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Gender specific associations between lipid levels and depressive symptomatology in community-dwelling elderly (The Esprit Study)

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Abbreviations: ApoE: Apolipoprotein E; CRP: C-reactive protein; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; LLA: lipid-lowering agent; T-C: total cholesterol; TG: triglyceride; 5-HTTLPR: serotonin transporter gene linked promoter region.

Abstract

Background: Lipids may affect depressive vulnerability in elderly, but the influence of gender differences and genetic vulnerability with regard to lipid dysfunction and depression has not been examined in prospective study.

Methods: Depression was assessed in a population of 1040 women and 752 men aged 65 years and over at baseline and after 7-year follow-up. Clinical level of depression (DEP) was defined as meeting one of two criteria: a score over 16 on the Centre for Epidemiology Studies Depression scale or a diagnosis of current major depression on the Mini International Neuropsychiatric Interview. Lipid levels, apolipoprotein E and serotonin transporter linked promoter region (5-HTTLPR) genotypes were evaluated at baseline.

Results: Multivariate analyses adjusted for socio-demographic and behavioral variables, measures of physical health including ischemic pathologies, and genetic vulnerability indicated gender-specific associations between dyslipidemia and DEP, independent of lipid lowering agent or apolipoprotein E. Men with low LDL-cholesterol levels were at twice higher risk of prevalent and incident DEP whereas in women low HDL-cholesterol levels were found significantly associated only with increased prevalent DEP (OR=1.5). A significant interaction was observed between low LDL-cholesterol and 5-HTTLPR genotype, men with s/s or s/l genotype being at increased risk of DEP (OR=6.0 and 2.7, respectively) in contrast with l/l homozygotes. No significant gene-environment interaction was observed for women.

Conclusions: DEP is associated with higher atherogenic risk in women (low HDL-cholesterol), whereas the reverse is observed in men (low LDL-cholesterol). Late-life depression may have a gender-specific complex etiology involving genetic vulnerability in men.

Dyslipidemia is a major risk factor for vascular disease which is in turn an important risk factor for depression in late-life (1). Previous studies have principally evaluated the association between lipid levels and depression, yielding inconsistent results with a higher prevalence of depressive symptomatology being associated with low (2, 3), and high total cholesterol (T-C) (4), or showing no significant association (5-7). Apart from heterogeneity in study design, depression evaluation and sample size, inconsistencies could result from the fact that T-C comprises both low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C), which are inversely associated with vascular risk factors. However, the few studies having examined them separately have also yielded contradictory results (4, 5, 8).

The fact that the studies did not stratify by sex could also explain these inconsistencies. Elderly men and women differ both in lipid levels as well as risk factors and progression of cardiovascular disease; gender differences being apparent long before disease manifestation (9, 10). HDL-C was reported to be a more significant cardiovascular disease risk factor in women than in men whereas LDL-C is more significant in men (11). However, well-designed studies examining lipoprotein fractions and gender separately are rare and not adequately powered to adjust for a large range of confounders (12, 13).

Genetic vulnerability to depression has also rarely been taken into consideration. In a recent meta-analysis, Lopez-Leon et al reported significant evidence for five major depressive disorder susceptibility genes, two of them being also associated with lipids, apolipoprotein E (ApoE) and serotonin transporter (5-HTT) (14). ApoE is a major determinant in lipoprotein metabolism, cardiovascular disease and immunoregulation, each of these disorders being implicated in major depression (15). Regarding the linked promoter region of 5-HTT (5-HTTLPR), LDL-C levels have been found to be higher in persons with long polymorphism

(l/l) than in those with short polymorphism (s/s) (16) although not systematically (17). Finally, despite the potential for interactive effects between 5-HTTLPR polymorphism and cholesterol levels on depression, this has only been investigated recently in one Korean study but without taking into consideration gender differences (17).

Thus, while there is some evidence to suggest that lipids may affect depressive vulnerability, this hypothesis has yet to be tested within a large prospective study able to take into account multiple independent and interactive causes of depression. In the present study, we were able to take into account gender specificities and to control for socio-demographic and behavioral variables, as well as history of psychiatric disorder and measures of physical health including ischemic pathologies which may independently contribute to both depressive symptomatology and lipid levels. Natural or lipid lowering agent (LLA)-induced hypolipidemia was considered, as well as genetic vulnerability to dyslipidemia or psychiatric disorder (genes coding for ApoE or 5-HTT).

Methods

Subjects

The data were derived from a longitudinal study of neuropsychiatric disorder in community-dwelling French elderly (the Esprit study). Eligible participants, who were at least 65 years of age and non-institutionalized, were recruited by random selection from the 15 electoral rolls of the Montpellier district between March 1999 and February 2001. Of the people initially drawn at random, 27.3% did not participate (of these, 3.3% were excluded owing to severe disability). Those who refused to participate were replaced by another person drawn at random from the same electoral division, so that each division was equally represented. Refusals were slightly older and more likely to be living alone than those who

agreed to participate (18). Ethics approval for the study was given by the national ethics committee. After obtaining written informed consent from all participants, interviews were administered by trained staff at baseline and after 2-, 4-, and 7 years of follow-up. Of the 2259 subjects recruited for the Esprit study, 2195 were free of dementia, of whom 42 did not have blood lipid evaluation. A further 130 subjects were not assessed for current psychiatric symptomatology and another 231 had missing data for at least one adjustment variable. The cross-sectional analyses were thus conducted on 1792 subjects. Non-demented persons not included had a lower educational level (χ^2=16.26, df=3, p=0.001), were older (χ^2=84.58, df=3, p<0.0001), more likely to have disabilities (χ^2=37.09, df=1, p<0.0001), cognitive dysfunction (χ^2=30.13, df=1, p<0.0001), ischemic pathologies (χ^2=22.53, df=1, p<0.0001), and current depressive symptomatology (χ^2=48.04, df=1, p<0.0001). They were also more likely to have hypertension (χ^2=10.32, df=1, p=0.001), had triglyceride (TG) (t=2.64, p=0.008) levels.

Outcome measures

The diagnosis of lifetime depression and anxiety disorders was made using the Mini-International Neuropsychiatry Interview (MINI), a standardized psychiatric examination validated in the general population (19) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (18). Positive cases were reviewed by a panel of psychiatrists. The Center for Epidemiologic Studies-Depression Scale (CES-D) is a validated instrument, the threshold of 16 corresponding to severe levels of depressive symptomatology considered to be of clinical significance (20). The presence of one of the two criteria at baseline, namely MINI diagnosis of current major depression or high levels of depressive symptomatology (CES-D$\geq$16), was designed to diagnose clinical level of depression (DEP), *i.e.* levels of psychopathology which would warrant clinical intervention. The other subjects without current major depression and with CESD $\leq$ 15 are referred to as a low symptom

group. In longitudinal analyses, incident DEP was identified from this low symptom group not treated by antidepressants at baseline, but who subsequently had incident DEP during at least one of the three follow-up examinations.

Socio-demographic and clinical variables

The standardized interview included questions on socio-demographic characteristics, height, weight, mobility, recent loss of appetite, smoking and alcohol consumption, and measures of blood pressure. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and those with score <26 were considered as having cognitive impairment (21). Detailed medical questionnaires (with additional information where necessary from general practitioners) were used to obtain information on history of vascular disease, including ischemic pathologies (*e.g.* angina pectoris, myocardial infarction, stroke, cardiovascular surgery, arteritis). We also recorded all drugs used during the preceding month, including LLA (*e.g.* statin or fibrate), antidepressants, and anxiolytics. Participants interviewed at home were asked to show medical prescriptions, drug packages and any other relevant information; those interviewed at the study centre were asked to come with their prescription forms. Venous blood samples were taken at baseline from subjects after fasting for >12h. T-C, HDL-C and TG levels were measured in serum by routine enzymatic methods. LDL-C was determined by the Friedwald formula (22). Genotyping of ApoE and 5-HTTLPR was performed as described previously (23).

Statistical Analysis

Unadjusted analyses were carried out using χ^2 tests or analysis of variance for qualitative and quantitative data respectively. For TG, due to skewed distribution,

logarithmically transformed values were used in the descriptive analysis and expressed as geometric means and SE ([Confidence interval: $m/SE^{1.96}$; $m \times SE^{1.96}$]). Men and women were examined in separate analyses as we found they differed with regard to both lipid levels and DEP (see Table 1). Associations between lipid classes and DEP were assessed using logistic regression models. Univariate odds ratios were stratified by sex and adjusted for age and educational level (model 0). Multivariate logistic regression included covariates that were found to be associated with DEP ($p<0.15$). Model 1 was stratified by sex and adjusted for age, education level, marital status, cognitive impairment, body mass index (BMI), mobility, ischemic pathologies, hypertension, diabetes, alcohol and tobacco intake, recent loss of appetite, and ApoE. Compared to model 1, model 2 was further adjusted for variables related to history of psychiatric disorder, *e.g.* history of past depression, lifetime anxiety disorder, and current use of antidepressant or anxiolytic drugs. 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 intermediary quartiles (reference value). The distribution of 5-HTTLPR did not deviate from Hardy-Weinberg equilibrium in men (χ^2=1.03, df=1, p=0.31) and women (χ^2=0.27, df=1, p=0.61). To test the hypothesis that 5-HTTLPR genotype might modify the relationship between lipid levels and DEP, we added the interaction term to the full model and tested for its significance using Wald's χ^2 test given by the logistic regression model. When the interaction was significant we stratified by 5-HTTLPR genotype.

A Cox model with delayed entry was used in the longitudinal analysis of incident DEP over 7-year follow-up (median [IQR] = 7.4 [3.7-7.6] years), adjusted on the above confounding factors, and taking age as the basic time scale and birth as the time origin to avoid the problem of non-proportionality of the risk with age (24). SAS (v9.1) was used for the statistical analyses with a significance level of $p<0.05$ (SAS Institute,Inc.,North Carolina).

Results

Population characteristics

At baseline, 29.9% of the 1792 participants were identified as having DEP, 2.5% with current major depression at MINI and 27.4% with high levels of depressive symptomatology, *i.e.* with CES-D score≥16 but without major depression. LLA use was reported by 26.2% of persons. Women had a higher prevalence of depression than men and also higher T-C, HDL-C, and LDL-C levels but lower TG levels. Men and women were found to differ on all characteristics except for age, LLA use, and 5-HTTLPR **(Table 1).**

Associations between baseline lipid levels and DEP

We first examined the cross-sectional associations between lipid levels and DEP at baseline, using a logistic regression model adjusted for age and education level and stratified by sex (model 0) (**Table 2**). In men, low LDL-C levels were significantly associated with an increased risk of DEP (OR=1.90; 95%CI=1.25-2.89, p=0.003). In women, low HDL-C levels were associated with an increased risk of DEP (OR=1.42, 95%CI=1.04-1.94, p=0.03). LLA use was not associated with a significant risk of DEP in men (OR=0.90; 95%CI=0.60-1.36, p=0.63) or women (OR=1.18; 95%CI=0.89-1.58, p=0.26). In a multivariate regression model (model 1) the same associations were observed for low LDL-C in men and low HDL-C in women as well as after adjusting for other confounders related to lifetime psychiatric disorder (model 2).

For men, a significant interaction was observed between LDL-C level and 5-HTTLPR (Wald χ^2=12.32, df=4, p=0.02). Men with lowest quartile LDL-C levels and two s alleles were at high risk of DEP (OR=6.00, 95%CI=1.40-25.63, p=0.02 compared to middle-quartiles LDL-C) and this was also the case for men with only one s allele (OR=2.69, 95%CI=1.15-

6.29, p=0.02), but not for men with low LDL-C levels and l/l genotype (OR=0.71, 95%CI=0.20-2.56, p=0.60) (**Table 3**). In women, we observed no significant interaction between low HDL-C levels and other covariates including 5-HTTLPR (Wald χ^2=1.31, df=4, p=0.86) except for a trend for ischemic pathologies (Wald χ^2=5.04, df=2, p=0.08 in model 2). Women with low HDL-C levels and without ischemic pathologies were at significantly higher risk of DEP (OR=1.64, 95%CI=1.14-2.37, p=0.008), whereas no significant associations were observed for women with ischemic pathologies (OR=0.72, 95%CI=0.18-2.88, p=0.64).

In longitudinal analyses, among the 1131 persons without DEP at baseline, 61 men (11.5%) and 162 women (27.0%) were identified with incident DEP (including both new cases and recurrent cases) over the 7-year follow-up period. Multivariate Cox model stratified by gender showed a significant association for men between low LDL-C levels and incident DEP (HR=1.98, 95%CI=1.06-3.72, p=0.03, in the multi-adjusted model 2). In women, no significant associations were observed between low HDL-C levels and incident DEP (p=0.27).

Discussion

Association between serum lipid levels and DEP and gender differences

Our results indicate an increased risk in DEP associated with low serum lipid levels independently of ApoE genotype, consistent with two previous studies having found no interaction between ApoE ε4 allele and T-C levels on late-life depressive symptomatology (5, 6, 25). In addition, we observed no significant difference as a function of LLA use, suggesting that absolute low levels rather than reduction from high lipid concentrations might be associated with depression. This is in agreement with randomized controlled trials in which

no modification in depressive symptomatology has been reported in patients with, or at risk of, coronary disease receiving LLA (26, 27).

Up to now, most cross-sectional studies having evaluated the associations between lipids levels and depressive symptomatology without gender stratification have yielded inconsistent results. Interestingly, in our stratified multi-adjusted analysis, the associations were clearly restricted to cholesterol fractions with different patterns according to gender. For men, DEP was associated with lower LDL-C levels, whereas for women, the risk was associated with low HDL-C levels. In the two studies having examined only male samples, a significant association with low LDL-C was found in one case (28) but not in the other one (29). Only two small gender-stratified studies have been performed finding no significant association with low LDL-C in men while for women, one study reported an association with low HDL-C (12) but not the other one (13). These both studies however, were not adequately powered to adjust for a large range of confounders precluding definitive conclusion. We did not find significant associations with low T-C levels, as previously (28-31) although not universally (7, 12, 13, 32) reported. This could be related to elderly general population who frequently have hypercholesterolemia (in our sample 32.8% of persons had T-C levels >6.2 mmol/l). Together with the fact that T-C comprises both LDL-C and HDL-C (which have opposite relationships with vascular risk) cholesterol fractions may be more valuable markers for late depression than T-C.

Are serum lipid levels predictive of late-life depression?

Although we found significant associations in cross-sectional analyses for men and women, we could observe significant associations with incident DEP over the 7-year follow-up only for men. The absence of association for women in longitudinal analyses could be

probably explained by their high HDL levels (only 1.7% had values under the “normal” range <1.02 mmol/l). This percentage may be further decreased during the 7-year follow-up. Finally, HDL-C level changes that may have occurred between baseline and follow-up measurement were not necessarily captured, which might have led to an underestimation of the associations.

Of the four longitudinal studies which have examined men and women separately, Shibata et al (13) observed a significant association between incident depressive symptomatology and low baseline T-C levels in 195 men and Strandberg et al (12) with high HDL-C levels in 103 men. Neither of these studies found significant associations in women. It should be noted however that, in men, no associations were observed in cross-sectional analyses and only age (12), education and baseline depressive symptomatology score (13) were considered as confounding factors. No significant associations were observed with T-C or HDL-C levels in a multi-adjusted study of 29,133 men (29). Only one study examined the associations between changes in lipid levels during follow-up and incident depressive symptomatology. A decline in T-C levels over 5 years (but not low baseline T-C levels) predicted incident depressive symptomatology in 526 men (33). Further large cohort studies examining gender separately are required to address the question of whether decline in lipids would be a better predictor of incident depression than baseline levels.

Biological hypotheses linking depression, and HDL-C or LDL-C alterations: towards a gender-specific etiology?

For men, our results strongly suggest dyslipidemia to be a risk factor for DEP. The reverse possibility, *i.e.* DEP as a risk factor of low LDL-C due to a decrease in appetite is notably unlikely considering (i) the absence of significant association with low TG or T-C

which would be expected in case of loss of appetite or weight loss, (ii) the robustness of the association even after controlling for recent loss of appetite or BMI and, (iii) the significant association observed in longitudinal analyses.

LDL-C is the major carrier of cholesterol, notably required for the regulation of cell membrane viscosity. Reduction in serum cholesterol and LDL-C could be associated with decreased brain cell membrane cholesterol which might result in changes in density and functioning of serotoninergic transporters or receptors (34). Our results indicate that lower 5-HTTLPR activity associated with the s allele may confer increased vulnerability for late-life depression in the presence of lower LDL-C levels in men. We did not find significant association between this polymorphism and alterations in lipid levels including LDL-C (data not shown). At the present time, only one study in a Korean population (59% of women) has examined the interaction between 5-HTTLPR and lipid levels reporting a lack of association with LDL-C but a significant association with lower HDL-C levels in s allele carriers but not in l/l homozygotes (17). However, the very low number of depressed cases in this category (n=7 compared to 41 in s/l and 53 in s/s) and hence lack of power, notably due to a lower prevalence of l/l genotype in East Asian populations may make hazardous definite conclusion. Difference in ethnic groups as well as the absence of gender stratification could explain inconsistencies.

Late-life DEP in women appeared to be associated with an atherogenic lipid profile. Low HDL-C is an important risk factor for vascular disease (35) with stronger effects in women than men (11). There is some evidence that depression may be associated with a greater risk for cardiac events in women (36) and that the association may be bidirectional. Although no conclusions can be drawn from our data about causal relationships for women, they do not however, suggest depression to be a risk factor for dyslipidemia. Indeed, in our

study the associations between low HDL-C and DEP remained significant after controlling for a number of vascular factors, as well as in women without ischemic pathologies, which makes it unlikely that vascular disorders constitute a confounding factor. Lastly, the possibility that earlier affective disorder increases risk for both (cardio)vascular pathology and late-life depression is also unlikely since we controlled for history of psychiatric disorder.

HDL-C has anti-inflammatory properties and reduced HDL-C concentrations notably contribute to the onset of the inflammatory response that typically occurs in the pathogenesis of atherosclerosis right from its earliest stages (37). Depressive symptomatology has also been reported to be associated with elevated inflammatory markers (notably C-reactive protein, CRP) in patients without heart disease, but none of these studies evaluated the specific confounding effect of HDL-C (4 , 38). CRP levels were measured in 15% of our sample, *i.e.* 160 women. In a multivariate model adjusted for age and education level, low HDL-C levels remained independently associated with an increased risk of DEP in the 148 women without ischemic pathologies even after adjustment for high CRP levels (≥median value, 1.76mg/l) (OR=2.50, 95%CI=1.16-5.49, p=0.02). Although the low numbers of subjects preclude drawing definite conclusions, it is tempting to hypothesize that this mechanism may come into play in the early initiation and progression of the disease in women in bridging depression and cardiovascular disease. Whether depression is an early, and cardiovascular disease a late, complication of an underlying metabolic problem, involving HDL-C, remains to be clarified.

The physiological underpinnings of these gender differences remain speculative but may involve phenotype or genetic vulnerability differences (see for review (39)). Depression has been described as a non-homogenous construct consisting of somatic/ as well as cognitive/ affective symptoms. Somatic depression characterized by hypersomnia, appetite

increase, anxiety, and fatigue has been reported to be much more prevalent in women than men, but not pure depression (40). It is however unlikely that the somatic dimension of depressive symptoms may be related to pro-atheriogenic cholesterol in women whereas the cognitive dimension would be related to anti-atherogenic cholesterol. Indeed, in our data after adjusting for somatic covariates the associations were unchanged for women as for men.

A more likely explanation might involve polygenic vulnerability and hormonal factors. A sex-specific genetic architecture of quantitative traits and interacting relationships have been reported for dyslipidemia and depression, as well as other serotoninergic, immune, and HPA axis related measures (41, 42). More particularly, the impact of sex on the penetrance and expressivity of various lipid traits with distinct level of sexual dimorphism according to cholesterol fractions has been reported (42). A gender based genome-wide association study recently identified several loci involved in distinct lipid traits (*e.g.* abnormal HDL-C or LDL-C levels) and with different sex-specific effects regarding key enzymes involved in lipid transport and metabolism (43). Steroid hormones and steroid-related genes (*e.g.* receptors) have also been associated with gender different effects on lipid metabolism, neurotransmitter turnover and depressive symptoms (44-46). Hence, the difference both in hormonal and lipid levels might lead to differential expressivity of the underlying genetic networks, and gene(s) by cellular environment interactions could result in differential effects of the same variation in men and women.

Limitations and strengths

There is a potential bias due to refusal and exclusion of some participants. These persons were older, with a lower education level, with overall poorer health, and had higher TG levels. Although this could be a limitation to generalizability, the consequence is that associations

between lipid levels and depression outcomes might be underestimated. However, additional analyses with all sample using imputation procedure led to comparable results (data not shown). Some of the covariates were self-reported and may be subject to recall bias with depressed participants responding more negatively about their health. However, similar associations were seen in the unadjusted and adjusted analysis, suggesting that any bias did not have a substantial influence on the results. For women, no definite conclusions can be drawn about the direction of the relationship between low HDL-C and DEP. However, the association remained significant after controlling for vascular factors or stratifying by ischemic pathologies, which makes unlikely that vascular disorders constitute a confounding factor. We cannot exclude however, the possibility that there are other unknown confounding factors including subclinical disease (in addition to that detectable through the analysis of lipids, glycemia, and hypertension). Finally, to evaluate DEP, we used a dimensional approach based on symptom severity rather than a categorical approach. Since we had no way of ascertaining the precise reasons for antidepressant prescription, subjects without DEP and taking antidepressants were excluded at baseline for longitudinal analyses. It is unlikely however, that this small number of subjects would bias the results, on the contrary it would have weakened the observed associations.

Despite these limitations, this study has a number of strengths. The data came from a large population-based prospective study of subjects aged 65 years and over and therefore the results are relevant to elderly persons living in the community. DEP was assessed by trained staff using two distinct measures validated in the general population, including a structured diagnostic interview (19, 20). The fasting nature of the lipid sample will have improved the accuracy of the associations compared to random samples. We controlled for a large number of covariates thus minimizing any confounding and in contrast with most community-based studies, gender differences were examined.

Conclusions

We observed an increased prevalence of DEP among men with a low LDL-C level and in women with low HDL-C level. These associations were not explained by several confounders, *e.g.* behavioral, clinical, psychiatric factors and disability. Our findings provide some epidemiological support for lipidic vascular factors in the etiology of late-life depression in women and genetic vulnerability in men and may thus reflect gender-related differences in depression. Future large longitudinal studies are needed to unravel the mechanisms involved and to demonstrate causal association with chronically low lipid levels. Another major point of our study concerns the definition of "normal" lipid values in elderly persons especially for LDL-C whose lower threshold is recommended to be <3mmol/l (47). In our study, men in the lower LDL-C concentration quartile (<3.05mmol/l) were at nearly two-fold increased risk of DEP (6-fold for those with high genetic vulnerability) which may have clinical consequence in terms of mental health and co-morbidity. Our work adds to the growing interest in whether adequate managing of lipid risk factors can improve DEP in the elderly, and implies that different strategies should be developed in men and women. This also suggests that LDL-C serum levels in men might be a sensitive biological marker which may lie in a narrow range above which cardiovascular risk may prevail and below which depression may predominate.

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