Plasma lipids and cerebral small vessel disease

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ABSTRACT

Objectives: We examined the cross-sectional association between lipid fractions and 2 MRI markers of cerebral small vessel disease, white matter hyperintensity volume (WMHV) and lacunes, representing powerful predictors of stroke and dementia.

Methods: The study sample comprised 2,608 participants from the 3C-Dijon Study (n = 1,842) and the Epidemiology of Vascular Aging Study (EVA) (n = 766), 2 large French population-based cohorts (72.8 ± 4.1 and 68.9 ± 3.0 years; 60.1% and 58.4% women, respectively). Analyses were performed separately in each study and combined using inverse variance meta-analysis. Lipid fractions (triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol) were studied as continuous variables. WMHV was studied both in a continuous and dichotomous manner, the latter reflecting the age-specific top quartile of WMHV (EXT-WMHV). Analyses were adjusted for age and sex.

Results: Increasing triglycerides were associated with larger WMHV in the 3C-Dijon Study (β ± SE = 0.0882 ± 0.0302, p = 0.0035), in the EVA Study (β ± SE = 0.1062 ± 0.0461, p = 0.021), and in the combined analysis (β ± SE = 0.0936 ± 0.0252, p = 0.0002) and with higher frequency of lacunes in the 3C-Dijon Study (odds ratio [OR] = 1.65 [95% confidence interval 1.10–2.48], p = 0.015), in the EVA Study (OR = 1.58 [95% confidence interval 0.93–2.70], p = 0.09), and in the combined analysis (OR = 1.63 [95% confidence interval 1.18–2.25], p = 0.003). Associations were attenuated but maintained after adjusting for other vascular risk factors or for inflammatory markers. Associations were present and in the same direction both in participants taking and those not taking lipid-lowering drugs but tended to be stronger in the former for EXT-WMHV. Increasing low-density lipoprotein cholesterol tended to be associated with a decreased frequency and severity of all MRI markers of cerebral small vessel disease in both studies.

Conclusions: Increasing triglycerides but not other lipid fractions were associated with MRI markers of cerebral small vessel disease in older community persons. *Neurology®* **2014;83:1844–1852**

GLOSSARY

CI = confidence interval; **CRP** = C-reactive protein; **DWMHV** = deep white matter hyperintensity volume; **EVA** = Epidemiology of Vascular Aging Study; **EXT-WMHV** = age-specific top quartile of white matter hyperintensity volume; **HDL** = high-density lipoprotein; **IL-6** = interleukin 6; **LDL** = low-density lipoprotein; **OR** = odds ratio; **PVWMHV** = periventricular white matter hyperintensity volume; **SE** = standard error; **SVD** = small vessel disease; **TG** = triglyceride; **WMH** = white matter hyperintensity; **WMHV** = white matter hyperintensity volume.

The relation of dyslipidemia with cerebrovascular disease is complex and incompletely understood. In contrast with the strong undisputed association between high low-density lipoprotein (LDL) cholesterol and myocardial infarction,[1] epidemiologic studies have failed to demonstrate a robust association of hypercholesterolemia with risk of stroke.[2,3] A possible explanation is that the association might differ by stroke subtype. Several studies have reported an association between decreasing cholesterol and intracerebral hemorrhage,[4,5] while some studies have established a relationship between hypercholesterolemia and risk of ischemic stroke.[5] Small vessel

Supplemental data at Neurology.org

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

disease (SVD) is a major cause of both ischemic stroke and intracerebral hemorrhage.[6] It is highly prevalent in the general population, even in the absence of clinical stroke, as revealed by brain MRI in large community-based samples.[7,e1] MRI markers of SVD (MRI-SVD), such as white matter hyperintensity volume (WMHV) and lacunes, are associated with a faster cognitive decline, an increased risk of dementia and stroke, and increased mortality rates at the community level.[8,e2] Data on the association of dyslipidemia with MRI-SVD are scarce. Moreover, most studies have focused on total or LDL cholesterol, while little data are available on triglycerides (TGs).[9,10] Our aim was to assess the relationship between lipid fractions (TGs, LDL cholesterol, and high-density lipoprotein [HDL] cholesterol) and 2 MRI markers of SVD, WMHV and lacunes, both powerful predictors of stroke, cognitive decline, and dementia.

METHODS

Study population. The 3C-Dijon Study is a longitudinal, population-based, prospective cohort study, which has been described elsewhere.[11] Briefly, 4,931 noninstitutionalized persons aged 65 years or older were recruited from the electoral rolls of Dijon, France, between March 1999 and March 2001. Participants enrolled between June 1999 and September 2000 who were younger than 80 years and could come to the examination center (n = 2,763) were proposed to undergo a brain MRI at baseline. Although 2,285 subjects were willing to participate, because of financial limitations, 1,924 MRI examinations were performed. After exclusion of participants with brain tumor (n = 8), missing data for either MRI-SVD (n = 58) or lipid levels (n = 16), the final sample comprised 1,842 participants.

The Epidemiology of Vascular Aging Study (EVA) is another independent longitudinal, population-based, prospective cohort study.[12,13] Briefly, 1,389 participants, aged 59 to 71 years, were recruited from electoral rolls of Nantes, France, from June 1991 to June 1993. At 4-year follow-up, MRI examination was proposed to all subjects (n = 1,188). Although 1,045 subjects agreed to participate, because of financial limitations, 845 MRI scans were performed. After exclusion of participants with brain tumor (n = 7), missing data for MRI-SVD (n = 58) or lipid levels (n = 14), the final sample comprised 766 participants.

Standard protocol approvals, registrations, and patient consents. The Ethics Committee of Kremlin-Bicêtre University Hospital approved both study protocols and all participants signed an informed consent.

MRI examination and variable definition. MRI acquisition was performed using a 1.5-tesla and a 1.0-tesla scanner (Siemens, Erlangen, Germany) in the 3C-Dijon Study and the EVA Study, respectively.[13,14] T2-weighted images included a fast multislice double-echo 2-dimensional axial acquisition, a proton density axial acquisition, and a fast 3-dimensional spoiled gradient-echo T1-weighted axial acquisition. Raw data converted to the ACR-NEMA (American College of Radiology–National Electrical Manufacturers Association) standard format were then transferred for analysis and storage to the MRI study coordinating center (Department of Neurofunctional Imaging, Caen). Fully automated detection and location of white matter hyperintensities (WMH) as well as WMHV measurement were performed using a newly developed image processing software.[14] Image analysis comprised 3 steps: (1) preprocessing (registration, removal of nonbrain tissue, correction of bias field); (2) WMH detection on T2 images and removal of false positives; and (3) postprocessing (WMH probability map generation at the individual level and sample level, morphometry, and WMH location and classification). False positives originating from the CSF/Virchow-Robin spaces, with intensities comparable to those of WMH on T2 images, were removed using SPM99 (Statistical Parametric Mapping) software. An improved CSF mask was computed and aligned on the T2 volume, utilizing high-resolution T1 volumes and the spatial normalization matrix (SNM-1MNI). WMH with >50% of their voxels coinciding with CSF mask were identified and removed. Some false positives corresponded to voxels that were white matter but not hyperintensities, i.e., voxels with a very low intensity but a higher probability of belonging to the WMH than to the white matter category (this may occur because the variance of WMH voxels is larger than that of white matter). Consequently, WMH with a mean T2 signal intensity below that of white matter were excluded.[15]

For each detected WMH, the following morphologic parameters were computed: coordinates of center of mass, dimension of principal axis, and Euclidian distance to the ventricular system. When a WMH was located within 10 mm of the ventricular system, it was classified as periventricular WMH; otherwise, it was classified as deep WMH.[16] Periventricular WMH volume (PVWMHV) and deep WMH volume (DWMHV) were estimated by adding up the volumes of all hyperintensities detected in each of these areas.

Lacunes of presumed vascular origin were assessed on T1-, T2-, and proton density-weighted images by the same investigator (Y.Z.), using a standardized assessment grid to review all MRI scans visually. Lesion characteristics were visualized in axial, coronal, and sagittal planes simultaneously. Lacunes of presumed vascular origin were defined as focal lesions of 3–15 mm in size with the same signal characteristics as CSF on all MRI sequences, located in the basal ganglia, brainstem, or white matter,[17] in agreement with the STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) criteria.[18] They were discriminated from dilated Virchow-Robin spaces using multiplanar reformatting: lesions having a typical vascular shape and following perforating vessel orientation were classified as dilated Virchow-Robin spaces.[17] Subjects with cortical infarcts in the cerebrum, cerebellar infarcts, or large subcortical infarcts (>15 mm) were excluded from analyses of lacunes.

Laboratory testing. All participants were in a fasting status when blood was drawn. Centralized measurements of baseline serum total cholesterol, HDL cholesterol, and TGs were performed using enzymatic methods. LDL cholesterol was calculated with the Friedewald formula.[e3] Measurements closest to the MRI were used (baseline for the 3C-Dijon Study and exam 3 for the EVA Study with a mean ± SD of 2.3 ± 2.3 months and 7.3 ± 5.3 months between lipid measurements and MRI examination, respectively).

Covariates. Hypertension was characterized by systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive drug intake. Body mass index was computed as the ratio of weight (kg) to the square of height (m^2). Diabetes was characterized by fasting blood glucose ≥7 mmol/L, antidiabetic drug intake, or medical history of diabetes. Hypercholesterolemia was defined as fasting total cholesterol ≥6.2 mmol/L or lipid-lowering drug intake. Lipid-lowering drug intake was restricted to the use of statins and/or fibrates. Smoking status was classified as never, former, and current smoker in the 3C-Dijon Study and as current smoker in the EVA Study. History of cardiovascular disease was characterized by a history of stroke, myocardial infarction, angina pectoris, or peripheral artery disease. Interleukin 6 (IL-6) and C-reactive protein (CRP) were studied in tertiles. Methods for genotyping the *APOE* ε polymorphism and for quantifying plasma IL-6 and CRP have been described previously.[19,20] *APOE* ε4 (*APOE* ε2) carrier status was defined as the presence of at least one ε4 (ε2) allele.

Statistical analyses. WMHV was studied as a continuous variable (WMHV) or as a dichotomized variable age-specific top quartile of WMHV [EXT-WMHV] corresponding to the age-specific top quartile of WMHV over white matter mask volume (age strata were as follows: age < 70, 70 ≤ age < 75, and age ≥ 75 years). WMHV, DWMHV, and PVWMHV were log-transformed (natural log of [volume in mL + 1], as previously described[21]). Lacunes were defined as the presence of at least one lacune vs none. TG levels were log-transformed to remove skewness.

To explore the cross-sectional associations of lipid levels with WMHV, EXT-WMHV, and lacunes, we performed linear or logistic regressions adjusted for age and sex; analyses using WMHV as a dependent variable were additionally adjusted for white matter mask volume.[14] In a second model, we further adjusted for vascular risk factors (body mass index, systolic blood pressure, antihypertensive drug intake, smoking status, diabetes, other lipid levels, lipid-lowering drug intake). Analyses were run separately in each study. Combined estimates were obtained using fixed-effects inverse variance weighted meta-analysis in the absence of heterogeneity ($I^2 < 50\%$ or $p > 0.05$) and random effects otherwise. The linearity of associations between lipid fractions and MRI-SVD was assessed (1) by comparing the log-likelihood of a model with lipid level quintiles to the log-likelihood of a model in which the lipid level was substituted by the median value of the corresponding quintile using a 3-*df* χ^2 test, and (2) using 3-knot and 5-knot restricted cubic spline functions based on a previously reported method.[e4,e5] Linearity was checked visually for the covariates.

In sensitivity analyses, we ran analyses stratified on lipid-lowering drug intake and restricted the population to participants without history of stroke or cardiovascular disease at baseline; we ran analyses stratified on sex and sex-specific median age. We also examined whether any of the observed associations were mediated by *APOE* ε polymorphism or inflammation, in secondary analyses adjusting for *APOE* ε4 or *APOE* ε2 carrier status, and for circulating levels of IL-6 and CRP.

To further explore the relation of TGs with MRI-SVD, we tested the association of lipid levels with WMHV subtypes according to their location (DWMHV and PVWMHV). Finally, to examine whether lipid fractions were associated with severity of MRI-SVD, we created a severity score ranging from 0 to 2: 0 for participants without lacune or EXT-WMHV; 1 for participants with either ≥1 lacune or EXT-WMHV; and 2 for participants with both ≥1 lacune and EXT-WMHV. We used multinomial logistic regression (generalized logit model), relating lipid fractions to this score.

Analyses were performed using Statistical Analyses System software version 9.2 (SAS Institute, Cary, NC) and Review Manager 5.1.

Table 1 Baseline characteristics of the 3C-Dijon Study and the EVA Study participants

	3C-Dijon Study (n = 1,842)	EVA Study (n = 766)
Age, y	72.8 ± 4.1	68.8 ± 3.0
Women	1,111 (60.3)	448 (58.5)
Triglycerides, mmol/L	1.2 ± 0.6	1.3 ± 0.6
Total cholesterol level, mmol/L	5.7 ± 0.9	6.1 ± 1.0
HDL cholesterol level, mmol/L	1.6 ± 0.4	1.7 ± 0.5
LDL cholesterol level, mmol/L	3.6 ± 0.8	3.8 ± 0.9
Hypercholesterolemia	1,045 (56.7)	510 (66.6)
Lipid-lowering drug intake	618 (33.5)	251 (32.8)
Systolic blood pressure, mm Hg	148.6 ± 22.4	135.1 ± 18.2
Diastolic blood pressure, mm Hg	84.8 ± 11.5	77.1 ± 10.6
Hypertension	1,416 (76.9)	419 (54.7)
Smoker	719 (39.0)	29 (10.2)[a]
Diabetes	158 (8.6)	10 (1.3)
Prevalent stroke	66 (3.6)	10 (1.3)
Prevalent dementia	7 (0.4)	NA
WMHV, cm^3	5.50 ± 4.99	4.54 ± 4.11
WMHV, median (IQR)	4.02 (2.76, 6.33)	3.35 (2.19, 5.42)
Lacunes	148 (8.0)	82 (10.7)

Abbreviations: EVA = Epidemiology of Vascular Aging Study; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; NA = not available; WMHV = white matter hyperintensity volume.
Values are mean ± standard error or n (%), unless otherwise stated. Diabetes = fasting blood glucose ≥7 mmol/L, use of antidiabetic drugs, or medical history of diabetes; hypercholesterolemia = total cholesterol ≥6.2 mmol/L or lipid-lowering drug intake; hypertension = systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive drugs; smoker = ever smoker for the 3C-Dijon Study and current smoker for the EVA Study.
[a] More than 62% undetermined.

RESULTS

Baseline characteristics of study participants are detailed in table 1. Associations of lipid fractions with age, sex, vascular risk factors, inflammatory markers, and *APOE* ε genotype are shown in table e-1 on the *Neurology*® Web site at Neurology.org.

TGs and MRI-SVD. In the 3C-Dijon Study, the EVA Study, and the meta-analysis, increasing TG levels were associated with larger WMHV (combined effect estimate [β] ± standard error [SE] = 0.0936 ± 0.0252, $p = 0.0002$) and with increased frequency of EXT-WMHV (meta-odds ratio [OR] [95% confidence interval, CI] = 1.44 [1.16–1.79], $p = 0.001$) (tables 2 and 3). In the 3C-Dijon Study and in the meta-analysis, increasing TG levels were also significantly associated with higher frequency of lacunes (meta-OR = 1.63 [95% CI 1.18–2.25], $p = 0.003$) (tables 2 and 3). Tests of nonlinearity for associations of TGs with EXT-WMHV, lacunes, and WMHV were nonsignificant, except for a

Table 2 Association between lipid levels and MRI markers of small vessel disease: 3C-Dijon Study and EVA Study

	No.	Triglycerides β ± SE/OR (95% CI)	p	LDL cholesterol β ± SE/OR (95% CI)	p	HDL cholesterol β ± SE/OR (95% CI)	p
3C-Dijon Study							
Model adjusted for age and sex							
WMHV[a]	1,780	0.0882 ± 0.0302	0.0035	−0.0198 ± 0.0149	0.18	−0.0492 ± 0.0326	0.13
EXT-WMHV	446/1,780	1.41 (1.09, 1.84)	0.0093	0.90 (0.79, 1.03)	0.11	0.88 (0.66, 1.18)	0.40
Lacune	148/1,842	1.65 (1.10, 2.48)	0.015	0.90 (0.73, 1.12)	0.37	0.87 (0.55, 1.38)	0.55
Model adjusted for age, sex, and vascular risk factors[b]							
WMHV[a]	1,771	0.0727 ± 0.0362	0.045	−0.0159 ± 0.0159	0.32	0.0218 ± 0.0380	0.57
EXT-WMHV	443/1,771	1.38 (0.999, 1.89)	0.0505	0.91 (0.79, 1.05)	0.21	1.26 (0.89, 1.77)	0.19
Lacune	146/1,832	1.70 (1.04, 2.78)	0.035	0.88 (0.70, 1.11)	0.28	1.33 (0.78, 2.29)	0.30
EVA Study							
Model adjusted for age and sex							
WMHV[a]	766	0.1062 ± 0.0461	0.021	−0.0335 ± 0.0214	0.12	−0.0160 ± 0.0442	0.72
EXT-WMHV	194/766	1.49 (1.01, 2.21)	0.046	0.86 (0.71, 1.04)	0.12	0.84 (0.57, 1.23)	0.38
Lacune	85/763	1.58 (0.93, 2.70)	0.09	1.00 (0.77, 1.31)	0.97	0.87 (0.50, 1.51)	0.62
Model adjusted for age, sex, and vascular risk factors[b]							
WMHV[a]	754	0.0987 ± 0.0533	0.064	−0.0305 ± 0.0220	0.16	0.0408 ± 0.0508	0.42
EXT-WMHV	189/754	1.31 (0.82, 2.11)	0.26	0.87 (0.71, 1.06)	0.17	1.07 (0.67, 1.69)	0.77
Lacune	81/748	1.31 (0.69, 2.49)	0.41	0.99 (0.74, 1.31)	0.94	1.22 (0.63, 2.37)	0.55
Meta-analysis							
Model adjusted for age and sex							
WMHV[a]	2,546	0.0936 ± 0.0252	0.0002	−0.0243 ± 0.0122	0.047	−0.0375 ± 0.0262	0.15
EXT-WMHV	640/2,546	1.44 (1.16, 1.79)	0.001	0.89 (0.79, 0.99)	0.03	0.87 (0.69, 1.09)	0.23
Lacune	233/2,605	1.63 (1.18, 2.25)	0.003	0.94 (0.80, 1.12)	0.50	0.87 (0.61, 1.24)	0.44
Model adjusted for age, sex, and vascular risk factors[b]							
WMHV[a]	2,525	0.0810 ± 0.0300	0.007	−0.0209 ± 0.0129	0.10	0.0287 ± 0.0304	0.35
EXT-WMHV	632/2,525	1.36 (1.04, 1.77)	0.02	0.90 (0.80, 1.01)	0.07	1.19 (0.90, 1.56)	0.22
Lacune	227/2,580	1.54 (1.04, 2.28)	0.03	0.92 (0.77, 1.10)	0.37	1.29 (0.85, 1.96)	0.24

Abbreviations: β = regression coefficient; CI = confidence interval; EVA = Epidemiology of Vascular Aging Study; EXT-WMHV = age-specific top quartile of large white matter hyperintensity volume; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio; SE = standard error; WMHV = white matter hyperintensity volume.
Triglycerides = log-transformed triglycerides; WMHV = WMHV at baseline, log transformed.
[a] Additionally adjusted for white matter mask volume.
[b] Vascular risk factors: triglycerides, HDL cholesterol, LDL cholesterol, lipid-lowering drug intake, systolic blood pressure, blood pressure–lowering medication, smoking status, diabetes, body mass index.

borderline significant deviation for the association of TGs with EXT-WMH in the 3C-Dijon Study when using restricted cubic spline functions (3 knots).

Associations of TGs with MRI-SVD were largely maintained after adjustment for vascular risk factors (tables 2 and 3), and results were similar after excluding participants with self-reported prevalent stroke or after excluding individuals with a self-reported history of cardiovascular disease in the 3C-Dijon Study (data not shown). Associations of TGs with MRI-SVD were in the same direction in participants with and without lipid-lowering drug intake. In the EVA Study, the association of TGs with EXT-WMHV was significantly stronger in participants with lipid-lowering drug intake than in those without (p for interaction: 0.040). Associations were substantially unaltered by adjustment for *APOE* ε genotype, even after further adjustment for vascular risk factors (table 4). Adjustment for IL-6 and CRP levels attenuated associations between TGs and MRI-SVD, which were no longer significant after further adjusting for vascular risk factors (table 4). Associations with WMH burden tended to be more marked in women and in the older half of the samples, and associations with lacunes more marked in men,

Table 3 Associations between lipid fractions and MRI-SVD, stratified by lipid-lowering drug intake: 3C-Dijon Study and EVA Study

		Triglycerides			LDL cholesterol			HDL cholesterol		
	No.	β ± SE/OR (95% CI)	*p*	*pi*	β ± SE/OR (95% CI)	*p*	*pi*	β ± SE/OR (95% CI)	*p*	*pi*
3C-Dijon Study										
No lipid-lowering drug intake, model adjusted for age and sex										
WMHV[a]	1,192	0.0476 ± 0.0380	0.21	0.057	−0.0318 ± 0.0186	0.09	0.17	−0.0359 ± 0.0394	0.36	0.55
EXT-WMHV	294/1,192	1.35 (0.97, 1.88)	0.074	0.63	0.88 (0.75, 1.04)	0.15	0.64	0.91 (0.64, 1.30)	0.62	0.93
Lacune	98/1,224	1.88 (1.14, 3.11)	0.013	0.44	0.96 (0.73, 1.26)	0.77	0.33	0.75 (0.43, 1.32)	0.33	0.75
Lipid-lowering drug intake, model adjusted for age and sex										
WMHV[a]	588	0.1663 ± 0.0503	0.0010		0.0137 ± 0.0275	0.62		−0.0755 ± 0.0583	0.19	
EXT-WMHV	152/588	1.58 (1.02, 2.44)	0.040		0.94 (0.74, 1.19)	0.59		0.82 (0.49, 1.37)	0.45	
Lacune	50/618	1.24 (0.62, 2.51)	0.54		0.78 (0.53, 1.16)	0.22		1.25 (0.53, 2.92)	0.61	
EVA Study										
No lipid-lowering drug intake, model adjusted for age and sex										
WMHV[a]	515	0.0680 ± 0.0551	0.22	0.23	−0.0209 ± 0.0253	0.41	0.43	−0.0245 ± 0.0526	0.64	0.64
EXT-WMHV	127/515	1.10 (0.67, 1.78)	0.71	0.040	0.91 (0.72, 1.13)	0.39	0.55	1.00 (0.63, 1.59)	0.99	0.33
Lacune	60/518	1.27 (0.67, 2.41)	0.46	0.21	1.07 (0.79, 1.45)	0.67	0.29	0.67 (0.34, 1.31)	0.24	0.22
Lipid-lowering drug intake, model adjusted for age and sex										
WMHV[a]	251	0.2018 ± 0.0858	0.019		−0.0564 ± 0.0430	0.19		−0.0042 ± 0.0821	0.96	
EXT-WMHV	67/251	3.05 (1.50, 6.19)	0.0020		0.79 (0.56, 1.13)	0.20		0.57 (0.28, 1.14)	0.11	
Lacune	25/245	2.59 (0.95, 7.07)	0.063		0.81 (0.45, 1.44)	0.47		1.42 (0.56, 3.58)	0.46	
Meta-analysis										
No lipid-lowering drug intake, model adjusted for age and sex										
WMHV[a]	1,707	0.0542 ± 0.0313	0.08		−0.0280 ± 0.0150	0.06		−0.0318 ± 0.0315	0.31	
EXT-WMHV	421/1,707	1.26 (0.96, 1.66)	0.09		0.89 (0.78, 1.02)	0.09		0.95 (0.71, 1.25)	0.69	
Lacune	158/1,742	1.62 (1.09, 2.41)	0.02		1.01 (0.82, 1.23)	0.95		0.72 (0.47, 1.10)	0.13	
Lipid-lowering drug intake, model adjusted for age and sex										
WMHV[a]	839	0.1754 ± 0.0434	<0.0001		−0.0067 ± 0.0232	0.77		−0.0516 ± 0.0475	0.28	
EXT-WMHV	219/839	2.06 (1.09, 3.89)	0.03[b]		0.89 (0.73, 1.08)	0.24		0.72 (0.48, 1.09)	0.12	
Lacune	75/863	1.58 (0.89, 2.81)	0.12		0.79 (0.57, 1.09)	0.16		1.33 (0.71, 2.48)	0.38	

Abbreviations: β = regression coefficient; CI = confidence interval; EVA = Epidemiology of Vascular Aging Study; EXT-WMHV = age-specific top quartile of large white matter hyperintensity volume; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio; *pi* = *p* value for interaction between lipid-lowering drug intake and each lipid fraction; SE = standard error; SVD = small vessel disease; WMHV = white matter hyperintensity volume. Triglycerides = log-transformed triglycerides; WMHV = WMHV at baseline, log transformed.
[a] Additionally adjusted for white matter mask volume.
[b] Random effects reported (I^2 >50%).

although there was no significant interaction with age or sex (table e-2). Of note, results were similar when using the log-transformed ratio of WMHV over white matter mask volume as the dependent variable instead of WMHV with additional adjustment for white matter mask volume. When distinguishing WMH according to their location, increasing TG levels were significantly associated with larger PVWMHV in the meta-analysis ($\beta \pm SE = 0.0908 \pm 0.0261$, $p = 0.0005$), and also with DWMHV ($\beta \pm SE = 0.0413 \pm 0.0172$, $p = 0.02$). Finally, we observed a graded association of TGs with increasing MRI-SVD severity in the meta-analysis: OR = 2.19 (95% CI 1.39–3.46), $p = 0.0007$, for presence of both lacunes and EXT-WMHV vs none, OR = 1.28 (95% CI 1.02–1.60), $p = 0.03$, for presence of either lacunes or EXT-WMHV vs none.

Other lipid fractions and MRI-SVD. LDL cholesterol was nearly always associated with a decreased severity and frequency of MRI-SVD in both samples. However, only the associations of LDL with decreasing WMHV and lower frequency of EXT-WMHV reached significance in the meta-analysis (tables 2, 3, and e-2). After controlling for vascular risk factors, *APOE* ε genotype, or

Table 4 **Association between lipid levels and MRI markers of small vessel disease, 3C-Dijon Study, additionally adjusted for circulating CRP and IL-6 levels and for *APOE* ε4 or *APOE* ε2 carrier status**

		Triglycerides		LDL cholesterol		HDL cholesterol	
	No.	β ± SE/OR (95% CI)	p	β ± SE/OR (95% CI)	p	β ± SE/OR (95% CI)	p
Model adjusted for age, sex, CRP, and IL-6[a]							
WMHV[b]	1,663	0.0733 ± 0.0312	0.019	−0.0189 ± 0.0154	0.22	−0.0255 ± 0.0350	0.47
EXT-WMHV	411/1,663	1.37 (1.04, 1.81)	0.023	0.90 (0.78, 1.03)	0.14	0.96 (0.70, 1.31)	0.78
Lacune	131/1,691	1.53 (0.997, 2.36)	0.051	0.84 (0.66, 1.06)	0.14	0.80 (0.48, 1.34)	0.40
Model adjusted for age, sex, CRP, IL-6, and vascular risk factors[a]							
WMHV[b]	1,658	0.0682 ± 0.0370	0.065	−0.0149 ± 0.0165	0.36	0.0349 ± 0.0398	0.38
EXT-WMHV	408/1,658	1.38 (0.99, 1.92)	0.058	0.91 (0.78, 1.06)	0.24	1.31 (0.91, 1.89)	0.14
Lacune	129/1,686	1.52 (0.91, 2.56)	0.11	0.83 (0.64, 1.06)	0.14	1.18 (0.66, 2.13)	0.58
Model adjusted for age, sex, and *APOE* ε4 carrier status[c]							
WMHV[b]	1,749	0.0941 ± 0.0303	0.0019	−0.0187 ± 0.0150	0.21	−0.0520 ± 0.0329	0.11
EXT-WMHV	434/1,749	1.45 (1.11, 1.89)	0.0060	0.90 (0.78, 1.03)	0.12	0.89 (0.66, 1.19)	0.44
Lacune	145/1,808	1.67 (1.11, 2.51)	0.014	0.89 (0.71, 1.11)	0.29	0.85 (0.53, 1.35)	0.49
Model adjusted for age, sex, *APOE* ε4 carrier status, and vascular risk factors[c]							
WMHV[b]	1,740	0.0785 ± 0.0364	0.031	−0.0144 ± 0.0161	0.37	0.0212 ± 0.0383	0.58
EXT-WMHV	431/1,740	1.42 (1.03, 1.97)	0.033	0.91 (0.79, 1.05)	0.21	1.30 (0.92, 1.84)	0.14
Lacune	143/1,798	1.69 (1.03, 2.78)	0.038	0.87 (0.68, 1.09)	0.23	1.33 (0.77, 2.30)	0.31
Model adjusted for age, sex, and *APOE* ε2 carrier status[c]							
WMHV[b]	1,749	0.0931 ± 0.0304	0.0022	−0.0180 ± 0.0153	0.24	−0.0527 ± 0.0329	0.11
EXT-WMHV	434/1,749	1.44 (1.10, 1.88)	0.0070	0.90 (0.79, 1.04)	0.15	0.89 (0.66, 1.19)	0.42
Lacune	145/1,808	1.66 (1.10, 2.50)	0.015	0.90 (0.72, 1.12)	0.36	0.84 (0.53, 1.35)	0.47
Model adjusted for age, sex, *APOE* ε2 carrier status, and vascular risk factors[c]							
WMHV[b]	1,740	0.0768 ± 0.0368	0.037	−0.0137 ± 0.0166	0.41	0.0203 ± 0.0385	0.60
EXT-WMHV	431/1,740	1.41 (1.02, 1.96)	0.038	0.91 (0.79, 1.06)	0.25	1.29 (0.91, 1.83)	0.15
Lacune	143/1,798	1.67 (1.01, 2.76)	0.043	0.88 (0.69, 1.11)	0.28	1.32 (0.76, 2.28)	0.32

Abbreviations: β = regression coefficient; CI = confidence interval; CRP = C-reactive protein; EXT-WMHV = age-specific top quartile of large white matter hyperintensity volume; HDL = high-density lipoprotein; IL-6 = interleukin 6; LDL = low-density lipoprotein; OR = odds ratio; SE = standard error; WMHV = white matter hyperintensity volume.
Triglycerides = log-transformed triglycerides; WMHV = WMHV, log-transformed.
[a] CRP and IL-6 in tertiles.
[b] Additionally adjusted for white matter mask volume.
[c] *APOE* ε24 excluded.

inflammatory markers, this association was no longer significant.

We did not observe any significant association of HDL cholesterol with MRI-SVD in either dataset, or in the meta-analysis (tables 2 and 3).

DISCUSSION In 2 independent studies comprising a total of 2,608 community-dwelling older persons, we found that increasing TG levels were associated with increasing frequency and severity of MRI-SVD. These associations were attenuated but largely maintained after adjusting for vascular risk factors and inflammatory markers. They were consistent in individuals with and without lipid-lowering drug intake, although associations with EXT-WMHV were stronger in the former. No robust association was observed between other lipid fractions and MRI-SVD. LDL cholesterol tended to be associated with decreasing frequency and severity of all MRI markers of SVD in both studies, reaching significance for WMHV and EXT-WMHV in the meta-analysis, but this weak association was no longer significant after additional adjustment for vascular risk factors, *APOE* ε genotype, or inflammatory markers.

Results of previous smaller studies were inconsistent, a few studies suggesting an association between TGs and larger WMH burden[22,23] or higher frequency of lacunes[24] while others did not.[25,e6] In our dataset, the consistent associations between TGs and MRI-SVD observed in 2 independent population-based studies with various measures of MRI-SVD, the graded relationship of TGs with increasing MRI-SVD severity, and the fact that associations were maintained after various adjustments and subgroup analyses, strongly support that these associations are not spurious.

The putative mechanisms underlying the relationship between TGs and MRI-SVD are still hypothetical. First, inflammation could be a key mediator. Indeed, TG levels are strongly associated with inflammatory markers,[26] as confirmed in our dataset, and inflammatory biomarkers were reported to be associated with MRI markers of cerebrovascular disease.[19,27] The lipolysis of TG-rich lipoproteins by the lipoprotein lipase was also shown to be associated specifically with endothelial cell inflammation due to free fatty acid production.[28] Adjusting for CRP and IL-6 levels in our analyses attenuated the relationship between TGs and MRI-SVD, supporting a possible mediating effect of inflammation. The association of TGs with white matter disease was more prominent for PVWMHV, in agreement with a stronger association of inflammatory markers with periventricular WMH.[27] Second, TG levels have been associated with blood-brain barrier dysfunction, which could contribute to the pathogenesis of WMH,[29,e7] especially periventricular WMH,[30] and of lacunes.[31] Third, TG levels were reported to adversely affect small-artery compliance, possibly contributing to chronic white matter hypoperfusion.[32,e8] Fourth, it was proposed that dietary TG intake could increase β-amyloid synthesis and facilitate β-amyloid delivery to the brain, thus potentially promoting cerebral amyloid angiopathy,[33,34] because lipoproteins that cross the blood-brain barrier can transport β-amyloid.[35,e9] Finally, *APOE* ε polymorphism could be a potential mediator, because APOE is a key player in lipid metabolism,[36] and *APOE* ε2 and *APOE* ε4 were associated with MRI-SVD.[20] However, adjustment for *APOE* ε genotype did not modify the relationship between TGs and MRI-SVD in our dataset.

Several studies did not report any association between LDL cholesterol and MRI-SVD.[24,25,37,38,e6] One study found a significant relationship between decreasing LDL cholesterol levels and worsening of white matter lesion grade in 1,919 community persons aged 65 years or older.[38] Another study reported an association between hyperlipidemia (defined by hypercholesterolemia, hypertriglyceridemia, or use of lipid-lowering drugs) and decreased WMH severity in 1,135 acute ischemic stroke patients.[37] The absence of an association between increasing LDL cholesterol and MRI-SVD, and even trends toward the opposite, in our dataset is in agreement with published data. Supporting this finding, data of the MRI substudy of the PROSPER (Prospective Study of Pravastatin in Elderly at Risk) randomized controlled trial did not find any association between statin intake and WMH progression after nearly 3 years of follow-up in 535 individuals with a history of or at risk of vascular disease.[39] This could suggest that LDL is not as deleterious for small arteries as it is for large arteries. However, this result might only be a chance finding.

Strengths of our study include the large sample size, the consistent results across 2 independent population-based samples, and the use of volumetric MRI measurements following the same protocol. Limitations comprise the cross-sectional design and the older age of our population. Moreover, the sample is not representative of the French general population of that age, because individuals taking part in a cohort study with regular follow-up examinations are more likely to be more health-conscious and have fewer risk factors and less disease than individuals who do not. Another selection bias might occur from MRI examination, because people who had restrictions for this examination could not be included. These limitations are common to all population-based prospective studies, regardless of the sampling method used. As a result, the 3C-Dijon Study and EVA Study participants with brain MRI were healthier and had fewer vascular risk factors than those who did not undergo MRI (table e-3). Lipid levels measured in late life can decrease because of behavioral changes, presence of comorbidities, or initiation of lipid-lowering drugs. Midlife lipid levels, which better reflect exposure to dyslipidemia over a lifespan, were not available.[40,e10] Moreover, a survival bias cannot be excluded, because individuals with very high LDL cholesterol or TG levels may have died early of vascular disease before being included. However, results were similar across age strata, including in the younger EVA Study participants, suggesting that survival bias is not the only explanation. Our analyses were restricted to ischemic MRI-SVD because MRI sequences enabling the detection of cerebral microbleeds were not available.

Increasing TG levels were associated with larger WMHV and higher frequency of lacunes in older community persons. Decreasing LDL cholesterol displayed a borderline significant association with larger WMHV and EXT-WMHV. These results warrant further examination in other population-based studies, including younger individuals and midlife measurements of lipid levels. Because MRI lesions have a pivotal role in the deterioration of brain function, understanding the underlying pathomechanisms is of critical importance.

AUTHOR CONTRIBUTIONS

Mrs. Sabrina Schilling: analysis and interpretation, statistical analysis, drafting/revising the manuscript. Dr. Christophe Tzourio: study concept or design, analysis and interpretation, study supervision or coordination, drafting/revising the manuscript, obtaining funding. Dr. Carole Dufouil: drafting/revising the manuscript. Dr. Yicheng Zhu: acquisition of data, drafting/revising the manuscript. Dr. Claudine Berr: drafting/revising the manuscript. Dr. Annick Alpérovitch: drafting/revising the manuscript, obtaining funding. Dr. Fabrice Crivello: acquisition of data, drafting/revising the manuscript. Dr. Bernard Mazoyer: acquisition of data, drafting/revising the manuscript. Dr. Stéphanie Debette: study concept or design, analysis and interpretation, statistical analysis, study supervision or coordination, drafting/revising the manuscript.

ACKNOWLEDGMENT

The authors thank the participants of the 3C-Dijon Study and EVA Study for their important contributions.

STUDY FUNDING

The 3-City Study is conducted under a partnership agreement among the Institut National de la Santé et de la Recherche Médicale (INSERM), the Victor Segalen–Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Education Nationale (MGEN), Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques." Christophe Tzourio has received investigator-initiated research funding from the French National Research Agency (ANR). Stéphanie Debette is a recipient of a "Chaire d'Excellence Junior" grant from the Agence Nationale de la Recherche (ANR) and is supported by a grant from the Fondation Leducq. The EVA Study was performed under an agreement between INSERM (Institut National de la Santé et de la Recherche Médicale); the Merck, Sharp, and Dohme–Chibret Laboratories (West Point, PA); and the EISAI Company, Paris, France.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received February 27, 2014. Accepted in final form August 13, 2014.

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