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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,

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