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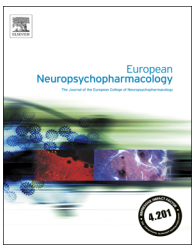

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Gender-specific associations between lipids and cognitive decline in the elderly

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Abstract
The aim of this study was to examine the associations between serum lipid levels and cognitive function in a community-based sample of non-demented subjects aged 65 years and over. Participants were 2737 men and 4118 women from a population-based cohort recruited from three French cities. Visual memory, verbal fluency, psychomotor speed, and executive abilities were evaluated at baseline, and after 2, 4, and 7 years of follow-up. Lipid levels were evaluated at baseline. Multiadjusted Cox models stratified by gender were adjusted for sociodemographic and lifestyle characteristics, mental and physical health, and genetic vulnerability to dyslipidemia (apolipoprotein E and A, and cholesteryl ester transfer protein) and taking into account baseline vascular pathologies. In men, a hypercholesterolemic pattern in late-life (high total cholesterol (T-C), low HDL-C, high LDL-C levels) was associated with a 25 to 50% increased risk of decline over 7 years in psychomotor speed, executive abilities, and verbal fluency. Specific associations with low T-C and low LDL-C levels were also observed which may depend on genetic vulnerability to dyslipidemia (related to apolipoprotein A5 and cholesteryl exchange transfer protein). In contrast, in women, a 30% higher rate of decline was found in psychomotor speed with high HDL-C levels and in executive abilities with low levels of LDL-C and triglycerides, in interaction with hormonal treatment. For men and women, vascular pathologies only slightly outweighed the risk related to lipids. This suggests a complex

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gender-specific pattern of cognitive decline involving genetic vulnerability in men and hormonal status in women.

1. Introduction

Cholesterol is a risk factor for vascular disease which is, in turn, an important risk factor for cognitive decline and dementia. The relationship between total cholesterol (T-C) and cognition in the elderly is however, currently a matter of debate; a higher prevalence of mild cognitive impairment and cognitive decline being associated with both low and high T-C, or showing no significant association (Anstey et al., 2008; Shepardson et al., 2011). Inconsistencies could result from heterogeneity in study design, sample characteristics, and lack of examination of cholesterol components, low- and high density lipoprotein cholesterol (LDL-C and HDL-C) being inversely associated with vascular disease.

A potential shortcoming is that substantial ageing-related vascular pathophysiological changes may already be present, outweighing the risk related to lipids. Gender differences have also not been examined although men and women differ with regard to lipid levels, therapeutic recommendations, and cardiovascular risk factors and the fact that hormonal status can modulate lipid levels in elderly women (Dupuy et al., 2008; LaRosa, 1992; Mendelsohn and Karas, 2005; Polk and Naqvi, 2005; The NCEP Expert Panel, 2002). In particular, a change to a potentially atherogenic profile is seen in women after menopause which can be corrected by hormone treatment (Dupuy et al., 2008; Nerbrand et al., 2004). Genetic interactions have also focused on apolipoprotein E (APOE), a major determinant in lipoprotein metabolism and a risk factor for Alzheimer's disease, but rarely on other polymorphisms involved in dyslipidemia phenotype, such as APOA5 and cholesteryl ester transfer protein (CETP) promoting the exchange of triglyceride (TG) for cholesteryl ester in lipoprotein (De Andrade et al., 2011; Sanders et al., 2010).

We hypothesized first that lipids may be associated with a higher risk of cognitive decline differently in men and women and second, that these associations in the elderly could have lesser impact due to underlying vascular pathologies. We examined the relationship between lipid levels and cognitive decline in community-dwelling men and women over 7 years of follow-up, while taking into account a large number of potential confounders including genetic vulnerability to dyslipidemia and/or to cognitive decline as well as hormone treatment for women as a potential modifier.

2. Experimental procedures

2.1. Study population

Subjects were recruited as part of the Three-City study, a multi-site cohort study of 9294 community-dwelling persons aged 65 years and over from the electoral rolls of three French cities (Bordeaux, Dijon, and Montpellier) between 1999 and 2001 (The 3C Study Group, 2003). The study protocol was approved by the Ethics Committee of the Bicêtre University-Hospital (France). Written informed consent was obtained from each participant. Participants were administered standardized questionnaires and neuropsychological tests, and underwent clinical examinations including diagnosis of dementia at baseline and at 2, 4, and 7-year follow-up (respectively wave 1, 2, and 3).

Of the 9080 dementia-free participants included at baseline, we excluded 555 subjects who did not have blood lipid measurement. A further 995 subjects had no follow-up data (686 had died), and another 674 had missing data for at least one adjustment variable, leaving 6855 subjects in the analysis. Excluded non-demented persons had lower education and cognitive scores at baseline, were older, more frequently widowed and depressed, and more likely to have history of vascular pathologies, disabilities, and diabetes ($p<10^{-4}$). They were also more frequently women ($p=0.007$), more likely to have lower HDL-C ($p=0.003$) and higher T-C, LDL-C, and TG levels ($p<0.0001$) and less frequently treated with lipid lowering agents ($p=0.0002$).

2.2. Cognitive measures and dementia

A short battery of cognitive tests designed to assess different areas of cognitive functioning was administered by trained staff at baseline and at each follow-up (two, four and seven years). The Benton's Visual Retention Test (BVRT) assessed immediate visual memory (Benton, 1965). Isaacs Set Test provided a measure of verbal fluency or semantic access as participants were given 30 s to generate as many words as possible within a given semantic category (animals, colors, fruits and cities) (Isaacs and Kennie, 1973). The Trail Making Tests are timed visual motor tasks where participants need to connect consecutively numbered circles (A) or alternate number and letter circles (B). Trail Making Test A assess psychomotor speed and Trail Making Test B involving a cognitive switching task assess executive abilities (Reitan, 1965). All tests were administered at baseline, and waves 1, 2, and 3 of the follow-up, except the Trail Making Tests which were not administered in wave 1. Consequently, analyses relating to these tasks involved only 5827 participants.

The cognitive score distribution being not normal for the use of criteria based on standard deviation, cognitive decline over the 7-year follow-up period was defined as being in the first (worst) quintile of the distribution of the differences. A difference score was first calculated between cognitive scores obtained at any follow-up and the baseline score. The number of difference scores depended on the number of follow-ups a subject had data for (from one to three). The quintile of the individual maximum of the difference scores was calculated. The decliners were defined as those participants belonging to the worst quintile of the worst difference scores and the time of decline was the first visit when the subject fell below the cut-off. Decline corresponded to a decrease from baseline by at least 3 points on the Benton test or at least 10 points on the Isaacs test and an increase of at least 22 s on the Trail Making Test A or 57 s on the Trail Making Test B.

A three-step procedure was used to diagnose cases of dementia as described previously (Ancelin et al., 2013; The 3C Study Group, 2003). Briefly, screening was first based on a thorough neuropsychological examination by trained psychologists. Data on activities of daily living, severity of cognitive disorders, and, where possible,

magnetic resonance images or computed tomography scans were collected. In addition, in Montpellier and Bordeaux all participants were examined by a neurologist. In Dijon only persons suspected of having a cognitive deficit on the basis of their neuropsychological performance underwent further examination by a specialist. Finally, in the 3 centers, all suspected dementia cases were analyzed and validated by a common independent committee of neurologists according to DSM-IV criteria (American Psychiatric Association, 1994). The participants with dementia at baseline were excluded from the present study.

2.3. Socio-demographic and clinical variables

The standardized interview included questions on socio-demographic and lifestyle (including smoking and alcohol consumption) characteristics and an inventory of all drugs used over the preceding month. Blood pressure was measured twice in a sitting position using a digital electronic tensiometer OMRON_M4, and the average was used in the analyses. Hypertension (≥160/95 mm Hg or treated) and diabetes (fasting glycemia ≥7 mmol/l or treated) were assessed and body mass index (BMI) was evaluated from measured weight and height (normal <25, overweight [25-30[, and obese ≥30 kg/m^2). Mobility was assessed using the Rosow and Breslau (1966) scale. History of vascular pathologies (stroke, angina pectoris, myocardial infarction, arteritis, and cardio-vascular surgery) was established according to standardized questions with additional information where necessary from general practitioners, and chronic respiratory disorders were recorded. Depressive symptomatology was assessed by the Center for Epidemiological Studies-Depression Scale (Radloff, 1977). Venous blood samples were taken at baseline after fasting for >12 h. Lipid levels were evaluated in serum by routine enzymatic methods (Dupuy et al., 2008) and genotyping of APOE (ε2/ε3/ε4), APOA5 (*rs662799*), and CETP (*rs1800775*) polymorphisms was carried out by the Lille Genopole (http://www.genopole-lille.fr/spip/). For women, current and past use of hormonal treatment and detailed information relating to the type of treatment was obtained at baseline. Treatment use was validated by presentation of the prescription or the medication itself and past users were shown photos to aid with recall. Hormone treatment consisted in estradiol combined or not with oral progesterone or synthetic progestin.

2.4. Statistical analyses

The Chi2 test for categorical variables and the Student t test for continuous variables were used to identify sex differences. Cox proportional hazards models with delayed entry taking age as the basic time scale and birth as the time origin (Thiebaut and Benichou, 2004) were used to determine whether baseline lipid levels were associated with risk of clinically significant cognitive decline (as defined above). This model took into account all information up to time of censoring, either by death or loss to follow-up, or the time of observed cognitive decline, thus minimizing selection bias due to cohort attrition. Lipid variables were categorized into three classes corresponding to the quartile of the highest lipid levels, the quartile of the lowest lipid levels and the two intermediate quartiles (reference) to detect non-linear associations.

Hazard Ratios (HRs) were first adjusted for centre, education, and baseline cognitive performance in addition to age (model 1). Multivariate analyses further included covariates associated with cognitive decline at $p<0.15$ (to avoid potential bias related to a stricter definition of confounder); marital status, BMI, mobility, anticholinergic use, depression, hypertension, diabetes, lipid lowering agent, APOEε4, APOA5, CETP, and hormone treatment for women (model 2). The potential effect modification by APOA, CETP, or hormone treatment for women was considered by including appropriate interaction terms in the final multivariate Cox models (models 2). For *p*-values of interaction <0.10, subsequent analyses were stratified to determine independent group effects. Analyses were carried out using SAS software (version 9.2) with a 5% significance level.

3. Results

3.1. Subjects

The analyzed sample consisted of 2737 men and 4118 women with a mean (SD) age of 73.6 (5.3) for men and 73.8 (5.2) for women. At baseline, women and men were found to differ on all characteristics except for APOE and CETP; women being older ($p=0.02$), with lower education, more frequently single or widowed, depressed, and confined to home but having less vascular pathology ($p<10^{-4}$) (Table 1). Women had lower cognitive performance (except on the Isaacs test) and also higher T-C, HDL-C, and LDL-C levels but lower TG levels than men ($p<10^{-4}$), and used more frequently lipid lowering agents ($p=0.003$).

Due to significant interactions between lipids and gender for some cognitive tests (*cf*. for instance Trail Making Test B with HDL-C, χ^2 (2, $n=5827$)=10.59, $p=0.005$), the following analyses were stratified by gender.

3.2. Lipid levels and risk of cognitive decline in men

In Cox models adjusted for age, center, education, and baseline cognitive performance, men with high T-C levels (upper quartile) showed a significant 32% higher risk of decline over 7 years on the Isaacs test compared to intermediate quartiles (Table 2, model 1). Both low and high T-C levels were associated with an increased risk of decline on the Trail Making Test A, by 39 and 50% respectively, and a U-shaped association with cognitive decline was also observed for LDL-C. Low HDL-C was associated with an increased risk by 31% of decline on the Trail Making Test A. For Trail Making Test B, high T-C and low HDL-C were also associated with higher cognitive decline by 36 and 49%, respectively. The same associations were observed in the multiadjusted model 2. TG was not associated with decline in men regardless of the cognitive task, and no significant associations were found between any lipids and decline on the Benton test (data not shown).

An interaction was found between T-C and APOA5 (χ^2 (2, $n=2737$)=4.96, $p=0.08$), for decline on the Isaacs test (Table 3). Only men with the AA polymorphism of APOA5 and high T-C levels were at increased risk of decline (HR=1.44, 95%CI=1.16-1.78, (χ^2 (1, $n=2366$)=11.27, $p=0.0008$). We also observed an interaction between T-C and CETP (χ^2 (2, $n=2287$)=4.48, $p=0.10$), for decline on the Trail Making Test B; the risk of decline associated with low T-C levels being increased in men with the CC polymorphism (HR=1.66, 95%CI=1.04-2.65, χ^2 (1, $n=682$)= 4.45, $p=0.04$).

A sensitivity analysis was performed examining the men without vascular pathologies. We found the same pattern as

for the whole sample except that the association between high LDL-C and decline on the Trail Making Test A remained significant in the multiadjusted model (HR=1.37, 95% CI=1.06-1.77, χ^2 (1, n=1809)=5.98, p=0.015) and that with low HDL-C was even stronger (HR=1.44, 95%CI=1.10-1.89, χ^2 (1, n=1809)=7.08, p=0.008) (data not shown).

Table 1 Characteristics of the study population (n=6855).

Characteristic	Men (n=2737)		Women (n=4118)		χ^2 statistic	p[a]
	n	%	*n*	%		
Age					9.90	0.02
65-69	706	25.8	1020	24.8		
70-74	952	34.8	1350	32.7		
75-80	688	25.1	1176	28.6		
80+	391	14.3	572	13.9		
Education					229.20	$<10^{-4}$
5 years	587	21.5	1032	25.1		
9 years	843	30.8	1661	40.3		
12 years	534	19.5	860	20.9		
12+	773	28.2	565	13.7		
Marital status					944.99	$<10^{-4}$
Married	2263	82.7	1886	45.8		
Single or divorced	213	7.8	794	19.3		
Widowed	261	9.5	1438	34.9		
BMI (kg/m^2)					199.82	$<10^{-4}$
Normal (<25)	1038	37.9	2213	53.7		
Overweight [25-30[	1353	49.4	1358	33.0		
Obese (≥30)	346	12.6	547	13.3		
Mobility[b]	82	3.0	254	6.2	35.49	$<10^{-4}$
Lipid Lowering Agents					11.37	0.003
No	1944	71.0	2838	69.0		
Fibrate	333	12.2	619	15.0		
Statin	460	16.8	659	16.0		
Depressive symptoms[c]	371	13.6	1153	28.0	198.40	$<10^{-4}$
Anticholinergic use	118	4.3	397	9.6	67.21	$<10^{-4}$
Vascular pathologies[d]	603	22.0	504	12.2	116.44	$<10^{-4}$
Diabetes[e]	342	12.5	280	6.8	64.66	$<10^{-4}$
High Blood Pressure[f]	1652	60.4	2202	53.5	31.67	$<10^{-4}$
At least 1 APOEε4	566	20.7	801	19.5	1.55	0.21
APOA5 (*rs662799*)					4.11	0.04
AA	2366	86.5	3628	88.1		
AG or GG	371	13.6	490	11.9		
CETP (*rs1800775*)					1.75	0.19
CC	810	29.6	1158	28.1		
AA or AC	1927	70.4	2960	71.9		
Verbal fluency[g] (Isaacs Set Test score <39)	545	19.9	819	19.9	0.0006	0.98
Visual memory[g] (Benton score <10)	647	23.6	1272	30.9	42.87	$<10^{-4}$
Psychomotor speed[g] (Trail Making Test A score>70 s)	460	16.9	887	21.8	23.57	$<10^{-4}$
Executive abilities[g] (Trail Making Test B score>140 s)	483	18.3	840	21.3	8.77	0.003
	Mean	**SD**	**Mean**	**SD**	*t statistic*	p[a]
T-C (mmol/l)	5.52	0.91	5.99	0.97	−20.20	$<10^{-4}$
LDL-C (mmol/l)	3.50	0.80	3.70	0.87	−9.82	$<10^{-4}$
HDL-C (mmol/l)	1.44	0.34	1.74	0.39	−33.37	$<10^{-4}$
TG (mmol/l)	1.28	0.60	1.21	0.53	5.43	$<10^{-4}$

Abbreviations: APO=apolipoprotein; BMI=body mass index; CETP=cholesteryl ester transfer protein HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; SD=standard deviation; T-C=total cholesterol; TG=triglyceride.

[a]The Chi2 test and the Student *t* test were used for categorical and continuous variables.

[b]Mobility: assistance required to perform at least one of the three Rosow-Breslau items (relating to confinement to home and neighbourhood).

[c]The presence of depressive symptoms was assessed using the Center for Epidemiological Studies-Depression Scale (Radloff, 1977) with a cut-off of ≥ 16.

[d]History of stroke, myocardial infarction, angina pectoris, or arteritis and cardio-vascular surgery.

[e]Diabetes defined as glucose ≥ 7 mmol/l or treated.

[f]High blood pressure defined as $\geq 160/95$ mm Hg or treated.

[g]The % of subjects with lowest cognitive performances at baseline are reported (lowest quintile except for Trail Making Tests, highest quintile).

Table 2 Adjusted models for association between lipid levels and cognitive decline over 7-year follow-up in men.

		Model 1[a]			Model 2[b]		
		HR [95%CI]	χ^2 statistic	*p*	HR [95%CI]	χ^2 statistic	*p*
Isaacs (*n*=2737)							
T-C[c]							
	<4.92	1.08 [0.88-1.33]	0.59	0.44	1.03 [0.84-1.27]	0.08	0.78
	≥6.09	1.32 [1.08-1.61]	7.39	0.007	1.36 [1.11-1.66]	8.80	0.003
Trail Making Test A (*n*=2287)							
T-C[c]							
	<4.92	1.39 [1.11-1.75]	8.25	0.004	1.44 [1.15-1.82]	9.82	0.002
	≥6.09	1.50 [1.20-1.88]	12.34	0.0004	1.49 [1.19-1.87]	11.83	0.0006
LDL-C[c]							
	<2.95	1.34 [1.07-1.67]	6.45	0.01	1.42 [1.13-1.78]	8.93	0.003
	≥4.00	1.25 [0.99-1.57]	3.64	0.06	1.23 [0.97-1.54]	2.96	0.09
HDL-C[c]							
	<1.19	1.31 [1.04-1.65]	5.40	0.02	1.28 [1.01-1.61]	4.25	0.04
	≥1.63	1.14 [0.91-1.43]	1.34	0.25	1.16 [0.92-1.45]	1.54	0.21
Trail Making Test B (*n*=2287)							
T-C[c]							
	<4.92	1.22 [0.97-1.55]	2.78	0.10	1.22 [0.96-1.55]	2.66	0.10
	≥6.09	1.36 [1.07-1.71]	6.48	0.01	1.34 [1.06-1.69]	5.77	0.02
HDL-C[c]							
	<1.19	1.49 [1.18-1.88]	10.96	0.0009	1.43 [1.12-1.81]	8.48	0.004
	≥1.63	1.21 [0.95-1.53]	2.41	0.12	1.23 [0.96-1.56]	2.76	0.10

Abbreviations: APO=apolipoprotein; BMI=body mass index; CETP=cholesteryl ester transfer protein; CI=confidence interval; HDL-C=high density lipoprotein cholesterol; HR=hazard ratio; LDL-C=low density lipoprotein cholesterol; T-C=total cholesterol.

[a]Model 1: adjusted for age, center, education level, and baseline cognitive performances.

[b]Model 2: Model 1+adjusted for marital status, BMI, lipid lowering agent use, anticholinergic use, mobility, hypertension, diabetes, depression, APOE4, APOA5, and CETP.

[c]Expressed as mmol/l. Lipid variables were categorized into three classes corresponding to the quartile of the highest lipid levels, the quartile of the lowest lipid levels and the two middle quartiles (reference, HR=1). The lipid variables for which none of the low and high quartiles were associated with dementia at *p*-value >0.15 were not reported in the Table.

Table 3 Total cholesterol levels in men and cognitive decline according to genetic vulnerability to dyslipidemia related to APOA5 and CETP polymorphism in men.

	T-C[a]	HR[b]	[95% CI]	χ^2 statistic	*p*
Isaacs (*n*=2737)					
APOA5					
AA (*n*=2366)	<4.92	1.01	[0.81-1.26]	0.003	0.95
	≥6.09	1.44	[1.16-1.78]	11.27	0.0008
AG or GG (*n*=371)	<4.92	1.59	[0.81-3.12]	1.84	0.17
	≥6.09	0.96	[0.49-1.90]	0.01	0.91
Trail Making Test B (*n*=2287)					
CETP (*rs1800775*)					
CC (*n*=682)	<4.92	1.66	[1.04-2.65]	4.45	0.04
	≥6.09	1.35	[0.82-2.21]	1.38	0.24
AA or AC (*n*=1605)	<4.92	1.06	[0.79-1.41]	0.14	0.71
	≥6.09	1.28	[0.98-1.68]	3.17	0.08

Abbreviations: APO=apolipoprotein; BMI=body mass index; CETP=cholesteryl ester transfer protein; CI=confidence interval; HR=hazard ratio; T-C=total cholesterol.

[a]Expressed as mmol/l. Lipid variables were categorized into three classes corresponding to the quartile of the highest lipid levels, the quartile of the lowest lipid levels and the two middle quartiles (reference, HR=1).

[b]Model 2: adjusted for age, center, education level, and baseline cognitive performances, marital status, BMI, lipid lowering agent use, anticholinergic use, mobility, hypertension, diabetes, depression, APOE4 and APOA5 (for TMTB), and CETP (for Isaacs).

3.3. Lipid levels and cognitive decline in women

In women, after multivariable adjustment, both high LDL-C and high HDL-C levels were significantly associated with a greater decline on the Trail Making Test A, by 20 and 29%, respectively (Table 4, model 2). Low levels of LDL-C and TG were associated with a greater decline on the Trail Making Test B by 29 and 24%, respectively. T-C was not significantly associated with cognitive decline regardless of the task and no significant associations were found between any lipids and decline on the Isaacs and Benton tests (data not shown).

An interaction was found between hormone treatment and HDL-C (χ^2 (4, *n*=3540)=8.36, *p*=0.08) for decline on the Trail Making Test A (Table 5). The increased risk of decline on the Trail Making Test A was significant for women who had never used hormone treatment and with high HDL-C levels (HR=1.35, 95%CI=1.09-1.67, χ^2 (1, *n*=2367)=7.53, *p*=0.006) and for current hormone treatment users with low HDL-C (HR=2.13, 95%CI=1.14-3.96, χ^2 (1, *n*=563)=5.64, *p*=0.018).

In sensitivity analyses, when examining the group of women without vascular pathologies, the same pattern was observed with LDL-C and TG for Trail Making Test B, as well as with HDL-C and Trail Making Test A (and interaction with hormone treatment, χ^2 (4, *n*=3142)=9.01, *p*=0.06). However, the association between high LDL-C levels and Trail Making Test A failed to be significant (HR=1.19, 95%CI=0.97-1.45, χ^2 (1, *n*=3142)=2.76, *p*=0.10 in model 2). Conversely, there was an association between low TG and decline on the Trail Making Test A (HR=1.28, 95%CI=1.04-1.57, χ^2 (1, *n*=3142)=5.45, *p*=0.02 in model 2) which was only significant in women who had never used hormone treatment (HR=1.32, 95%CI=1.03-1.67, χ^2 (1, *n*=2066)=5.02, *p*=0.025) (data not shown).

4. Discussion

Our results show significant associations between lipids and cognitive decline in the elderly, independent of APOE genotype as well as numerous potential co-determinants of decline, including vascular factors and lipid lowering agent use. The associations differed between men and women and were specific to certain cognitive abilities (Trail Making Test A and B), sensitive to alterations in psychomotor speed, visuospatial ability, and cognitive functioning. As no effect was found on the Benton Test of visual memory, this suggests that frontal executive and psychomotor skills are likely to be affected by lipid status. These effects are consistent with observations that frontal areas may be particularly vulnerable to early cognitive impairment (Howieson et al., 2008; Iachini et al., 2009).

Of the studies having examined whole samples without gender stratification, a number of prospective studies found no significant associations with T-C, LDL-C, HDL-C, and TG (Reitz et al., 2005, 2008; Solfrizzi et al., 2004; Teunissen et al., 2003; van den Berg et al., 2007). Solomon et al. (2009) reported positive associations between midlife (but not late-life) T-C and cognitive decline in episodic memory and fluency. None of the studies examined executive functioning and considered gender stratification or examined elderly men specifically.

In our study, a hypercholesterolemic late-life pattern (high T-C, low HDL-C, high LDL-C) was related to an increased risk of cognitive decline in executive abilities and psychomotor speed in elderly men, with vascular pathologies only slightly outweighing the risk related to lipids. A more unexpected association with low T-C and LDL-C levels was also observed. This dual pattern may depend on genetic vulnerability to dyslipidemia. In our study, high T-C

Table 4 Adjusted models for association between lipid levels and cognitive decline over 7-year follow-up in women.

		Model 1[a]			Model 2[b]		
		HR [95%CI]	χ^2 statistic	*p*	HR [95%CI]	χ^2 statistic	*p*
	Trail Making Test A (n=3540)						
LDL-C [c]							
	<3.10	1.07 [0.88-1.30]	0.50	0.48	1.05 [0.87-1.28]	0.27	0.61
	≥4.26	1.20 [1.00-1.44]	3.92	0.05	1.20 [1.00-1.45]	3.72	0.05
HDL-C [c]							
	<1.45	1.09 [0.90-1.32]	0.70	0.40	1.04 [0.85-1.26]	0.13	0.72
	≥1.98	1.26 [1.05-1.51]	6.30	0.01	1.29 [1.07-1.55]	7.30	0.007
	Trail Making Test B (n=3540)						
LDL-C [c]							
	<3.10	1.32 [1.11-1.57]	10.26	0.001	1.29 [1.08-1.54]	7.88	0.005
	≥4.26	1.12 [0.93-1.34]	1.45	0.23	1.09 [0.90-1.30]	0.78	0.38
TG [c]							
	<0.85	1.20 [1.01-1.43]	4.30	0.04	1.24 [1.04-1.49]	5.55	0.02
	≥1.45	1.03 [0.86-1.24]	0.14	0.71	0.99 [0.82-1.19]	0.01	0.90

Abbreviations: APO=apolipoprotein; BMI=body mass index; CETP=cholesteryl ester transfer protein; CI=confidence interval; HDL-C=high density lipoprotein cholesterol; HR=hazard ratio; LDL-C=low density lipoprotein cholesterol; TG=triglyceride.

[a]Model 1: adjusted for age, center, education level, and baseline cognitive performances.

[b]Model 2: Model 1+adjusted for marital status, BMI, lipid lowering agent use, anticholinergic use, mobility, hypertension, diabetes, depression, APOE4, APOA5, CETP, and hormone treatment.

[c]Expressed as mmol/l. Lipid variables were categorized into three classes corresponding to the quartile of the highest lipid levels, the quartile of the lowest lipid levels and the two middle quartiles (reference, HR=1). The lipid variables for which none of the low and high quartiles were associated with dementia at *p*-value>0.15 were not reported in the Table.

levels increased the risk of cognitive decline in men carrying the AA polymorphism of APOA5. This polymorphism has been reported to interact with lipoprotein metabolism (Lee et al., 2011) and to increase the overweight risk related to a high fat diet as compared to the G allele (Corella et al., 2007). Furthermore, in our sample, low T-C levels were associated with increased cognitive decline in men carrying the CC polymorphism of CETP (*rs1800775*), *i.e.* those at higher cardiovascular risk, but not in men with the A allele associated to lower CETP activity (Thompson et al., 2008).

We found an increased risk of decline in psychomotor speed in women with high LDL-C. Low HDL-C levels were also associated, as for men, with an increased risk for decline in psychomotor speed but this was only observed in postmenopausal women currently taking hormone treatment. Conversely, in women who had never used hormone treatment the risk was increased with high HDL-C levels. Estrogen levels in postmenopausal women are lower than for men of the same age but can be restored by hormone treatment which can also modify the lipid pattern in postmenopausal women (Dupuy et al., 2008). In this 3C cohort, we have already reported that compared to current users, women who had never used hormone treatment were at increased risk of decline in psychomotor speed over 4-year follow-up (Ryan et al., 2009). We also observed that some variants of estrogen receptors can increase the risk of decline in psychomotor speed (Ryan et al., 2013). The reason for the greater cognitive decline in the women who had never used HT and with higher HDL-C levels remains to be clarified but could involve genetic vulnerability related to HDL-C (Voight et al., 2012) as well as estrogen receptors or metabolizing enzymes which could modulate the response of HDL-C to hormonal treatment (Herrington et al., 2002; Smiderle et al., 2012).

Only two prospective studies on metabolic syndrome have examined cognitive decline in women specifically, finding no significant association between low HDL-C or high TG and decline on global cognitive performance (Komulainen et al., 2007; Yaffe et al., 2009). Solomon et al. reported a bidirectional relationship between cholesterol and poor cognitive status in a sample of 63% women; high midlife T-C but decreasing T-C after midlife being associated with poorer late-life cognition (Solomon et al., 2007, 2009). They observed a tendency to an interaction between sex and T-C changes over time in relation to late-life cognition, but due to size limitation, they could not draw definite conclusions (Solomon et al., 2007). Hormonal status relating to menopause and hormone treatment was not taken into account although the age at first midlife cholesterol evaluation ranged between 40 and 69 years which corresponded to pre-, peri- and post-menopausal women, whereas for late-life evaluation women aged between 65 and 79 years were all postmenopausal.

Our results thus show a complex pattern of associations between lipids and cognitive decline in psychomotor speed and executive functioning in the elderly, which may depend on genetic vulnerability to dyslipidemia in men and hormonal status in postmenopausal women. In men, the risk of decline in executive dysfunction was associated with a hypercholesterolemic pattern. This specific effect on frontal executive functions could be related to microalterations in white

Table 5 Lipid levels in women and cognitive decline on the Trail Making Test A according to hormone treatment[a].

Hormone treatment	HDL-C[b]	HR[c]	[95% CI]	χ^2 statistic	*p*
Current	<1.45	2.13	[1.14-3.96]	5.64	0.018
(*n*=563)	≥1.98	1.22	[0.67-2.25]	0.43	0.51
Past	<1.45	1.16	[0.71-1.88]	0.36	0.55
(*n*=610)	≥1.98	0.99	[0.60-1.64]	0.0005	0.98
Never	<1.45	0.93	[0.74-1.18]	0.34	0.56
(*n*=2367)	≥1.98	1.35	[1.09-1.67]	7.53	0.006

Abbreviations: APO=apolipoprotein; BMI=body mass index; CETP=cholesteryl ester transfer protein; CI=confidence interval; HDL-C=high density lipoprotein cholesterol; HR=hazard ratio.

[a]Estradiol-based hormonal treatment.

[b]Expressed as mmol/l. Lipid variables were categorized into three classes corresponding to the quartile of the highest lipid levels, the quartile of the lowest lipid levels and the two middle quartiles (reference, HR=1).

[c]Model 1: adjusted for age, center, education level, and baseline cognitive performances, marital status, BMI, lipid lowering agent use, anticholinergic use, mobility, hypertension, diabetes, depression, APOE4, APOA5, and CETP.

matter lesions and other subcortical vascular changes and could be amongst the earliest signs of vascular mild cognitive impairment which are more likely to evolve towards either vascular or mixed vascular and Alzheimer's dementia (Howieson et al., 2008; Iachini et al., 2009; Shim et al., 2008). This is partly compatible with our recent finding that in men specifically, low HDL-C levels was a risk factor for all-cause dementia including vascular dementia but not Alzheimer's disease (Ancelin et al., 2013). In women however, a quite distinct pattern is observed with a hypolipidemic/antiatherogenic pattern (*i.e.* high HDL-C, low LDL-C, and low TG levels) being associated with the risk of cognitive decline. Such lipidic pattern is associated with inflammation, poor nutritional status, and frailty (Corti et al., 1997; Hu et al., 2003) and may thus reflect a change in dietary habits accompanying pathology and/or be a marker for early neurodegenerative changes. In our previous study, TG levels were found associated with a decreased risk of Alzheimer's disease in women (Ancelin et al., 2013). The reasons for these inconsistencies remains to be clarified but could be related to the fact that cognitive impairment and dementia are quite heterogeneous conditions, with gender differences in risk profiles and progression from cognitive impairment to dementia which appeared to be better predicted by vascular factors in men but increased frailty in women (Artero et al., 2008; Ritchie et al., 2010).

The physiological underpinning of these gender differences remains speculative but could involve polygenic vulnerability and hormonal factors. A sex-specific genetic architecture of quantitative traits and interacting relationships has been reported for dyslipidemia and susceptibility to cardiovascular and neuropsychiatric disease, as well as other inflammation and immune related measures (Weiss et al., 2006). More particularly, the impact of sex on the penetrance and expressivity of various lipid traits with distinct levels of sexual dimorphism according to cholesterol fractions has been reported (Weiss et al., 2006). A gender based genome-wide association study identified several loci involved in distinct lipid traits (*e.g.* abnormal TG or HDL-C levels) and with different sex-specific effects regarding key enzymes involved in lipid transport and metabolism (Aulchenko et al., 2009). Steroid hormones and steroid-related genes have also been associated with gender-specific effects on lipid metabolism, neurotransmitter turnover and cognitive dysfunction and dementia (Ancelin and Ritchie, 2005; Sowers et al., 2006; Sundermann et al., 2010). Hence, differences in both lipid and hormonal levels could lead to differential expression of the underlying genetic networks, with gene(*s*) by cellular environment interactions resulting in differential effects of the same variation in men and women.

A limitation of this study could have been the exclusion of participants, those lost to follow-up being more likely to have cognitive decline and worse health which may limit the generalizability of our results. As a precaution we undertook additional analyses using imputation procedures which gave similar results (data not shown). The limited cognitive battery used precludes drawing definite conclusions regarding identifications of specific cognitive domains. We cannot exclude the possibility that other biological parameters and/or subclinical disease (in addition to that detectable through the analysis of lipids, glycemia, and hypertension) may confound the associations. We do not have the rates of lipid change across time which may also participate to the bidirectional relationship; poorer late-life cognition having been associated with high midlife T-C, as well as decreasing T-C after midlife (Solomon et al., 2009). Finally, since multiple analyses have been performed we cannot exclude that some associations were due to a chance finding. A number of associations reaching traditional significance levels remained however, significant even after applying overly conservative Bonferroni correction ($p<0.0063$ for four lipid classes, two genders and taking into account that tasks explored independent cognitive abilities).

The strengths of this study relate to its prospective, community-based design, large size and extensive information obtained on clinical status and ability to take into account a large number of confounders and genetic vulnerability to dyslipidemia. Few studies have taken into account cholesterol components and gender-specific associations while taking into account hormone treatment for women. Fasting lipid sampling would have maximized the accuracy of the associations compared to samples taken randomly during the day.

In conclusion, our findings suggest that public health interventions to improve preclinical vascular risk status

may still have an impact over 65 years although different strategies should be developed for men and women. Additional large prospective studies with comprehensive neuropsychological battery are required to clarify the processes underlying the role of lipids as a function of gender differences.

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Contributors

M.L. Ancelin generated the working hypotheses for this study and wrote the manuscript. E. Ripoche performed the statistical analysis I. Carrière supervised analysis and assisted with manuscript revision. A.M Dupuy, C. Samieri, O. Rouaud and C. Berr were responsible for data management within their respective centre and assisted with manuscript revision; K. Ritchie is chief investigator of the Montpellier centre for the 3C study and assisted with manuscript revision. All authors have approved the final version of the manuscript.

Conflict of interest

Dr. Ritchie serves on scientific advisory boards for the Biomedical Research Centre, King's College London, and London and MRC Strategic Steering Committee (Longitudinal Health and Aging Research Unit). All other authors declare that they have no conflicts of interest.

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