

Lipid Lowering Agents, Cognitive Decline, and Dementia: The Three-City Study

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Accepted 23 February 2012

Abstract. The aim of this prospective cohort study was to evaluate the effects of lipid lowering agent (LLA) intake on cognitive function in 6,830 community-dwelling elderly persons. Cognitive performance (global cognitive functioning, visual memory, verbal fluency, psychomotor speed, and executive function), clinical diagnosis of dementia, and fibrate and statin use, were evaluated at baseline, and 2, 4, and 7 year follow-up. Multivariate Cox models were stratified by gender and adjusted for sociodemographic characteristics, mental and physical health including vascular risk factors, and genetic vulnerability (apolipoprotein E and cholesteryl ester transfer protein). For women but not men, fibrate use was specifically associated with an increased risk over 7 years of decline in visual memory only (HR = 1.29, 95% CI = 1.09–1.54, $p = 0.004$), and did not increase risk for incident dementia. This association was independent of genetic vulnerability related to apolipoprotein E and cholesteryl exchange transfer protein polymorphisms and occurred only in women with higher low density lipoprotein (LDL)-cholesterol levels and treated with fibrate (HR = 1.39, 95% CI = 1.08–1.79, $p = 0.01$) and not in those with lower LDL-cholesterol levels irrespective of fibrate treatment. For both genders, no significant associations were found between statins (irrespective of their lipophilicity) and either cognitive decline or dementia incidence. This prospective study, adjusting for multiple confounders, found no evidence that LLA given in late life reduced the risk of cognitive decline and dementia, but did raise the possibility that women with treatment-resistant high LDL-cholesterol may be at increased risk of decline in visual memory.

Keywords: Alzheimer's disease, apolipoprotein E, cholesteryl exchange transfer protein, cognitive aging, elderly, fibrate, prospective cohort, statin

INTRODUCTION

Although there is some evidence from experimental studies that lowering cholesterol may slow the expression of Alzheimer's disease (AD), systematic

reviews from epidemiological and clinical studies, however, provide little evidence that low cholesterol may be associated with a decrease risk of cognitive decline or AD in the elderly (for reviews, see [1, 2]). Similarly, studies of the potential neuroprotective role of lipid lowering agents (LLA) remain inconclusive [3]. While some studies indicate that statins may moderately reduce risk of AD but not cognitive decline, other studies have been unable to confer this association. Inconsistencies could notably result

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from heterogeneity in study design, analytic methods, sample size, cognitive evaluation (generally limited to global cognition), and LLA characteristics (e.g., use of statin versus non-statin LLA, and lipophilicity influencing capacity to cross the blood brain barrier), with very few studies specifically examining fibrates. A common problem has been failure to take into account the numerous potential vascular confounders for cognitive decline. Of particular importance is the clinical context in which lipid treatment occurs; statins being generally prescribed in the first instance for the management of low density lipoprotein-cholesterol (LDL-cholesterol), whereas fibrate prescription generally following statin treatment failure, intolerance, or in cases of atherogenic dyslipidemia [4]. This point needs to be taken into account in clinical analyses as persons receiving fibrates are therefore likely to constitute a separate clinical sub-group from those receiving statins.

Genetic vulnerability has not been systematically considered despite a possible interactive effect between lipid levels and apolipoprotein E (ApoE). Surprisingly, cholesteryl ester transfer protein has not been examined although it is not only involved in the etiology of atherogenic dyslipidemia phenotype but has also been associated with slower memory decline and lower incident dementia [5]. Cholesteryl exchange transfer protein (CETP) promotes the exchange of triglycerides for cholesteryl ester in lipoprotein, and statin and fibrate may inhibit its activity.

In addition, cholesterol is a precursor for male and female steroids. However, gender differences have not been examined although they have been reported in relation to cognition and progression to dementia [6], to the association between lipid levels and LLA effects [7], risk factors and progression of cardiovascular disease, and therapeutic recommendations for cholesterol management [4, 8, 9].

This large prospective study aims to examine the relationship between LLA use and cognitive decline and dementia onset in community-dwelling elderly taking into account LLA type, gender, genetic vulnerability, and multiple competing factors associated with cognitive decline.

METHODS

Study participants

Subjects were recruited as part of a multi-site cohort study of community-dwelling persons aged 65 years and over, randomly selected from the electoral rolls of

three French cities between 1999 and 2001 [10]. The 3C study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France). Written informed consent was obtained from each participant. Participants were administered standardized questionnaires and underwent clinical examinations at baseline and at 2, 4, and 7-year follow-up (respectively, wave 1, 2, and 3). Of the 9,080 dementia-free participants included at baseline, 1,181 subjects having only one cognitive evaluation at baseline, 1,062 subjects having missing data for at least one adjustment variable, and seven subjects treated with both fibrate and statin were excluded leaving 6,830 subjects in the analysis. Among the subjects excluded 693 deceased. The mean (SD) age of the analyzed sample was 73.6 (5.3) for men and 73.8 (5.2) for women. Subjects not included in the analysis were significantly older, with lower education levels, and worse physical and mental health, lower baseline cognitive scores, and were less frequently statin users ($p < 0.005$ for each comparison).

Cognitive measures and dementia

The Isaacs Set Test provided a measure of verbal fluency or semantic access (number of items produced within 30 s), the Benton Visual Retention Test assessed visual memory, the Trail Making Tests (TMT) A and B psychomotor speed and executive function, respectively, and the Mini Mental State Examination (MMSE) was used as a global measure of cognitive function [10]. All tests were administered at baseline, and waves 1, 2, and 3 of the follow-up, except the TMT which was not given in wave 1.

A three-step procedure was used to diagnose cases of dementia [10]. First, screening was based on a thorough neuropsychological examination by trained psychologists (see above). 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 by a common independent committee of neurologists according to DSM-IV [11] criteria. This committee reviewed all potential cases of dementia to obtain a consensus on its diagnosis and etiology based on all available information. AD was diagnosed according to National Institute of Neurological and Communicative Disorders and

Stroke and the Alzheimer's Disease and Related Disorders Association criteria. The onset of dementia was the date of the follow-up interview when dementia was diagnosed.

Socio-demographic and clinical variables

The standardized interview included questions on socio-demographic and lifestyle characteristics with evaluation of hypertension and diabetes as well as an inventory of all drugs (including LLA and anticholinergic drugs as defined previously [12]) used over the preceding month. Medical prescriptions and the medications themselves were checked by the interviewer. History of ischemic pathologies (stroke, angina pectoris, myocardial infarction, and cardio-vascular surgery) and chronic respiratory disorders were established according to standardized questions. Depressive symptomatology was assessed by the Center for Epidemiological Studies-Depression Scale [13] with a 16 cut-off point. Venous blood samples were taken at baseline from subjects after fasting for >12 h. Lipid levels were evaluated in serum by routine enzymatic methods [7] and genotyping of ApoE and CETP (rs1800775 and rs5882 polymorphisms) was performed.

Statistical analyses

The χ^2 test for categorical variables and the Student *t* test for continuous variables were used to identify treatment group differences. Cognitive decline was evaluated over the 7-year follow-up period. The score distribution being not normal for the use of criteria based on standard deviation, cognitive decline was defined as being in the first quintile of the distribution of the differences, i.e., in the worst quintile. More specifically, a difference score was first calculated between cognitive scores obtained at any follow-up and the baseline score. The number of difference scores for a given subject thus depended on the number of follow-ups for which there was data, from only one difference (the subject was only followed up once in the 7-year period) up to 3 differences (the subject had data on each follow-up). The quintile of the individual maximum of the difference scores was then calculated. The group of decliners was then 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. Decliners were thus defined as persons having decreased from baseline by at least 3 points on the MMSE or on the Benton test or at least

10 points on the Isaacs test and an increase of at least 22 s on the TMTA or 57 s on the TMTB. Cox proportional hazards models with delayed entry taking age as the basic time scale and birth as the time origin [14] were used to determine whether baseline LLA use was associated with risks of cognitive decline and dementia incidence. This model enabled to take into account the full information until time of censoring, either by death or loss to follow-up, or the time of observed cognitive decline (or dementia), thus minimizing selection bias due to cohort attrition. After gender stratification, hazard ratios (HRs) were adjusted for center, educational level, and baseline cognitive performance in addition to age, which was already taken into account in the model (minimally adjusted model 0). Multivariate analyses further included selected covariates associated with cognitive decline (at $p < 0.15$), namely marital status, body mass index, mobility, as well as alcohol intake for men and anticholinergic use, depression, chronic respiratory disorders, and hormone treatment for women (model 1). Final multi-adjusted models were further adjusted for ischemic pathologies, diabetes, hypertension, LDL-cholesterol and triglyceride levels (categorized into quartiles), APOE ϵ 4, and CETP for both gender (model 2). For incident dementia, the analysis was undertaken on 7,056 subjects without missing data for baseline adjustment variables but with possibly missing repeated cognitive testing. Analyses were carried out using SAS software (version 9.2) with a significant level of $p < 0.05$. In the Tables, we reported data without correcting for multiple testing as we consider Bonferroni adjustment to be overly conservative given that the cognitive tests independently explore different aspects of cognitive functioning involving different cerebral areas (see the Discussion section).

RESULTS

Subject characteristics

Within this elderly community-dwelling sample, 936 of the 6,830 subjects (13.7%) were taking fibrates at baseline and 1,119 (16.4%) statins. No subjects were taking nicotinic acid and derivatives and only 11 subjects were taking bile acid sequestrants. Fibrates consisted of fenofibrate (72.0% of fibrates), ciprofibrate (15.7%), bezafibrate (9.6%), and gemfibrozil (2.7%). The lipophilic statins were simvastatin (36.7% of statins), cerivastatin (15.0%), and lovastatin (0.1%) and hydrophilic statin were pravastatin (26.9%), atorvastatin (17.5%), and fluvastatin (3.8%). Women were more frequent fibrate users (14.9%) than

Table 1
Characteristics of the study population as a function of lipid lowering agent use at baseline

Characteristic	Men		<i>p</i> ^a	Women		<i>p</i> ^a
	Lipid lowering agent			Lipid lowering agent		
	No (<i>n</i> = 1928) %	Yes (<i>n</i> = 781) %		No (<i>n</i> = 2847) %	Yes (<i>n</i> = 1274) %	
Age, y						
65–69	25.4	27.3	0.006	24.9	24.6	< 0.0001
70–74	33.7	37.4		31.1	36.7	
75–80	25.0	25.5		28.2	29.1	
80+	15.9	9.8		15.8	9.6	
Education, y						
5	21.2	22.4	0.30	24.5	26.5	0.13
9	29.9	32.5		39.9	41.4	
12	19.9	19.1		21.2	20.0	
12+	29.0	26.0		14.4	12.2	
Marital status						
Married	81.4	85.0	0.07	44.1	49.3	0.005
Single or divorced	8.5	6.4		20.4	17.4	
Widowed	10.1	8.6		35.6	33.4	
BMI (kg/m ²)						0.002
Normal (<25)	40.4	32.3	0.0004	55.5	50.0	
Overweight [25–30]	47.8	54.0		31.3	36.7	
Obese (≥30)	11.8	13.7		13.2	13.3	
Mobility ^b	3.3	2.3	0.40	6.6	5.2	0.20
Alcohol (g/day)						
0	8.6	6.0	0.07	27.9	24.7	0.05
1–36	72.8	74.4		70.8	73.4	
>36	18.6	19.6		1.3	1.9	
Depressive symptoms ^c	13.8	13.1	0.61	28.0	28.1	0.96
Anticholinergic use	4.2	4.6	0.59	9.6	9.9	0.79
Chronic respiratory disorders ^d	8.3	6.5	0.13	7.2	5.2	0.01
Ischemic pathologies ^e	17.2	33.9	< 0.0001	10.9	15.2	0.0001
Diabetes ^f	11.0	16.1	0.0002	5.5	9.6	< 0.0001
High blood pressure ^g	58.0	66.1	0.0001	51.3	58.3	< 0.0001
At least 1 ApoEε4	18.1	27.3	< 0.0001	17.2	24.4	< 0.0001
CETP1 (rs1800775)						
AA	30.1	30.9	0.56	30.7	31.0	0.49
CA	40.6	38.4		41.5	39.7	
CC	29.3	30.7		27.8	29.3	
CETP2 (rs5882)						
AA	47.1	47.1	0.64	47.5	46.2	0.71
GA	42.8	43.9		42.4	43.0	
GG	10.1	9.0		10.1	10.8	
Global cognitive functioning at baseline (MMSE score < 24)	3.8	3.5	0.68	4.4	4.6	0.82
LDL-cholesterol (mmol/l) ^h	3.59 (0.80)	3.29 (0.78)	< 0.0001	3.85 (0.86)	3.38 (0.78)	< 0.0001
HDL-cholesterol (mmol/l) ^h	1.45 (0.34)	1.42 (0.34)	0.10	1.74 (0.39)	1.73 (0.40)	0.44
Triglycerides (mmol/l) ^h	1.15 (1.51)	1.22 (1.55)	0.001	1.13 (1.46)	1.06 (1.55)	< 0.0001

Abbreviations: ApoE, Apolipoprotein E; BMI, body mass index; LLA, Lipid lowering agent; MMSE, Mini Mental State Examination. ^aThe Chi2 test and the Student t test were used for categorical and continuous variables. ^bMobility: assistance required to perform at least one of the three Rosow–Breslau items (relating to confinement to home and neighborhood). ^cThe presence of depressive symptoms was assessed using the Center for Epidemiological Studies–Depression Scale [13] with a cut-off of ≥16. ^dChronic respiratory disorders including corticosteroid drug intake and self-reported bronchitis, wheezing, tachypnea, and asthma attacks (over the last 12 months). ^eHistory of stroke, myocardial infarction, angina pectoris, or arteritis and cardio-vascular surgery; ^fDiabetes defined as glucose ≥7 mmol/l or treated. ^gHigh blood pressure defined as ≥160/95 mm Hg or treated. ^hMean (SD) except for triglycerides (geometric mean).

men (11.8%, *p* = 0.001). For both men and women, LLA use was higher in subjects overweight, with ischemic pathologies, diabetes, high blood pressure,

low LDL-cholesterol levels, and carrying ApoE4 allele (*p* < 0.005) (Table 1). Men with higher triglyceride levels but women with lower triglyceride levels were

Table 2
Base-line lipid lowering agent use and cognitive decline over the 7-year follow-up period^a

		Model 0			Model 1			Model 2		
		HR (95% CI)	Global <i>p</i> -value	<i>p</i>	HR (95% CI)	Global <i>p</i> -value	<i>p</i>	HR (95%CI)	Global <i>p</i> -value	<i>p</i>
WOMEN (<i>n</i> = 4121 ^b)										
ΔBenton ≤ -3	Fibrate	1.24 (1.05–1.46)	0.04	0.01	1.23 (1.04–1.45)	0.05	0.01	1.29 (1.09–1.54)	0.01	0.004
	Statin	1.05 (0.89–1.24)		0.57	1.06 (0.90–1.26)		0.5	1.06 (0.89–1.26)		0.54
ΔTMTB ≥ 57	Fibrate	1.16 (0.95–1.41)	0.12		1.15 (0.94–1.40)	0.15		1.03 (0.83–1.28)	0.59	
	Statin	1.19 (0.98–1.46)			1.18 (0.97–1.45)			1.11 (0.91–1.37)		
MEN (<i>n</i> = 2709 ^b)										
ΔTMTA ≥ 22	Fibrate	1.20 (0.91–1.59)	0.11		1.20 (0.91–1.59)	0.10		1.14 (0.84–1.55)	0.46	
	Statin	0.81 (0.61–1.08)			0.81 (0.60–1.07)			0.89 (0.67–1.20)		

Abbreviations: ApoE, Apolipoprotein E; BMI, body mass index; MMSE, Mini Mental State Examination; TMT, Trail Making Test. ^aDecline corresponded to lowest quintile of performances, i.e., a decrease from baseline of at least 3 points on the Benton test (and MMSE) or at least 10 points on the Isaacs score and an increase from baseline of at least 57 seconds on the TMTB (22 for TMTA). ^bExcept for TMT, where *n* = 3532 for women and 2258 for men; The non significant associations concerning the other cognitive tasks were not reported (*p* > 0.40). Model 0: adjusted for age (time scale), centre, education, and baseline cognitive performance; Model 1: adjusted for age (time scale), centre, education, base-line cognitive performance, marital status, BMI, mobility (for men and women) as well as alcohol intake for men and depression, anticholinergic use, chronic respiratory disorder, and hormonal treatment for women; Model 2: adjusted for all the covariates in model 1, plus ischemic pathologies, diabetes, hypertension, LDL-cholesterol and triglyceride levels, ApoE4, and CETP.

more frequent LLA users (*p* < 0.001), whereas women using LLA had less frequently chronic respiratory disorders (*p* = 0.01). There was no significant association between LLA use and other non-vascular factors more related to general health such as depressive symptoms, mobility, and use of drugs with anticholinergic properties.

LLA use and cognitive decline

Cox models adjusted for age, center, education level, and baseline cognitive performance indicated that women taking fibrates but not statins at baseline showed greater decline over 7 years on the Benton visual recall test (HR = 1.24, 95% CI = 1.05–1.46, *p* = 0.04) (Table 2). The association was strengthened in a model further adjusted for other confounders including lipid levels, ischemic pathologies associated with LLA prescription, and genetic risk factors (HR = 1.29, 95% CI = 1.09–1.54, *p* = 0.004, model 2). No significant interactions were found for decline in visual recall in women between LLA use and triglyceride (*p* = 0.89), ApoE (*p* = 0.26), or CETP (*p* = 0.29). A significant interaction was found between fibrate use and LDL-cholesterol levels (*p* = 0.03). Women with moderate or high LDL-cholesterol levels (≥3.1 mmol/l, corresponding to the three upper quartiles) and treated with fibrate (*n* = 397) were at higher risk for decline in visual memory (HR = 1.39, 95% CI = 1.08–1.79, *p* = 0.01 in model 2) compared to those with low LDL-cholesterol levels (<3.1 mmol/l) not treated with fibrate (*n* = 469) whereas risk was not significantly modified for those having low

LDL-cholesterol and treated with fibrate (HR = 0.94, 95% CI = 0.67–1.30, *p* = 0.69, *n* = 218) or those with moderate or high LDL-cholesterol not treated by fibrate (HR = 0.94, 95% CI = 0.77–1.15, *p* = 0.54, *n* = 2378).

The same association was observed when considering the 636 women who were taking fibrate continuously throughout the 7-year follow-up (defined as a baseline intake and at least 2 consecutive fills within the 3 follow-up examinations) compared with never users of LLA (HR = 1.26, 95% CI = 1.02–1.56,

Table 3
Baseline lipid lowering agent use and 7-year incidence of dementia^a
(Cox model with delayed entry)

		HR ^b (95%CI)	Global <i>p</i> -value
Women (<i>n</i> = 4272)			
All dementia	Fibrate	1.08 (0.77–1.52)	0.51
	Statin	1.20 (0.88–1.64)	
Alzheimer's disease	Fibrate	1.12 (0.75–1.66)	0.66
	Statin	1.17 (0.80–1.70)	
Men (<i>n</i> = 2784)			
All dementia	Fibrate	0.85 (0.53–1.36)	0.53
	Statin	0.81 (0.53–1.23)	
Alzheimer's disease	Fibrate	1.04 (0.60–1.80)	0.94
	Statin	1.09 (0.67–1.76)	

^aThe median (interquartile range) follow-up was 6.7 (3.8–7.2) years. This analysis was undertaken on 7,056 subjects without missing data for baseline adjustment variables but with possibly missing repeated cognitive testing; 290 women and 193 men were diagnosed with incident dementia, of whom 206 women and 126 men had incident Alzheimer's disease. The 110 women and 87 men with other types of dementia (of whom 21 men and 22 women with vascular dementia) were excluded from the analysis of Alzheimer's disease. ^bAdjusted for age (time scale), center, and education (model 0).

$p=0.03$, in fully adjusted model 2). No significant effect was observed in men regardless of the cognitive domain and the LLA type. We did not observe significant associations as a function of statin lipophilicity in either gender (data not shown).

Dementia incidence

Within the 7,056 subjects included in the analysis, 483 incident cases of all dementias were diagnosed during the 7-year follow-up, of whom 332 had AD. Adjusted Cox models failed to find a significant association between fibrate or statin use at baseline and the incidence of dementia or AD in women or men (Table 3).

DISCUSSION

Our results indicate a significant 1.3-fold increased risk of decline in visual memory in elderly women treated with fibrates at baseline or continuously during the 7-year follow-up. The same results were obtained in the minimally and the fully adjusted model, which was able to take into account multiple co-determinants of cognitive decline, including pathologies associated with LLA treatment and genetic vulnerability related to both lipid levels and cognitive decline and dementia (e.g., ApoE and CETP). It should be noted that baseline global cognitive functioning was not significantly different between LLA users and non users and the same results were obtained in minimally and fully adjusted models for cognitive scores and incident dementia which suggests that an indication bias in which LLA prescribed for patients at higher risk of dementia could have confounded the associations would be highly unlikely. The association between fibrate use and decline in visual memory remained significant even after applying the conservative Bonferroni correction for multiple comparisons (2 genders \times 2 LLA types, $p < 0.0125$). No significant association between statin or fibrate use and cognitive decline was observed in men. There was no significant association between fibrate use at baseline and risk of developing dementia or AD over 7 years in men or women.

Very few studies have evaluated the specific effect of fibrates on cognitive function; being generally assimilated with other LLA (e.g., bile-acid binding resins or nicotinic acid and derivatives) as “non-statin cholesterol-lowering drugs” which collectively have been reported as having no significant association with dementia incidence [15–18], although one

study reports an association in younger elderly subjects only [19]. In the present study, we found that only women with both relatively high LDL-cholesterol levels (≥ 3.1 mmol/l) and taking fibrates were at higher risk for cognitive decline in visual memory but not those with lower LDL-cholesterol levels. This notably precludes a neurotoxic effect of fibrate *per se*. Fibrates and statins differ by their mechanism of action. Statins inhibit hydroxymethylglutaryl-CoA reductase the rate-limiting step in cholesterol biosynthesis producing a lowering of LDL-cholesterol levels. Fibrates are agonists for the nuclear transcription factor peroxisome proliferator-activated receptor- α with effects on ApoA-I, A-II, and C-III, lipoprotein lipase, and fatty acid oxidation, notably leading to a number of anti-atherogenic effects including triglyceride lowering and HDL-cholesterol increase. In various animal models, neuronal and vascular protective effects of fibrate have been reported which have recently been related to their capacity to modulate oxidative stress and inflammation [20, 21]. The negative effect found in this study on cognitive decline in visual memory may thus reflect a more severe form of hypercholesterolemia persisting despite fibrate treatment, considering that statin is generally the first-line drug to achieve LDL-cholesterol treatment goals, whereas fibrate prescription would only generally follow statin treatment failure or intolerance or elevated triglyceride levels and atherogenic dyslipidemia [4]. The association between decline in visual memory and fibrate use remained significant after controlling for triglycerides, vascular factors, and genetic vulnerability. We cannot exclude, however, the possibility that asymptomatic subclinical atherosclerosis could be involved to confound this association. The specific effect observed in elderly women treated with fibrate remains to be explained but may involve pharmacodynamic or metabolism properties as well as differences in patterns of vascular risk factors and lipid lowering capacity which can be modulated by hormonal status [4, 7]. Current hormonal treatment is known to be associated with decreased LDL-cholesterol levels in postmenopausal women [7]. Hormonal treatment was also found to be specifically associated with better visual memory in the large Women’s Health Initiative Memory Study randomized controlled trial [22] as well as in a subgroup of women of the 3C study [23]. Whether women with treatment-resistant high LDL-cholesterol and not treated with hormonal treatment may be at increased risk of decline in visual memory remains to be further examined.

For statins, we only observed non significant associations with cognitive function in the minimally

adjusted models but not in the fully adjusted model, suggesting that this was more likely related to the underlying burden of vascular illness rather than the statin itself (indication bias) [24, 25]. The absence of effect of statins on cognitive decline is in agreement with a number of clinical and epidemiological studies. Two large randomized controlled trials conducted in mid- to late-life adults at high risk for vascular disease did not show differential effect on cognitive function of the lipophilic simvastatin and the hydrophilic pravastatin which were taken by 64% of our sample [26–28]. Two prospective cohort studies reported a significant negative association between global cognition and dementia and statin use, but it was not adjusted for baseline cognitive performance, lipid levels, and/or vascular pathologies [29, 30]. Regarding incident AD, several prospective cohort studies did not find significant associations even when considering lipophilicity [17, 18, 31]. A cohort study reported a significant negative association after 9.2 years of follow-up independent of statin lipophilicity but it did not consider lipid components as confounders [16]. A negative association was recently reported in early old but not the very old [32]. No large randomized controlled trials with statins have so far reported an AD preventive effect [26, 28], nor an effect on AD evolution [33, 34].

A limitation of our study could have been the exclusion of participants, those lost to follow-up being more likely to have cognitive decline or dementia, low education level, to be older, and thus with worse physical and mental health. This may limit the generalizability of our results, and associations may have thus been underestimated. We did not consider treatment compliance, which may have caused classification bias. We did not have information on the reasons for prescribing fibrate or on precise initiation time and duration of medication use, which could not definitively address the question of the modifying role of prolonged use and of midlife optimal therapeutic window. We cannot exclude the possibility that there are other unknown factors including subclinical disease in addition to that detectable through the analysis of lipids, glycemia, and hypertension, which may confound the associations.

The strengths of this study relate to its prospective, community-based design, large size, and extensive information obtained on clinical status. LLA use was ascertained, thus minimizing exposure misclassification and evaluated at baseline and throughout the 7-year follow-up. We could examine separately fibrates and statins as well as statin lipophilicity related to blood brain barrier permeability. Finally, we have taken

into account a wide range of competing causes of cognitive dysfunction in the elderly, notably lifestyle, genetic, and health covariates especially those related to vascular disorders, thus limiting any potential confounding including prescription bias. We excluded cases of prevalent dementia from the analyses and were able to distinguish AD from other forms of dementia using a validated clinical diagnosis of dementia.

In conclusion, our study, adjusting for multiple confounders, found no evidence that LLA given in late life reduced the risk over 7 years of cognitive decline and incident dementia. It may on the other hand suggest that elderly women with treatment-resistant high LDL-cholesterol may be at increased risk of decline in visual memory, for which women were reported to be less resistant to insult and ageing than in verbal skills [35]. Further studies with a more comprehensive battery of cognitive tests are required to determine whether this risk is indeed specific to visual memory or may be observed in other areas of information processing. Whether these women constitute a sub-group which has given rise to cognitive compromise or even a pre-dementia syndrome perhaps decades before dementia diagnosis, remains to be evaluated.

ACKNOWLEDGMENTS

The 3C Study is conducted under a partnership agreement between Inserm, the Victor Segalen – Bordeaux II University and Sanofi-Synthelabo. The Fondation pour la Recherche Médicale funded the preparation and first phase of the study. The 3C-Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon and, the Fondation de France, the Ministry of Research-Inserm Programme “Cohorts and collection of biological material”. The Lille Génomorphe received an unconditional grant from Eisai. Part of this project is financed by two grants from the Agence Nationale de la Recherche (projects 07 LVIE 004 and 06-PNRA-005). We thank the Génomorphe of Lille, the Laboratories of Biochemistry of the University Hospitals of Dijon and Montpellier, the Town Council of Dijon and the Conseil Général of Côte d’Or. Neither funding source provided scientific input to the study.

Authors’ disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=1193>).

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