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# Sex differences in the associations between lipid levels and incident dementia

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**Running title:** Lipids and incident dementia in men and women

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**ABSTRACT**

Cholesterol is a risk factor for developing vascular pathologies, which is in turn an important risk factor for dementia. Previous studies linking lipids and dementia have yielded inconsistent results, which may be attributable to sex differences in the etiology of both vascular disease and dementia. The aim of this study was to evaluate the associations between lipids and incident dementia in 7053 community-dwelling elderly. Dementia was diagnosed at baseline, and 2, 4, and 7-year follow-up. Multivariate Cox models stratified by sex and history of vascular pathologies at baseline were adjusted for sociodemographic, mental and physical health variables and genetic vulnerability. In men without vascular pathologies, an increased incidence of all-cause dementia but not Alzheimer's disease (AD) was associated with high triglyceride (TG) (HR=1.55, 95%CI=1.04-2.32, p=0.03) and low HDL-cholesterol levels (HR=1.49, 95%CI=0.99-2.23, p=0.05). In women without vascular pathologies, low TG levels were associated with a decreased risk of AD (HR=0.65, 95%CI=0.43-0.97, p=0.03). A decreased risk was also found with high TG levels which may depend on genetic vulnerability to dyslipidemia-related to APOA5. For both sexes, no significant associations were found between total- or LDL-cholesterol and dementia or AD. Low HDL-cholesterol and high TG levels may be risk factors of dementia in elderly men whereas low TG is associated with decreased incident AD in women. This data suggests a complex sex-specific etiology of vascular dementia and AD.

*Key-words:* Lipids; Dementia; Alzheimer's disease; Elderly; Apolipoprotein; Atherosclerosis; Prospective cohort.

## INTRODUCTION

Cholesterol is a risk factor for vascular disease which is an important risk factor for dementia. Previous studies have however, yielded inconsistent results with a higher prevalence of dementia being associated with both low and high total cholesterol (T-C), or showing no association [1, 2]. Inconsistencies could result from heterogeneity in study design, sample characteristics (size and age), and lipid species. Many studies measured only T-C which comprises both low (LDL-C) and high density lipoprotein cholesterol (HDL-C), which are inversely associated with vascular risk factors. Few studies have examined triglycerides (TG).

Most studies have been conducted late in the life of participants when substantial ageing-related vascular pathophysiological changes may already be present outweighing the risk related to lipids. Shepardson et al. [2] recently suggested that studies finding a negative or no correlation with cholesterol levels were principally conducted late in the patient lives, whereas studies finding a positive correlation tended to be conducted earlier. Whether lipid levels may predict incident dementia in the elderly in the absence of vascular disease has however, not been examined although these subjects could constitute a distinct clinical subgroup. Sex differences have also not been studied although men and women differ with regard to lipid levels, therapeutic recommendations and risk factors for onset and progression of cardiovascular disease, even long before disease manifestation and progression to dementia [3-8].

Genetic interactions have focused on APOE, a major determinant in lipoprotein metabolism and cardiovascular disease and a risk factor for dementia, and other polymorphisms involved in the etiology of the atherogenic dyslipidemia phenotype, such as APOA5 and cholesteryl ester transfer protein (CETP) promoting the exchange of TG in lipoprotein, have not been examined [9, 10].

We hypothesized first that lipids increase the risk of dementia differently in men and women and second that these associations will have lesser impact due to underlying vascular pathologies. In this large multicentric prospective study, we are able to examine the relationship between lipids and dementia onset in community-dwelling elderly men and women over 7 years of follow-up. The

extensive clinical phenotyping of this cohort further permits adjustment by a large number of potential confounders and mediators, such as socio-demographic characteristics, lifestyle, mental and physical health (including vascular related factors such as hypertension and intima media thickness) as well as genetic vulnerability to dyslipidemia or dementia. In order to determine whether vascular pathologies may outweigh the effects of lipids, the associations were also examined in the subgroup of participants without vascular pathologies.

## METHODS

### *Study Participants*

Subjects were recruited as part of the Three-City (3C) study, a multi-site cohort study of community-dwelling persons aged 65 years and over selected from the electoral rolls of three French cities between 1999 and 2001 [11]. 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 underwent clinical examinations at baseline and at 2, 4, and 7-year follow-ups. Of the 9080 dementia-free participants included at baseline, 555 subjects did not have blood lipid evaluation. A further 995 subjects had no follow-up data, and another 477 had missing data for at least one adjustment variable leaving 7053 subjects in the analysis. Among the subjects excluded, 686 had died.

### *Diagnosis of Dementia*

A three-step procedure was used to diagnose cases of dementia [11]. First, screening was based on a thorough neuropsychological examination by trained psychologists including a battery of cognitive tests covering memory, attention, language, visuo-spatial abilities and global cognitive function. Severity of cognitive disorders, activities of daily living, and, where possible, magnetic resonance images or computed tomography scans were collected. Second, the participants suspected

of having dementia were examined by a neurologist in the three study centers. Finally, all suspected dementia cases were analyzed by a common independent committee of neurologists according to DSM-IV revised criteria [12]. This committee reviewed all potential cases of dementia to obtain a consensus on its diagnosis and etiology based on all existing information. With regard to the different subtypes of dementia, we considered the two most frequent causes of dementia as determined by committee (Alzheimer's disease [AD] according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria and vascular dementia based on history of vascular disease, Hachinski score, and MRI whenever possible) [11].

*Socio-demographic and Clinical Variables*

The standardized interview included questions on socio-demographic and lifestyle characteristics as well as an inventory of all drugs used over the preceding month based on medical prescriptions and the medications themselves. Height and weight were measured. 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>7mmol/l or treated) were assessed. Mobility was assessed as activity proxy according to the Rosow and Breslau scale [13] which evaluates ability to do heavy housework, walk half a mile, and climb stairs. History of vascular pathologies (stroke, angina pectoris, myocardial infarction, arteritis and cardio-vascular surgery) were established according to standardized questions with additional information where necessary from general practitioners. Depressive symptomatology was assessed by the Center for Epidemiological Studies-Depression Scale [14] with a 16 cut-off point. Venous blood samples were taken at baseline after fasting for >12 hours. Lipid levels were evaluated in serum by routine enzymatic methods [3] and genotyping of APOE, APOA5, and CETP polymorphisms was carried out at the French Lille Genopole (http://www.genopole-lille.fr/spip/). A B-mode ultrasound of the carotid arteries was also performed for participants aged $\leq$85 years

(73.7%) as previously described [15]. Mean intima media thickness (IMT) of the common carotid arteries was measured in areas free of any discrete plaques, 2-3cm below the carotid bifurcation [15].

*Statistical Analyses*

The Chi2 test for categorical variables and the Student t test for continuous variables were used to identify group differences. Cox models with delayed entry, taking age as the basic time scale and birth as the time origin [16] were used to determine whether baseline lipid levels (categorized into quartiles to detect non linear associations) were associated with incident dementia. The age of onset corresponded to the median of the interval between the last follow-up without dementia and the first follow-up with dementia. Analyses were performed after stratification by sex and history of vascular pathologies at baseline. Hazard ratios (HRs) were first adjusted for centre and educational level in addition to age, which was already taken into account in the model (model 1). Multivariate analyses further included covariates associated with incident dementia (at $p<0.15$); mobility, hypertension, diabetes, depression, anticholinergic use, APOE, APOA5, and CETP1 (model 2) as well as IMT (log-transformed to approximate normal distribution) or BMI (model 3). Analyses were carried out using SAS software (version 9.2).

## RESULTS

*Subject Characteristics*

The analyzed sample consisted of 4308 women and 2745 men with a mean (SD) age of 73.9 (5.3) and 73.7 (5.3) years, respectively. At baseline, women had higher T-C, HDL-C, and LDL-C levels but lower TG levels than men ($p<10^{-4}$) (**Table 1**). Women differed on all other characteristics except for genetic variables, being older, with lower education, more frequently depressed and confined to home. On the other hand, women had less often vascular pathologies (12.6% vs. 22%),

diabetes, and hypertension and were less frequently overweight ($p<10^{-4}$). Excluded non-demented persons had a lower educational level, were older, more likely to have vascular pathologies, disabilities, diabetes, and current depressive symptomatology ($p<0.0001$). They were also more likely to have hypertension ($p=0.001$), lower HDL-C ($p=0.004$) and higher T-C, LDL-C, and TG levels (<0.0001). Within the 7053 subjects included, 481 incident cases of all dementias were diagnosed during the 7-year follow-up, of whom 333 had AD, 27 vascular dementia and 55 mixed dementia.

*Dementia Incidence in Women*

In women, low TG levels (lowest quartile) were significantly associated with a decreased risk of incident dementia in the whole sample in minimally adjusted model as well as in the multiadjused model 2 (HR=0.71, 95%CI=0.52-0.96, p=0.03) but the association was not significant in women without vascular pathologies (p=0.13). A borderline significant association was observed between high LDL-C (upper quartile) and dementia but this was not significant after multi-adjustment (**Table 2**). We found no significant association between T-C or HDL-C and dementia or AD (data not shown).

Both low and high TG levels were significantly associated with a decreased risk of incident AD in the whole sample of women. A comparable pattern was observed in women without vascular pathologies but this was only significant for low TG levels (HR=0.65, 95%CI=0.43-0.97, p=0.03 in multiadjusted model, compared to HR=0.71, 95%CI=0.49-1.03, p=0.07 for high TG levels). A significant interaction was observed with APOA5 (p of interaction =0.005); this dual pattern of risk being only observed in the women carrying the AA polymorphism but the low number of demented women carrying the AG or GG polymorphism (n=30) precludes drawing definite conclusions.

*Dementia Incidence in Men*

In the whole sample of men, low HDL-C levels at baseline were associated with an increased

risk of incident dementia in the whole sample (by 45%) and a borderline association with high TG levels was also observed (model 1, **Table 3**). These associations failed to reach significance in the multiadjusted model (model 2) (p=0.08). The same pattern of associations were observed in men without vascular pathologies but in this case the association with high TG levels remained significant in the multiadjusted model (HR=1.55, 95%CI=1.04-2.32, p=0.03) and a borderline association was also observed for low HDL-C (HR=1.49, 95%CI=0.99-2.23, p=0.05).

Regarding incident AD, an increased risk was observed in men without vascular pathologies and high TG levels but this failed to reach the significance level (p=0.10 in model 2) and no significant associations were found with low HDL-C. There were no significant associations between T-C or LDL-C and dementia or AD in men (data not shown). In men as in women, we found no significant interactions between lipid levels and APOE or CETP polymorphisms on dementia risk (data not shown).

*Subsidiary Analyses*

Additional analyses were performed to examine the effects of other factors such as BMI or IMT in persons without vascular pathologies. When adding BMI to the multivariate model 2, exactly the same significant associations were observed for the risk of AD in women with low and high TG levels (HR=0.65, 95%CI=0.43-0.96, p=0.03 and HR=0.71, 95%CI=0.48-1.04, p=0.08, respectively) as well as for dementia in men with high TG levels (HR=1.54, 95%CI=1.03-2.31, p=0.04). For men with low HDL-C the same trend was observed although not significant (HR=1.41, 95%CI=0.93-2.14, p=0.10). Considering the stability of HR and 95%CI values through the successive adjustment steps and the fact that BMI was not significantly associated with the risk of dementia in this sample (p=0.10 in model 1) this is thus more likely due to a loss of power.

Subsidiary analyses were performed to examine whether subclinical vascular alterations could be involved. Carotid IMT, a surrogate marker of atherosclerosis has been measured in a subset of 2016 men and 3181 women aged younger than 85 years. In the multivariate models further adjusted

for IMT, high TG and low HDL-C levels remained significantly associated with an increase of more than 60% in dementia risk in men without vascular pathologies (**Table 4**). For women without vascular pathologies, the association between low TG and decreased risk of AD also remained significant after adjusting for IMT (HR=0.60, 95%CI=0.38-0.96, p=0.03). Moreover, the association with high TG was also significant for all-cause dementia as well as for AD (HR=0.47, 95%CI=0.28-0.77, p=0.003).

## DISCUSSION

*Serum Lipids and Incident Dementia in the Elderly*

Our results indicate a significant association between TG or HDL-C serum levels and the risk over 7 year of incident dementia in the elderly. The effects were independent of APOE and CETP genotype as well as numerous potential co-determinants of incident dementia, including vascular factors. Lipid lowering agent treatment was not significantly associated with incident dementia as already reported in this population [17]. We found no significant associations with T-C and LDL-C with incident AD and all-cause dementia as previously reported [18-23]. The Honolulu-Asia Aging Study also found no significant association with mid-life T-C but a greater early decline in T-C levels in men with all-cause dementia [24, 25]. Only two studies reported a negative association with high T-C levels in elderly; one showing no significant association with midlife T-C [26, 27] and the other reporting a positive correlation [28, 29]. Shepardson et al. [2] thus suggested that studies finding a negative correlation were principally conducted late in the patient lives, whereas studies finding a positive correlation tended to be conducted earlier. These studies however, concern Scandinavian populations with generally higher T-C levels than other ethnic white population and use of logistic regression and lack of adjustment for vascular factors could be problematic. LDL-C was only examined in the Northern Manhattan study which also found no significant associations with dementia and AD after 4-year follow-up [21-23].

A major finding of our study concerns TG and HDL-C and the fact that these associations differed between men and women. Most previous studies found no significant associations of incident dementia (all-cause, vascular, or AD) with HDL-C [19, 20, 22, 23, 30] and TG [20, 22, 23, 26]. These studies were of smaller size, non-stratified, predominantly with females and relatively high prevalence of vascular pathologies, which may explain negative finding assuming that dementia could be driven by more severe clinical vascular conditions overweighing the effects of lipids.

*Lipids and Incident Dementia in Men*

A significant association between high TG levels (as a metabolic syndrome component) and all-cause dementia was previously reported by our group in the same cohort (non-stratified sample) after a 4-year follow-up [30]. The only prospective study having examined men (middle age) separately showed a positive association between high mid-life TG levels and all-cause dementia after 25-year follow-up [24]. In the present study, in elderly men without vascular pathologies after a shorter observation period (7 years) we observed a 50% increase of all-cause dementia not only with TG, but also with HDL-C.

*Lipids and Incident Dementia in Women*

By contrast, in women lipid levels were not associated with a significant increased risk of dementia and AD, irrespective of the lipid species. The only longitudinal study having examined women separately evaluated only T-C levels and found no significant association with all-cause dementia or AD after 32-year follow-up [27]. In our study we found a significant association between low TG levels and a 40% decrease of AD in women without vascular pathologies and independently of the degree of atherosclerosis. High TG levels were also found to be associated with a decreased risk of incident AD and this may be limited to the women carrying the AA

polymorphism of APOA5, *i.e.* those at lower risk of early heart attack and atherosclerosis and may thus reflect a survival bias. A sex-dependent interaction for TG levels has recently been reported for another polymorphism of APOA5 which appeared modulated by menopausal status and APOE4 [9].

*Biological Hypotheses Linking Dementia to HDL-C or TG: Towards a Sex-specific Etiology?*

Sex differences in incidence rates have been reported according to the type of dementia, female being more at risk of AD and men of vascular and mixed dementia [31]. Cardiovascular risk factors have been reported to be preferentially risk factors for vascular dementia rather than AD although several reports suggest that both types of dementia share some risk factors and pathologic features with atherosclerosis [1, 32, 33]. In our study, lipid levels do not appear as independent risk factors for increased incident AD in elderly women and low TG levels even decreased the risk. For men, our results strongly suggest atherogenic pattern related to TG and HDL-C to be a risk factor for all-cause dementia. Reduced HDL-C and increased TG concentrations contribute to the onset of the inflammatory response that typically occurs in the pathogenesis of atherosclerosis even at its earliest stages [34-36]. In men without vascular pathologies, we observed a significant association independently of numerous vascular factors including hypertension and degree of atherosclerosis. This suggests high TG and low HDL-C to be asymptomatic risk factors of non-AD forms of dementia, likely vascular and/or mixed dementia in men, well before the onset of vascular pathologies.

Epidemiological studies to date have mainly focused on T-C, whereas there is increasing evidence of a differential effect of LDL-C, HDL-C and TG on brain function. The association between HDL-C and dementia rather than LDL-C may be attributed to a number of characteristics of these species including the fact that only HDL-like particles are found in CSF [37], and that only elevated HDL has been associated with both reduced hippocampal atrophy [38] and neuritic plaque

and neurofibrillary tangle formation in a dose-response relation [39]. The involvement of TG which is inversely associated with HDL-C remains to be evaluated.

The physiological underpinning of these sex 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 immune, and HPA axis related measures [40]. 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. Of the quantitative traits analyzed, TG and HDL-C but not LDL-C showed evidence for sex-specific linkage [40]. A sex based genome-wide association study recently 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 [41]. Steroid hormones and steroid-related genes have also been associated with sex-specific effects on lipid metabolism, neurotransmitter turnover and cognitive dysfunction and dementia [42-44]. Particularly, the relationship between estrogen receptor and dementia was reported to be specific to or driven by female gender and restricted to AD rather than other dementia causes and can be modulated by APOE [44]. Hence, differences in both hormonal and lipid 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.

*Limitations and Strengths*

A limitation of our study could have been the exclusion of participants, those lost to follow-up being more likely to have 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 cannot exclude the possibility that there are other unknown factors including subclinical disease (in addition to that detectable through the analysis of lipids, glycemia, hypertension, IMT), which may confound the associations. The number of incident cases of vascular dementia was too low to examine associations with this clinical subgroup.

The strengths of this study are its prospective, community-based design, large size, extensive information obtained on clinical status and ability to take into account a large number of potential confounders including IMT and other vascular factors. Few previous studies have taken into account both cholesterol components and sex-specific associations. Fasting lipid sampling would have maximized the accuracy of the associations compared to random samples.

In conclusion, this large prospective study showed an independent association between lipid levels late in life and the risk of incident dementia in persons without vascular disease at base-line. An atherogenic pattern related to high TG and low HDL-C levels may be early asymptomatic risk factors of dementia in men. Conversely, low and high TG levels are associated with decreased risk of incident AD in women. This data suggests a complex sex-specific etiology of vascular dementia and AD. Atherogenic lipids may contribute to the onset of the inflammatory response and thus constitute the earliest stages of vascular MCI and dementia pathogenesis in men, whereas lipids could interact with sex steroids to protect women from AD. Modification of TG and HDL-C even late in life may reduce not only the risk of cardiovascular disease but also the most prevalent age-related neurodegenerative disease, dementia. Our findings suggest that public health interventions to improve preclinical vascular risk status may still have an impact over 65 years, and should be sex-specific.

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## Table 1

## Baseline characteristics of the study population (n=7053)

| | Men (n=2745) | | Women (n=4308) | | |
|---|---|---|---|---|---|
| **Characteristic** | **n** | **%** | **n** | **%** | ***P*[a]** |
| Age, yr | | | | | 0.008 |
| 65-69 | 709 | 25.8 | 1057 | 24.5 | |
| 70-74 | 953 | 34.7 | 1399 | 32.5 | |
| 75-80 | 689 | 25.1 | 1237 | 28.7 | |
| 80+ | 395 | 14.4 | 615 | 14.3 | |
| Education, yr | | | | | $<10^{-4}$ |
| 5 | 589 | 21.5 | 1092 | 25.4 | |
| 9 | 845 | 30.7 | 1739 | 40.3 | |
| 12 | 536 | 19.5 | 891 | 20.7 | |
| >12 | 776 | 28.3 | 586 | 13.6 | |
| Mobility (confinement)[b] | 83 | 3.0 | 280 | 6.5 | $<10^{-4}$ |
| BMI ($kg/m^2$) | | | | | $<10^{-4}$ |
| < 25 | 1040 | 37.8 | 2313 | 53.4 | |
| [25-30[ | 1358 | 49.5 | 1422 | 33.2 | |
| ≥ 30 | 347 | 12.7 | 573 | 13.4 | |
| Depressive symptoms[c] | 372 | 13.6 | 1228 | 28.5 | $<10^{-4}$ |
| Anticholinergic use | 118 | 4.3 | 417 | 9.7 | $<10^{-4}$ |
| Vascular pathologies[d] | 605 | 22.0 | 543 | 12.6 | $<10^{-4}$ |
| Diabetes[e] | 343 | 12.5 | 305 | 7.1 | $<10^{-4}$ |
| High Blood Pressure[f] | 1660 | 60.5 | 2323 | 53.92 | $<10^{-4}$ |
| At least 1 APOEε4 | 571 | 20.8 | 841 | 19.5 | 0.20 |
| APOA5 (rs662799) | | | | | 0.06 |
| AA | 2376 | 86.5 | 3792 | 88.0 | |
| AG or GG | 370 | 13.5 | 516 | 12.0 | |
| CETP (rs1800775) | | | | | 0.98 |
| AA | 842 | 30.6 | 1321 | 30.7 | |
| CA or CC | 1904 | 69.4 | 2987 | 69.3 | |
| | **Mean** | **SD** | **Mean** | **SD** | ***p*[a]** |
| TG (mmol/l)[g] | 1.28 | 0.6 | 1.21 | 0.5 | $<10^{-4}$ |
| T-C (mmol/l)[g] | 5.52 | 0.9 | 5.99 | 1.0 | $<10^{-4}$ |
| LDL-C (mmol/l)[g] | 3.50 | 0.8 | 3.70 | 0.9 | $<10^{-4}$ |
| HDL-C (mmol/l)[g] | 1.44 | 0.3 | 1.73 | 0.4 | $<10^{-4}$ |

Abbreviations: BMI, Body Mass Index; CETP, cholesteryl ester transfer protein; HDL-C, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; 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 [13] (relating to confinement to home and neighborhood).

[c] The presence of depressive symptoms was assessed using the Center for Epidemiological Studies-Depression Scale[14] with a cut-off of ≥16.

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

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

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

[g] Mean (SD) except for TG (geometric mean).

**Table 2**

**Adjusted models for associations between lipid levels at baseline and incident dementia in elderly women according to the presence of vascular pathologies**

| | | ALL-CAUSE DEMENTIA | | | | | | ALZHEIMER'S DISEASE | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Model 1[a] | | | Model 2[b] | | | Model 1[a] | | | Model 2[b] | | |
| | | HR | 95%CI | p | HR | 95%CI | p | HR | 95%CI | p | HR | 95%CI | p |
| **Whole sample** (n=4308, 297 cases) | | | | | | | | (n=4220, 209 AD cases) | | | | | |
| **TG**[c] | <0.85 | 0.70 | 0.51-0.95 | 0.02 | 0.71 | 0.52-0.96 | 0.03 | 0.60 | 0.41-0.87 | 0.008 | 0.61 | 0.42-0.89 | 0.01 |
| | ≥1.45 | 0.97 | 0.74-1.27 | 0.83 | 0.84 | 0.64-1.11 | 0.23 | 0.74 | 0.53-1.03 | 0.07 | 0.67 | 0.47-0.94 | 0.02 |
| **LDL-C**[c] | <3.10 | 0.96 | 0.72-1.28 | 0.77 | 0.90 | 0.67-1.21 | 0.47 | | | | | | |
| | ≥4.26 | 1.27 | 0.98-1.66 | 0.08 | 1.20 | 0.92-1.57 | 0.18 | | | | | | |
| **Without vascular pathologies** (n=3765, 230 cases) | | | | | | | | (n=3710, 175 AD cases) | | | | | |
| **TG** | <0.85 | 0.76 | 0.55-1.07 | 0.12 | 0.77 | 0.55-1.08 | 0.13 | 0.65 | 0.43-0.96 | 0.03 | 0.65 | 0.43-0.97 | 0.03 |
| | ≥1.45 | 0.91 | 0.66-1.25 | 0.55 | 0.82 | 0.60-1.13 | 0.23 | 0.78 | 0.54-1.13 | 0.19 | 0.71 | 0.49-1.03 | 0.07 |
| **LDL-C** | <3.10 | 1.04 | 0.75-1.45 | 0.80 | 0.97 | 0.69-1.35 | 0.85 | | | | | | |
| | ≥4.26 | 1.30 | 0.96-1.75 | 0.09 | 1.22 | 0.90-1.65 | 0.20 | | | | | | |

Abbreviations: CETP, cholesteryl ester transfer protein; LDL-C, low density lipoprotein cholesterol; TG, triglyceride.

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

[b] Model 2: Model 1 + adjusted for mobility, hypertension, diabetes, depression, anticholinergic use, APOE, APOA5, and CETP1.

[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 other lipid variables not significantly associated with dementia and Alzheimer's disease at p-value > 0.15 in Model 1 were not reported in the Table.

**Table 3**

**Adjusted models for associations between lipid levels at baseline and incident dementia in elderly men according to the presence of vascular pathologies**

| | | ALL-CAUSE DEMENTIA | | | | | | ALZHEIMER'S DISEASE | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Model 1[a] | | | Model 2[b] | | | Model 1[a] | | | Model 2[b] | | |
| | | HR | 95%CI | p | HR | 95%CI | p | HR | 95%CI | p | HR | 95%CI | p |
| **Whole sample** (n=2745, 184 cases) | | | | | | | | (n=2685, 124 AD cases) | | | | | |
| **TG**[c] | <0.88 | 0.84 | 0.58-1.22 | 0.37 | 0.87 | 0.60-1.27 | 0.48 | 0.79 | 0.50-1.25 | 0.31 | | | |
| | ≥1.57 | 1.36 | 0.97-1.92 | 0.07 | 1.36 | 0.96-1.92 | 0.08 | 1.25 | 0.82-1.90 | 0.31 | | | |
| **HDL-C**[c] | <1.19 | 1.45 | 1.03-2.04 | 0.03 | 1.36 | 0.97-1.93 | 0.08 | 1.35 | 0.89-2.05 | 0.15 | | | |
| | ≥1.63 | 0.97 | 0.67-1.39 | 0.86 | 0.99 | 0.68-1.43 | 0.95 | 0.81 | 0.51-1.28 | 0.36 | | | |
| **Without vascular pathologies** (n=2140, 136 cases) | | | | | | | | (n=2101, 97 AD cases) | | | | | |
| **TG** | <0.88 | 0.87 | 0.56-1.34 | 0.52 | 0.89 | 0.58-1.38 | 0.61 | 0.83 | 0.50-1.39 | 0.47 | 0.91 | 0.54-1.52 | 0.71 |
| | ≥1.57 | 1.56 | 1.05-2.32 | 0.03 | 1.55 | 1.04-2.32 | 0.03 | 1.52 | 0.95-2.43 | 0.08 | 1.49 | 0.92-2.40 | 0.10 |
| **HDL-C** | <1.19 | 1.54 | 1.03-2.30 | 0.04 | 1.49 | 0.99-2.23 | 0.05 | 1.26 | 0.77-2.05 | 0.35 | | | |
| | ≥1.63 | 0.89 | 0.58-1.36 | 0.59 | 0.94 | 0.61-1.45 | 0.78 | 0.75 | 0.45-1.25 | 0.27 | | | |

Abbreviations: CETP, cholesteryl ester transfer protein; HDL-C, high density lipoprotein cholesterol; TG, triglyceride.

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

[b] Model 2: Model 1 + adjusted for mobility, hypertension, diabetes, depression, anticholinergic use, APOE, APOA5, and CETP1.

[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 other lipid variables not significantly associated with dementia and Alzheimer's disease at p-value > 0.15 in Model 1 were not reported in the Table.

**Table 4**

**Multivariate models for associations between lipid levels at baseline and incident dementia in persons without vascular pathologies further adjusted for baseline IMT[a]**

| | | ALL-CAUSE DEMENTIA | | | ALZHEIMER'S DISEASE | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95%CI | p | HR | 95%CI | p |
| **MEN** (n=1560, 95 cases) | | | | | (n=1529, 64 AD cases) | | |
| **TG[b]** | <0.88 | 0.95 | 0.56-1.61 | 0.85 | 0.90 | 0.47-1.73 | 0.74 |
| | ≥1.57 | 1.63 | 1.00-2.65 | 0.05 | 1.58 | 0.87-2.87 | 0.13 |
| **HDL-C[b]** | <1.19 | 1.64 | 1.02-2.66 | 0.04 | 1.32 | 0.74-2.37 | 0.35 |
| | ≥1.63 | 0.86 | 0.51-1.45 | 0.57 | 0.71 | 0.37-1.37 | 0.30 |
| **WOMEN** (n=2818, 171 cases) | | | | | (n=2769, 122 AD cases) | | |
| **TG** | <0.85 | 0.77 | 0.53-1.13 | 0.19 | 0.60 | 0.38-0.96 | 0.03 |
| | ≥1.45 | 0.62 | 0.42-0.93 | 0.02 | 0.47 | 0.28-0.77 | 0.003 |

Abbreviations: CETP, cholesteryl ester transfer protein; HDL-C, high density lipoprotein cholesterol; IMT, intima media thickness; TG, triglyceride.

[a] Multivariate model adjusted for age, center, education level, mobility, hypertension, diabetes, depression, anticholinergic use, APOE, APOA5, CETP1 and IMT (model 3).

[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).