ago, Cannon[1] hypothesized that loss of physiological homeostasis, for instance, through disease or the aging process, would lead to disturbances in intrinsic variability. This intraindividual variability in various physiological measures has become of increasing interest in recent years because both lowered heart rate variability and increased blood pressure variability have been repeatedly linked to adverse outcomes such as vascular events, impaired cognition, and mortality.[2–6] However, little is known about cholesterol variability, which may be considerable even on a day-to-day basis.[7,8] Recent evidence indicates that, in subjects with coronary artery disease, greater visit-to-visit variability in low-density lipoprotein cholesterol (LDL-C) is associated with higher risks of coronary and other cardiovascular events, stroke, and mortality independently of mean LDL-C levels.[9] Whether visit-to-visit variability in LDL-C is associated with cognitive performance is currently unknown.

Here, we assessed whether visit-to-visit variability in LDL-C is associated with cognitive function, independently of mean LDL-C levels, in 4428 participants of PROSPER (PROspective Study of Pravastatin in the Elderly at Risk). Additionally, to assess potential mechanisms behind this association, we examined the link between LDL-C variability and hippocampal volume, cerebral blood flow, and white matter hyperintensity load in a magnetic resonance imaging (MRI) substudy.

METHODS

Study Population

All subjects were participants of the PROSPER study, the study design of which has been described in detail elsewhere.[10] In short, this multicenter, randomized, placebo-controlled trial aimed to determine whether pravastatin reduces the risk of major cardiovascular and cerebrovascular events in participants 70 to 82 years of age with preexisting vascular disease (coronary, cerebral, or peripheral) or at higher risk for developing vascular disease because of a history of hypertension, cigarette smoking, or diabetes mellitus. For participants to be eligible for enrollment, their plasma total cholesterol was required to be 4.0 to 9.0 mmol/L with triglyceride concentrations <6.0 mmol/L. Participants were recruited in Scotland, Ireland, and the Netherlands. The study was approved by the institutional ethics review boards of each center, and all participants gave written informed consent. LDL-C variability and cognitive measures were available for 4428 participants. In addition, MRI measurements at the end of the study were available for 535 participants.

Assessment of LDL-C Variability

Lipid levels were assessed after an overnight fast, and LDL-C was measured directly. Lipoprotein profiles were quantified at the Centers for Disease Control–certified central lipoprotein laboratory in Glasgow. Visit-to-visit variability of LDL-C was calculated by means of the intraindividual standard deviation over each individual's measurements with the use of post-baseline measurements after 3, 6, 12, and 24 months. The coefficient of variation, another measure for LDL-C variability but standardized to the intraindividual mean LDL-C level over the same measurement period, was highly correlated with the intraindividual standard deviation (Pearson r=0.87). Baseline measurements were excluded to avoid including artificially induced variability from the beginning of statin therapy or as an initial response to dietary and lifestyle advice given to all participants at baseline. Throughout the trial, subjects received nutritional advice and health counseling and were encouraged to follow the National Cholesterol Education Program Step 1 diet or a local equivalent that provided <30% of total calories from fat (<10% as saturated fat) and a cholesterol intake of <300 mg/d.

Assessment of Cognition

Subjects with poor cognitive function (Mini Mental State Examination score <24) were excluded from enrollment in the main PROSPER study. Serving as outcome variables, cognitive function was evaluated through 4 cognitive measures.[11] The Stroop Color and Word Test was used to test selective attention, with total number of seconds needed to complete the third part of the test used as the outcome parameter. The Letter-Digit Coding Test assessed information processing speed, taking the number of correct digits filled in within 60 seconds, with higher scores denoting better performance. The

Picture-Word Learning Test was used as a verbal memory test, separately assessing immediate (number of recalled pictures over 3 learning trials) and delayed recall after 20 minutes, with higher scores denoting better performance. All cognitive outcomes were assessed at month 30 to maximize the availability of cognitive outcomes after the measurement of LDL-C variability.

MRI Substudy

Of the eligible Dutch participants of the main PROSPER study, 646 consented to participate in a nested MRI substudy, the methods and results of which have been published previously.[12] Subjects with intraorbital vascular clips, collagen disease, cardiac pacemakers, hearing implants, multiple sclerosis, or claustrophobia were excluded from participating. In the present study, we examined results from imaging performed after a mean±SD follow-up of 33±1.4 months. Data on visit-to-visit LDL-C variability and MRI outcomes were available for 535 participants.

A clinical MRI system operating at a field strength of 1.5 T was used for all imaging (Philips Medical Center, Best, the Netherlands). The integrated registration and segmentation tool of the Oxford Center for Functional MRI of the Brain was used to estimate the hippocampal volume.[13] With the use of the phase-contrast technique, cerebral blood flow was calculated by adding the flow from the left and right internal carotid arteries to the flow in both vertebral arteries and was subsequently standardized to whole-brain parenchymal volume.[12] Quantification of white matter hyperintensity load was performed with Software for Neuro-Image Processing in Experimental Research, an in-house-developed fully automatic segmentation method combining information from proton density, T2-weighted, and fluid-attenuated inversion-recovery images.[14]

Demographic and Clinical Characteristics

Participant characteristics were assessed at baseline. They included age, education (age of leaving school), body mass index, current smoking status (yes/no), alcohol intake (measured in units per week), and history of various clinical diseases.

Statistical Analyses

All analyses were conducted separately for the placebo and pravastatin arms. Demographic and clinical characteristics are presented as numbers with percentages, means with standard deviations, or medians with interquartile ranges when appropriate. Participant characteristics were compared over tertiles of LDL-C variability with ANOVA and the Pearson χ^2 test. The associations between postbaseline LDL-C variability and cognitive performance at month 30 and MRI measures at the end of the study were determined with multivariable linear regression models. Subjects with a minimum of 2 of 4 LDL-C measurements were included. Although reporting mean (SE) cognitive scores and MRI measures over tertiles of LDL-C variability to gain insight into the underlying distribution of neurocognitive function, we used intraindividual variability as a continuous covariate in the linear regression models. Adjusted unstandardized regression coefficients, 95% confidence intervals, and *P* values were reported. Covariate adjustments were based on their biological plausibility as potential confounders for the association between LDL-C variability and neurocognitive outcomes. These covariates consisted of diseases and factors that are known to influence LDL-C levels and have been linked to either cognitive or neurovascular impairment. For the minimally adjusted model, we included age, sex, country, education, average LDL-C, cognitive test version, and whole-brain parenchymal volume when appropriate. The fully adjusted model additionally included body mass index, current smoking status, alcohol intake, and history of diabetes mellitus, hypertension, and vascular disease. Data on these baseline covariates were complete for all participants. Possible violations of the assumptions of multiple linear regression were examined by visual inspection of the distribution of residuals through both histograms and normal P-P plots. We further checked for deviations of linearity and homoscedasticity by visually inspecting scatterplots of standardized residuals by standardized predicted values. In addition, we assessed variance inflation factors to examine the possibility of multicollinearity. We considered values of $P \leq 0.05$ statistically significant. All analyses were conducted with IBM SPSS Statistics version 20.0.

Sensitivity Analyses

Several sensitivity analyses were conducted to measure how robust the findings were to different subsets of the data and to elucidate possible mechanisms through which LDL-C variability might be associated with cognitive function. First, the association with cognitive performance at the end of the study was assessed, rather than cognition at month 30, using the same exposure measurement period. On average, this meant that cognitive performance was assessed 9 months later. A further consideration was the possible influence of the number of lipid measurements. Therefore, we restricted our analyses to those participants with all 4 measurements. We additionally performed separate analyses excluding history of and incident events of cerebrovascular and cardiovascular disease. Because both cancer and serious infection may influence LDL-C levels, we also carried out analyses excluding these incident disease states. Furthermore, blood pressure variability has been shown to be associated with cognition in recent years.[4] Because variability in LDL-C and blood pressure could arise from a common cause, we adjusted for systolic blood pressure variability to distinguish the effects of LDL-C variability from those mediated by blood pressure variability. Systolic blood pressure variability was defined as the intraindividual standard deviation over months 3 to 24, with blood pressure measured every 3 months, and these analyses were additionally adjusted for mean systolic blood pressure over the same measurement period. Furthermore, it is possible that LDL-C variability reflects consistent trends over time rather than an undulating pattern, for example, resulting from progressively reduced dietary intake in the context of an overall decline in health status. Therefore, we carried out analyses while adjusting for the average slope of LDL-C during the measurement period. Finally, because concomitant medication use may underlie differences in lipid variability, we performed analyses adjusting for baseline medication use of diuretics, angiotensin-converting enzyme I or II inhibitors, β-blockers, calcium channel blockers, nitrates, anticoagulants, antiarrhythmic medication, and glucose-lowering medication (insulin and noninsulin separately). For all sensitivity analyses, we report the results from the fully

adjusted model only, which were similar to those seen for the minimally adjusted model.

RESULTS

Demographic and Clinical Characteristics

Participant characteristics are given in Table 1. In both the placebo and pravastatin arms, participants in higher tertiles of visit-to-visit LDL-C variability had a higher systolic blood pressure variability (P=0.003 and P=0.006, respectively) and higher average LDL-C (both P<0.001), were more often female (P=0.001 and P=0.002), and were less likely to be Dutch than Scottish or Irish (P=0.047 and P=0.014) compared with the other tertiles. However, the difference in the proportion of female and male participants disappeared after variability was standardized to the intraindividual mean LDL-C by means of the coefficient of variation in both trial arms (P=0.67 and P=0.23, respectively). As shown in Table I in the online-only Data Supplement, the participants of the MRI substudy were largely representative of the Dutch participants.

Effect of Pravastatin on LDL-C

Statin therapy was associated with a reduction in both average LDL-C (−1.18 mmol/L; 95% confidence interval, −1.14 to −1.22) and mean visit-to-visit LDL-C variability (−0.02 mmol/L; 95% confidence interval, −0.01 to −0.04), as measured by the intraindividual standard deviation.

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Table 1. Baseline Characteristics Over Tertiles of LDL-C Variability

	Placebo (n=2226)				Pravastatin (n=2202)			
	Lowest Tertile* (n=742)	Middle Tertile† (n=742)	Highest Tertile‡ (n=742)	*P* Value	Lowest Tertile§ (n=734)	Middle Tertile¶ (n=735)	Highest Tertile‖ (n=733)	*P* Value
Continuous variables (mean±SD)								
Age, y	75.3±3.4	75.1±3.2	74.9±3.3	0.10	75.4±3.3	75.0±3.4	75.1±3.2	0.13
Education (age left school), y	15.3±2.3	15.0±1.9	15.2±2.0	0.15	15.3±2.2	15.3±2.3	15.2±2.1	0.76
Alcohol intake, units/mo	5.4±8.7	5.1±8.7	5.2±9.6	0.79	4.8±8.4	5.5±8.4	5.9±11.1	0.07
Body mass index, kg/m^2	26.9±4.2	27.0±4.4	27.1±4.1	0.79	26.8±1.8	26.8±3.9	26.9±4.0	0.89
Mean SBP, mm Hg#	153.9±16.0	153.4±17.2	153.8±16.1	0.82	153.0±16.4	153.7±17.4	153.7±16.4	0.62
SBP variability, mm Hg#	13.8±5.0	14.2±5.4	14.8±14.8	0.003**	13.7±5.3	14.0±5.2	14.6±5.5	0.006**
Mean LDL-C, mmol/L#	3.5±0.7	3.7±0.7	3.9±0.8	<0.001**	2.3±0.5	2.5±0.6	2.8±0.7	<0.001**
Categorical variables, n (%)								
Female	350 (47.2)	368 (49.6)	420 (56.6)	0.001**	364 (49.6)	360 (49.0)	419 (57.2)	0.002**
History of hypertension	462 (62.3)	458 (61.7)	464 (62.5)	0.95	480 (65.4)	450 (61.2)	467 (63.7)	0.25
History of diabetes mellitus	88 (11.9)	84 (11.3)	70 (9.4)	0.29	83 (11.3)	76 (10.3)	58 (7.9)	0.08
History of stroke or TIA	87 (11.7)	82 (11.1)	72 (9.7)	0.44	86 (11.7)	78 (10.6)	72 (9.8)	0.50
History of myocardial infarction	101 (13.6)	104 (14.0)	91 (12.3)	0.58	84 (11.4)	101 (13.7)	91 (12.4)	0.41
History of vascular disease	320 (43.1)	301 (40.6)	330 (44.5)	0.30	310 (42.2)	342 (46.5)	323 (44.1)	0.25
Current smoker	190 (25.6)	187 (25.2)	189 (25.5)	0.98	172 (23.4)	170 (23.1)	192 (26.2)	0.32
Country of origin, n (%)								
Scotland	296 (39.9)	300 (40.4)	301 (40.6)	0.047**	287 (39.1)	296 (40.3)	311 (42.4)	0.014**
Ireland	261 (35.2)	288 (38.8)	301 (40.6)		259 (35.3)	278 (37.8)	290 (39.6)	
The Netherlands	185 (24.9)	154 (20.8)	140 (18.9)		188 (25.6)	161 (21.9)	132 (18.0)	

P values were calculated with ANOVA and the Pearson χ^2 test when appropriate. LDL-C indicates low-density lipoprotein cholesterol; SBP, systolic blood pressure; and TIA, transient ischemic attack.

LDL-c variability ranges (mmol/L): *0.02 to 0.22, †0.22 to 0.35, ‡0.35 to 1.71, §0.00 to 0.18, ¶0.18 to 0.30, and ‖0.30-1.56.

#Calculated over months 3 to 24, similar to LDL-C variability.

**Significant.

Association Between LDL-C Variability and Cognitive Performance

In both the placebo and pravastatin groups, higher LDL-C variability was significantly associated with lower cognitive test scores (Table 2). Although most consistent for the memory measures (immediate recall, P=0.002 and P=0.006; delayed recall, P=0.001 and P≤0.001), statistically significant associations were also seen for the Stroop Color and Word Test (P=0.017 and P=0.11) and Letter-Digit Coding Test (P=0.20 and P=0.029) scores. These fully adjusted associations were essentially unchanged from those seen for the minimally adjusted model. We found no evidence for interaction between LDL-C variability and pravastatin treatment for all cognitive outcomes (Table II in the online-only Data Supplement).

Sensitivity Analyses for Cognitive Outcomes

As shown in the Figure, the associations between LDL-C variability and cognitive performance were essentially unchanged when the analyses were restricted to different subsets, or adjusted for various possible common causes of LDL-C variability and cognitive performance, in both trial arms.

Association Between LDL-C Variability and MRI Measures

We found no evidence for an association between LDL-C variability and hippocampal volume (P=0.779 and P=0.864, respectively). However, higher LDL-C variability was associated with lower total cerebral blood blow in the fully adjusted model (Table 3) in both the placebo and pravastatin groups (P=0.031 and P=0.050, respectively). Furthermore, higher LDL-C variability was associated with greater white matter hyperintensity load in the pravastatin group (P=0.046), but this association did not reach statistical significance in the placebo group (P=0.184). Additionally, no interaction was observed between LDL-C variability and pravastatin treatment for all MRI measures (Table III in the online-only Data Supplement). Further adjustments for whole-brain or gray matter–specific atrophy did not markedly change any of the results (data not shown).

Table 2. Cognitive Function at Month 30 Over Tertiles of LDL-C Variability

	Model	Lowest Tertile	Middle Tertile	Highest Tertile	β (95% CI)	*P* Value
Placebo (n=2226)						
Stroop card III, s needed	1	62.25 (0.91)	65.16 (0.93)	65.12 (0.94)	6.24 (0.92 to 11.56)	0.021*
	2	65.06 (1.21)	68.00 (1.23)	68.00 (1.23)	6.44 (1.13 to 11.75)	0.017*
LDT, digits coded correctly	1	23.67 (0.24)	22.93 (0.24)	22.99 (0.25)	−0.92 (−2.32 to 0.48)	0.196
	2	23.05 (0.32)	22.29 (0.32)	22.39 (0.32)	−0.91 (−2.30 to 0.49)	0.204
PLTi, pictures remembered	1	9.72 (0.07)	9.51 (0.07)	9.48 (0.07)	−0.68 (−1.09 to −0.27)	0.001*
	2	9.60 (0.10)	9.38 (0.10)	9.36 (0.10)	−0.66 (−1.07 to −0.25)	0.002*
PLTd, pictures remembered	1	10.56 (0.10)	10.24 (0.10)	10.16 (0.10)	−1.02 (−1.60 to −0.44)	0.001*
	2	10.36 (0.13)	10.03 (0.13)	9.97 (0.13)	−1.00 (−1.58 to −0.42)	0.001*
Pravastatin (n=2202)						
Stroop card III, s needed	1	62.39 (0.90)	61.77 (0.88)	64.66 (0.94)	3.94 (−0.88 to 8.75)	0.109
	2	65.17 (1.21)	64.70 (1.20)	67.54 (1.23)	3.89 (−0.92 to 8.70)	0.113
LDT, digits coded correctly	1	23.35 (0.25)	23.80 (0.25)	22.69 (0.27)	−1.51 (−2.86 to −0.15)	0.030*
	2	22.41 (0.34)	22.81 (0.34)	21.72 (0.34)	−1.51 (−2.86 to −0.15)	0.029*
PLTi, pictures remembered	1	9.66 (0.07)	9.65 (0.07)	9.37 (0.08)	−0.56 (−0.95 to −0.16)	0.006*
	2	9.38 (0.10)	9.36 (0.09)	9.08 (0.10)	−0.55 (−0.94 to −0.15)	0.006*
PLTd, pictures remembered	1	10.54 (0.10)	10.42 (0.10)	9.87 (0.11)	−1.22 (−1.78 to −0.66)	<0.001*
	2	10.14 (0.14)	10.00 (0.14)	9.46 (0.14)	−1.20 (−1.76 to −0.64)	<0.001*

The adjusted unstandardized regression coefficients and P values for trend were calculated with LDL-C variability (mmol/L) used as a continuous measure. Model 1 was adjusted for age, sex, country, education, mean LDL-C, and test version when appropriate. Model 2 was adjusted as model 1 plus body mass index, smoking status, alcohol intake, history of diabetes mellitus, hypertension, and vascular disease. Data are presented as mean (SE) cognitive test scores. CI indicates confidence interval; LDL-C, low-density lipoprotein cholesterol; LDT, Letter-Digit Coding Test; PLTd, 15-Picture Learning Test Delayed; PLTi, 15-Picture Learning Test Immediate; and Stroop, Stroop Color and Word Test.

*Significant.

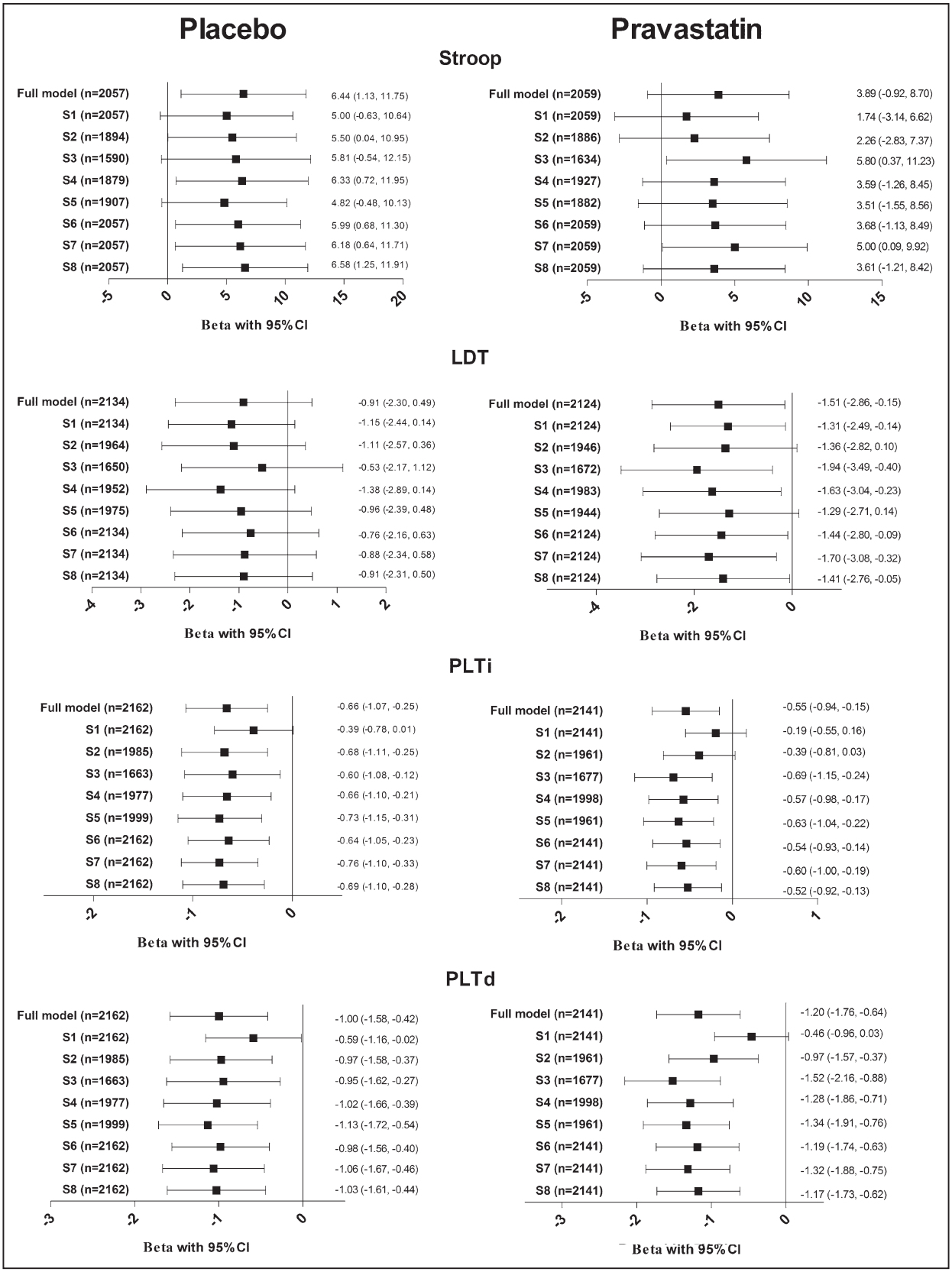

Figure. Sensitivity analyses of the association between low-density lipoprotein cholesterol (LDL-C) variability and cognitive performance.

Consecutively listed, these are as follows: S1, assessing cognition at end of study; S2, assessing only subjects with 4 (complete) LDL-C measurements; S3, excluding history of cerebrovascular and cardiovascular disease; S4, excluding incident (*Continued*)

Multiple Linear Regression Assumptions

We found no evidence of nonnormality, curvilinearity, heteroscedasticity, or multicollinearity in any of our models. This held true for all cognitive tests and MRI outcomes.

DISCUSSION

We found that higher visit-to-visit variability in LDL-C is robustly associated with lower cognitive performance independently of mean LDL-C levels. Although most consistent for both immediate and delayed memory-related outcomes, similar trends were present for selective attention and processing speed. In addition, we observed that higher variability is associated with lower cerebral blood flow and greater white matter hyperintensity load within an MRI substudy. All associations were independent of clinically overt cerebrovascular and cardiovascular disease and comorbidities. Of particular importance is that these associations were present in both the placebo and pravastatin treatment arms, with no evidence for interaction by pravastatin treatment. This advocates against increased LDL-C variability purely reflecting the known beneficial and harmful pleiotropic effects of statins or behavioral factors that may undermine response to lipid-lowering treatment, most notably nonadherence. Nonetheless, our findings that higher LDL-C variability is associated with lower neurocognitive function highlight the need for further investigations into the potential influence of lipid-lowering treatment on LDL-C variability and consequent adverse events. Although it should be noted that these events are uncommon and that adverse event reporting is not part of a systematic evaluation of neurocognitive function, currently available trial evidence suggests that neurocognitive adverse events may occur more frequently in individuals receiving proprotein convertase subtilisin-kexin type 9 inhibitors independently of on-treatment LDL levels.[15] At the same time, high-dose monthly regimens of proprotein convertase subtilisin-kexin type 9 monoclonal antibodies are known to produce substantial fluctuations of LDL-C between doses.[16] On the basis of our results, this increased variability could possibly contribute to the observed higher rate of neurocognitive events and should be examined by currently ongoing proprotein convertase subtilisin-kexin type 9 trials. To the best of our knowledge, this study is the first to examine the association between lipid variability and cognitive performance and provides further evidence that lipid variability could be of clinical significance. The implications of our findings are thus in line with those from the recently published results from the Treating to New Targets trial[9] but extend these findings to cognitive and neuroimaging outcomes.

Major strengths of the present study are its size, with >4400 participants providing data on lipid variability and cognitive performance, and the opportunity to perform these analyses in both the presence and absence of lipid-lowering therapy. Moreover, because of the exclusion of participants with Mini Mental State Examination scores <24, we were able to examine a fairly homogeneous population with regard to cognitive function. A limitation of the present study is the observational nature of the data, which prevents us from inferring causal relationships. Furthermore, our ability to look at cognitive performance at different time points and perform longitudinal analyses was limited by the number of and varying time intervals between postbaseline LDL-C measurements. In addition, we included a limited neurocognitive test battery, which did not provide information on various important cognitive domains such as visual-constructive function or language. A further possible limitation could be that we did not adjust for multiple testing. However, we did not consider our analyses to be hypothesis free because we included neurocognitive tests specifically known to be affected by neurovascular impairment, which are additionally known to be correlated. Applying multiple comparison methods such as Bonferroni in this case would therefore yield results that are too conservative. Finally, although lipid levels were measured after an overnight fast, we did not have data on the exact nature and timing of the last consumed meal. Although this might have influenced our results, it is very likely that any potential dietary effect would be random in nature.

There are several explanations for our findings, which roughly fall within 2 categories. First, it is possible that LDL-C variability is causally related to cognitive function. Histological studies have demonstrated that lipid-lowering treatments such as statins may lower the lipid content of human carotid plaques,[17] with recent animal studies suggesting that complete atherosclerotic regression of early lesions is possible through the lowering of lipid levels.[18] Thus, varying levels of LDL-C could theoretically lead to fluctuations in the composition of atherosclerotic plaques, possibly inducing plaque instability and thereby increasing the risk of (sub)clinical cerebrovascular damage.[19] Another pathway might be through endothelial dysfunction, which

Figure Continued. cerebrovascular and cardiovascular disease; S5, excluding incident serious infection and cancer; S6, adjusting for visit-to-visit systolic blood pressure variability; S7, adjusting for mean LDL-C slope during measurement period; and S8, adjusting for concomitant baseline medication use. Results are presented as adjusted unstandardized regression coefficients with 95% confidence intervals (CIs). LDT indicates Letter-Digit Coding Test; PLTd, 15-Picture Learning Test Delayed; and PLTi, 15-Picture Learning Test Immediate.

Table 3. MRI Measures at the End of the Study Over Tertiles of LDL-C Variability

	Model	Lowest Tertile	Middle Tertile	Highest Tertile	β (95% CI)	*P* Value
Placebo (n=269), n		89*	90†	90‡		
Hippocampal volume, mL	1	9.21 (0.13)	9.26 (0.13)	9.15 (0.13)	0.19 (−0.57 to 0.95)	0.622
	2	9.14 (0.15)	9.08 (0.16)	9.07 (0.16)	0.11 (−0.66 to 0.88)	0.779
Cerebral blood flow, $mL \cdot min^{-1} \cdot 100\ mL^{-1}$	1	48.09 (1.10)	48.43 (1.14)	45.30 (1.14)	−6.39 (−13.13 to 0.34)	0.063
	2	46.95 (1.33)	47.21 (1.44)	44.12 (1.40)	−7.66 (−14.61 to −0.70)	0.031#
WMHL, mL	1	7.79 (1.35)	7.06 (1.34)	8.56 (1.33)	4.74 (−3.33 to 12.80)	0.249
	2	7.76 (1.62)	7.10 (1.71)	8.75 (1.66)	5.69 (−2.72 to 14.09)	0.184
Pravastatin (n=266), n		88§	89¶	89‖		
Hippocampal volume, mL	1	9.31 (0.13)	9.34 (0.12)	9.36 (0.11)	−0.19 (−0.83 to 0.45)	0.557
	2	9.17 (0.17)	9.18 (0.16)	9.27 (0.15)	−0.06 (−0.72 to 0.61)	0.864
Cerebral blood flow, $mL \cdot min^{-1} \cdot 100\ mL^{-1}$	1	48.19 (1.05)	49.17 (1.02)	46.93 (1.09)	−6.17 (−12.78 to 0.44)	0.067
	2	48.80 (1.38)	49.89 (1.46)	47.33 (1.40)	−6.82 (−13.63 to −0.01)	0.050#
WMHL, mL	1	5.21 (1.30)	7.54 (1.22)	8.47 (1.26)	5.62 (−1.50 to 12.75)	0.121
	2	4.50 (1.69)	6.88 (1.71)	8.43 (1.62)	7.42 (0.15 to 14.69)	0.046#

The adjusted unstandardized regression coefficients and *P* values for trend were calculated with LDL-C variability (mmol/L) used as a continuous measure. Model 1 was adjusted for age, sex, education, mean LDL-C, and whole-brain parenchymal volume. Model 2 was adjusted as model 1 plus body mass index, smoking status, alcohol intake, history of diabetes mellitus, hypertension, and vascular disease. Data are presented as mean (SE) magnetic resonance imaging (MRI) measure. CI indicates confidence interval; LDL-C, low-density lipoprotein cholesterol; and WMHL, white matter hyperintensity load.

LDL-C variability ranges (mmol/L): *0.05 to 0.20, †0.20 to 0.32, ‡0.32 to 1.18, §0.03 to 0.16, ¶0.16 to 0.25, and ‖0.25-1.52.

#Significant.

can be caused by many of the risk factors that predispose to atherosclerosis.[20] Because individuals with elevated serum markers of endothelial dysfunction are at higher risk for developing cognitive impairment,[21] possibly through changes in cerebral blood flow,[22,23] increased LDL-C variability might lead to cognitive impairment. In line with this hypothesis, we observed that higher LDL-C variability was associated with lower cerebral blood flow but also with greater white matter hyperintensity load, which has been linked to endothelial (dys)function.[24]

Explanations within the second category dismiss a causal role for LDL-C variability. Here, visit-to-visit variability would rather reflect other processes leading to cognitive dysfunction. For example, despite the exclusion of participants with a diagnosis of cancer or serious infection from the analyses in a sensitivity analysis, undetected subclinical disease might have led to both increased lipid variability and cognitive impairment. This also holds true for liver disease, although participants with clinically significant liver damage were explicitly excluded from enrolling in the trial. Exploratory analyses with inflammatory markers (fibrinogen, interleukin-6, interleukin-10, C-reactive protein) measured at baseline did not reveal evidence of an association with LDL-C variability (all $P>0.1$, data not shown). Furthermore, numerous drugs may have unintended effects on lipid levels.[25] Whereas adjustment for baseline medication use did not materially change our findings, the exact timing of the start of a new drug, although known to be infrequent, was unfortunately not available within our study, and it was therefore not possible to take this into account. The observation that the associations were independent of blood pressure variability might imply that loss of homeostatic function does not underlie our present findings. However, more likely, it may signify that the different regulatory systems involved in homeostasis may be affected through different pathological pathways. Finally, because of the cross-sectional design of our analyses, we cannot rule out that subclinical cerebrovascular damage, for which cognitive dysfunction may be a marker, leads to increased LDL-C variability.

Conclusions

We showed for the first time that in older participants at risk for vascular disease, higher visit-to-visit LDL-C variability is associated with lower cognitive performance, lower cerebral blood flow, and greater white matter hyperintensity load. Our findings underscore the potential of LDL-C variability as a useful prognostic marker for different clinical outcomes. Future replication studies are needed to corroborate these findings and should ideally

also use longitudinal assessments of neuroimaging to further elucidate the possible relationship between LDL-C variability and cerebral blood flow and white matter hyperintensities.

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DISCLOSURES

None.

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FOOTNOTES

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Higher Visit-to-Visit Low-Density Lipoprotein Cholesterol Variability Is Associated With Lower Cognitive Performance, Lower Cerebral Blood Flow, and Greater White Matter Hyperintensity Load in Older Subjects

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SUPPLEMENTAL MATERIAL

Supplemental table 1. Characteristics of study participants included in the whole group, Dutch subsample, and magnetic resonance imaging (MRI) substudy.

	Overall cohort (n=4428)	Dutch subsample (n=960)	MRI substudy (n=535)
Continuous variables (mean ± SD)			
Age (years)	75.2 (3.3)	75.1 (3.3)	75.0 (3.2)
Education (age left school, years)	15.2 (2.1)	15.4 (2.9)	15.5 (2.9)
Alcohol intake (units/month)	5.3 (9.2)	6.9 (8.3)	6.7 (8.2)
Body mass index (kg/m^2)	26.9 (4.1)	26.8 (3.8)	26.7 (3.7)
Mean SBP (mmHg)*	153.6 (16.6)	156.6 (16.8)	156.6 (17.4)
SBP variability (mmHg)*	14.2 (5.4)	13.2 (5.2)	13.2 (5.4)
Mean LDL cholesterol (mmol/L)*	3.1 (0.9)	3.2 (0.9)	3.2 (0.9)
LDL-c variability (mmol/L)*	0.31 (0.21)	0.28 (0.20)	0.28 (0.20)
Stroop card III, seconds needed †	64.5 (26.1)	55.2 (20.0)	54.8 (20.0)
LDT, digits coded correctly †	22.9 (7.8)	26.7 (7.3)	27.1 (7.1)
PLTi, pictures remembered †	9.5 (2.0)	10.2 (2.1)	10.3 (2.0)
PLTd, pictures remembered †	10.2 (2.9)	11.3 (2.8)	11.3 (2.8)
Categorical variables (n, %)			
Female	2281 (51.5)	461 (48.0)	233 (43.6)
History of hypertension	2781 (62.8)	619 (64.5)	339 (63.4)
History of diabetes mellitus	459 (10.4)	158 (16.5)	88 (16.4)
History of stroke or TIA	477 (10.8)	158 (16.5)	87 (16.3)
History of myocardial infarction	572 (12.9)	144 (15.0)	64 (12.0)
History of vascular disease	1926 (43.5)	407 (42.4)	234 (43.7)
Current smoker	1100 (24.8)	228 (23.8)	113 (21.1)

LDL-c denotes low-density lipoprotein cholesterol; SBP, systolic blood pressure; TIA, transient ischemic attack; LDT, Letter-Digit Coding test; PLTi, 15-Picture Learning test immediate; PLTd, 15-Picture Learning test delayed.

* calculated over months 3 to 24, † at month 30.

Supplemental Table 2. Cognitive function, at month thirty, over treatment-specific tertiles of LDL-c variability (n=4428)

	Lowest tertile	Middle tertile	Highest tertile	Beta (95% CI)	P_{trend}	$P_{interaction}$
Stroop card III, seconds	65.09 (0.85)	66.34 (0.86)	67.77 (0.86)	5.10 (1.59, 8.62)	**0.004**	0.504
LDT, digits coded	22.73 (0.23)	22.56 (0.23)	22.06 (0.23)	-1.26 (-2.22, -0.31)	**0.010**	0.549
PLTi, pictures remembered	9.39 (0.07)	9.38 (0.07)	9.22 (0.07)	-0.63 (-0.91, -0.35)	**<0.001**	0.730
PLTd, pictures remembered	10.26 (0.10)	10.03 (0.10)	9.72 (0.10)	-1.12 (-1.52, -0.73)	**<0.001**	0.790

Data are presented as mean cognitive test scores (SE). The adjusted unstandardized regression coefficient, p-value for trend, and p-value for interaction between treatment and LDL-c variability were calculated using variability (mmol/L) as a continuous measure. LDT denotes Letter-Digit Coding test; PLTi, 15-Picture Learning test immediate; PLTd, 15-Picture Learning test delayed.

Adjusted for age, gender, country, education, mean LDL cholesterol, pravastatin use, test version where appropriate, BMI, smoking status, alcohol intake, history of diabetes mellitus, hypertension, and vascular disease.

Supplemental Table 3. MRI measures, at end of study, over treatment-specific tertiles of LDL-c variability (n=535)

	Lowest tertile	Middle tertile	Highest tertile	Beta (95% CI)	P_{trend}	$P_{interaction}$
Hippocampal volume (ml)	9.16 (0.11)	9.14 (0.11)	9.22 (0.11)	0.11 (-0.38, 0.61)	0.646	0.848
Cerebral blood flow (ml/min/100 ml)	47.70 (0.96)	48.37 (1.01)	45.60 (0.97)	-6.13 (-10.80,-1.47)	**0.010**	0.746
WMHL (ml)	6.20 (1.15)	7.02 (1.18)	8.71 (1.13)	6.64 (1.36, 11.93)	**0.014**	0.840

Data are presented as mean MRI measure (SE). The adjusted unstandardized regression coefficient, p-value for trend, and p-value for interaction between treatment and LDL-c variability were calculated using variability (mmol/L) as a continuous measure. WMHL denotes white matter hyperintensity load. Adjusted for age, gender, education, mean LDL cholesterol, whole-brain parenchymal volume, pravastatin use, BMI, smoking status, alcohol intake, history of diabetes mellitus, hypertension, and vascular disease.