Longitudinal Association of Carotid Plaque Presence and Intima-Media Thickness With Depressive Symptoms in the Elderly

The Three-City Study

Christof Prugger, Ophelia Godin, Marie-Cécile Perier, Karen Ritchie, Catherine Helmer, Jean-Philippe Empana, Christophe Tzourio, Carole Dufouil

Objective—To investigate prospectively whether subclinical vascular disease is associated with future depressive symptoms in the elderly.

Approach and Results—A multicenter cohort of community-dwelling individuals aged 65 to 85 years was examined for carotid plaque presence and common carotid artery intima-media thickness at baseline and followed up after 2, 4, 7, and 10 years. At baseline and follow-up examinations, depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D). High level of depressive symptoms was defined as a CES-D score >16 in men and >22 in women. Among 4125 participants (58% women) at baseline, men more frequently showed carotid plaque presence and had higher mean common carotid artery intima-media thickness than women. After adjustment for major cardiovascular risk factors, carotid plaque presence was associated with a higher CES-D score at the 10-year follow-up in men (+1.46; 95% confidence interval, 0.71–2.20; \(P<0.001\)), but not in women. When restricting analyses to individuals without cardiovascular disease at baseline, carotid plaque presence increased the likelihood of high-level depressive symptoms at follow-up examinations in men (odds ratio, 1.47; 95% confidence interval, 1.06–2.05; \(P=0.022\)), but not in women. One SD increase in log-transformed common carotid artery intima-media thickness was associated with a higher CES-D score at the 10-year follow-up in women (+0.55; 95% confidence interval, 0.16–0.95; \(P=0.006\)) and men (+0.40; 95% confidence interval, 0.02–0.78; \(P=0.037\)). Common carotid artery intima-media thickness did not increase the likelihood of high-level depressive symptoms at follow-up in both sexes.

Conclusions—Subclinical vascular disease is associated with the progression of depressive symptoms in elderly men and women and the occurrence of high level of depressive symptoms in elderly men. (Arterioscler Thromb Vasc Biol. 2015;35:1279-1283. DOI: 10.1161/ATVBAHA.114.305061.)

Key Words: atherosclerosis ■ carotid arteries ■ depression ■ epidemiology ■ risk factors

Clinically relevant depressive symptoms are common in the elderly population and have been associated with the onset and prognosis of cardiovascular disease (CVD).\(^1,2\) Unraveling the mechanisms contributing to depression development in late life may identify targets for intervention and thus carry substantial implications for CVD prevention. Various age-related processes possibly contribute to the development of depression among the elderly.\(^3\) In particular, vascular disease has been postulated to increase the risk of late life depression.\(^4\) This so-called vascular depression hypothesis is supported by neuroimaging studies describing positive associations of cerebral white matter lesions with future depressive symptoms.\(^5,6\) Although the origin of these cerebral hyperintensities in late life depression is thought to be vascular, it may also be heterogenous.\(^7\) Therefore, additional and more specific evidence on early markers of vascular disease with regard to depression development is needed. Carotid plaque and carotid intima-media thickness represent 2 distinct biologically and genetically determined markers of subclinical atherosclerosis and

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arteriosclerosis,8,9 which can be measured inexpensively and noninvasively by ultrasound imaging. Carotid plaque reflects the cumulative exposure to atherosclerotic risk factors, whereas carotid intima-media thickness is more the result of aging and accumulated exposure to blood pressure. To date, few studies have investigated the relationship between subclinical vascular disease and depression in older adults: 1 cross-sectional study showed an association for generalized extracoronary atherosclerosis,10 but this finding was not confirmed by the only prospective study.11 Because depressive states change over time in the elderly,12 repeated measurements of depressive symptoms may allow to better examine their relationship with subclinical vascular disease. We, therefore, investigated the association of carotid plaque presence (CPP) and common carotid artery intima-media thickness (CCA-IMT) with future depressive symptoms in elderly individuals from the Three-City Study. The objective of our study was to examine whether carotid plaque and intima-media thickness are prospectively related to depressive symptoms evaluated ≤5 times during a period of 10 years.

### Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

#### Study Population

The study population included 4125 (93.0%) of eligible participants at baseline with depressive symptoms measured at least once at follow-up examinations. Mean age was 73.41 (SD, 4.87) years at baseline and 57.8% were women (Table 1).

#### Subclinical Vascular Disease at Baseline

At baseline, men more frequently showed CPP (54.0% versus 43.3%; \( P<0.001 \)) and had higher mean CCA-IMT (0.73 versus 0.70 mm; \( P<0.001 \)) than women (Table 1). A history of CVD at baseline was present in 14.6% of men and 4.3% of women (\( P<0.001 \)).

#### Depressive Symptoms at Baseline and Follow-Up

Women had a higher median Epidemiologic Studies Depression Scale (CES-D) score than men at baseline (8 versus 5; \( P<0.001 \)). Mean CES-D scores at baseline and follow-up and the frequency of high level of depressive symptoms (HLDS) and antidepressant use at follow-up examinations are shown in Table I in the online-only Data Supplement.

In light of higher CES-D scores and lower levels of CPP and CCA-IMT in women than at baseline, as well as different cutoffs for HLDS in men and women (CES-D >16 and >22, respectively), longitudinal associations were quantified by sex.

#### Longitudinal Associations With CES-D Score

The Figure shows longitudinal associations of baseline CPP and CCA-IMT with CES-D score at follow-up examinations. Baseline CPP was associated with a significantly higher CES-D score at the 10-year follow-up in men (+1.46; 95% confidence interval [CI], 0.71–2.20; \( P<0.001 \)), but not in women after adjustment for age, study center, and antidepressant use, and major CVD risk factors. Furthermore, 1 SD increase in log-transformed baseline CCA-IMT was associated with a significantly lower CES-D score at the 10-year follow-up in women (−1.46; 95% CI, −2.20–−0.72; \( P<0.001 \)). Mean CES-D score at baseline and follow-up was significantly different when further adjusting for age, study center, antidepressant use, and major CVD risk factors. Furthermore, 1 SD increase in log-transformed baseline CCA-IMT was associated with a significantly lower CES-D score at the 10-year follow-up in women (−1.46; 95% CI, −2.20–−0.72; \( P<0.001 \)). Results remained largely unchanged when further adjusting for cognitive performance at baseline and incident dementia, coronary heart disease and stroke during follow-up, and when restricting analyses to individuals without a history of CVD at baseline (Table II in the online-only Data Supplement).

#### Longitudinal Associations With HLDS

Table 2 presents longitudinal associations of baseline CPP and CCA-IMT with HLDS at follow-up examinations. Baseline CPP increased the likelihood of HLDS at follow-up in men (odds ratio, 1.36; 95% CI, 1.02–1.81; \( P=0.035 \)), but not in women after adjustment for age, study center, and antidepressant use (model 1). The association among men was borderline significant when further adjusting for major CVD risk factors.

### Table 1. Baseline Characteristics of Study Participants, by Sex (n=4125)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men (n=1739)</th>
<th>Women (n=2386)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>73.25 (4.85)</td>
<td>73.53 (4.88)</td>
<td>0.072</td>
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<tr>
<td>Carotid plaque presence, n (%)</td>
<td>939 (54.0)</td>
<td>1034 (43.3)</td>
<td>&lt;0.001</td>
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<td>CCA-IMT, mm, mean (SD)</td>
<td>0.73 (0.13)</td>
<td>0.70 (0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CES-D score, median (IQR)</td>
<td>5 (2–9)</td>
<td>8 (4–13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Higher education, n (%)</td>
<td>576 (33.1)</td>
<td>481 (20.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE score, median (IQR)</td>
<td>28 (27–29)</td>
<td>28 (27–29)</td>
<td>0.645</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>143 (8.2)</td>
<td>86 (3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>1063 (61.1)</td>
<td>338 (14.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>26.29 (3.41)</td>
<td>25.13 (4.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, mean (SD)</td>
<td>5.50 (0.88)</td>
<td>5.95 (0.94)</td>
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<tr>
<td>HDL cholesterol, mmol/L, mean (SD)</td>
<td>1.43 (0.35)</td>
<td>1.75 (0.39)</td>
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<td>Diabetes mellitus, n (%)</td>
<td>210 (12.2)</td>
<td>148 (6.4)</td>
<td>&lt;0.001</td>
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<td>SBP, mm/Hg, mean (SD)</td>
<td>150.43 (21.12)</td>
<td>149.97 (21.16)</td>
<td>&lt;0.001</td>
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<tr>
<td>DBP, mm/Hg, mean (SD)</td>
<td>84.45 (11.23)</td>
<td>81.20 (10.73)</td>
<td>&lt;0.001</td>
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<tr>
<td>Antihypertensive medication, n (%)</td>
<td>815 (46.9)</td>
<td>1090 (45.7)</td>
<td>0.452</td>
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<tr>
<td>History of CVD, n (%)</td>
<td>254 (14.6)</td>
<td>102 (4.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CCA-IMT indicates common carotid artery intima-media thickness; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; MMSE, Mini-Mental State Examination; and SBP, systolic blood pressure.
CCA-IMT did not increase the risk of incident HLDS. In this study, we report on the association of CPP and CCA-IMT with the occurrence of HLDS complement recent findings of the only previous study that prospectively investigated this relationship. Within the Rotterdam Study, genotyping related to baseline CCA-IMT and HLDS at follow-up examinations.

When testing for effect modification by sex in pooled analyses, a borderline significant interaction with CPP (P = 0.052) was observed in the association with HLDS.

Discussion
In this study, we report on the association of CPP and CCA-IMT with future depressive symptoms in community-dwelling elderly who had no HLDS and who were free of current and past major depressive episodes at baseline examination. Baseline CCA-IMT was associated with a higher CES-D score at follow-up in women and men. Baseline CPP was associated with a higher CES-D score and an increased likelihood of HLDS at follow-up in men only. The association of CPP with HLDS in men was particularly significant and independent of major CVD risk factors among individuals without a history of CVD. Overall, subclinical vascular disease was associated with the progression of depressive symptoms in both sexes and the occurrence of HLDS in men.

Progression of Depressive Symptoms and Occurrence of HLDS
Our study results about the association of baseline CPP and CCA-IMT with the occurrence of HLDS complement recent findings of the only previous study that prospectively investigated this relationship. Within the Rotterdam Study, generalized extracoronary atherosclerosis including CPP and CCA-IMT did not increase the risk of incident HLDS. In contrast to this study, however, only 1 interim examination was performed to evaluate the presence of HLDS during a follow-up period of 6 years. Thus, we extend the results of this previous study using a much longer follow-up with ≤5 repeated assessments of depressive symptoms. Our results hint toward an effect of subclinical vascular disease on the occurrence of HLDS in men.

On the basis of our present data, some issues may explain the lack of a significant association of CPP with CES-D and HLDS among women. Although the majority of individuals under study were women, the prevalence of CPP was substantially lower in women than in men. This suggests that we may have lacked power in the analysis among women. A significant association of CPP with CES-D score was observed at the 7-year follow-up only. Whether this finding is spurious or reflects a time-dependent effect of CPP on the CES-D score remains to be investigated. That the association disappeared at the 10-year follow-up might be explained by the higher attrition rate at this examination.

We acknowledge that CPP does not capture the entire prognostic information provided by carotid plaque. Other quantitative markers such as plaque area and volume are more predictive of CVD and may have shown a significant association with depressive symptoms in women. However, this information was not available in this study. Finally, despite differences in exposure, a true sex difference in the association between CPP and depressive symptoms represents an alternative explanation for our findings.

Pathophysiological Pathways
Several pathophysiological pathways may underlie the observed association of CPP and CCA-IMT with depressive symptoms.

First, and in accordance with the vascular depression hypothesis, vascular disease because of atherosclerosis and arteriosclerosis may cause depression in late life. CCA-IMT and CPP predict future CVD events including stroke, which could be on the pathway between subclinical vascular disease and depressive symptoms; however, significant associations among individuals without a history of CVD at baseline independently from incident CHD and stroke indicate that the relationships unlikely reflect a psychological manifestation from overt CVD.

Second, reverse causality may be an issue, in that depression preceded the development of CPP and the increase of CCA-IMT. Although we excluded participants with past and current depressive episodes, we cannot completely rule out misclassification related to the scales we used and, therefore, the possibility of such episodes before study inclusion. However, it is unlikely that such misclassification would be related to baseline CPP and CCA-IMT.

Third, residual confounding may account for the observed association, for instance by health conditions related to both
Taken together, we observed robust longitudinal associations of CPP and CCA-IMT with future depressive symptoms suggesting that subclinical vascular disease may be on the pathophysiological pathway toward depression in late life.

**Perspectives**

A positive association of CPP and CCA-IMT with depressive symptoms may have major public health relevance, particularly in light of the aging population. However, before direct implications can be drawn from our study results, they need to be confirmed by independent studies that should include larger population samples, reassess CPP and CCA-IMT during follow-up, measure additional markers such as plaque area and volume, and investigate clinical depressive disorders. If confirmed, our findings may suggest that prevention of CPP and of its risk factors may forestall the progression of depressive symptoms and the occurrence of HLDS in late life. This may constitute complementary approaches for the prevention of late life depression and the reduction of CVD risk: similarly to patients at high risk of CVD, a systematic evaluation of depressive symptoms may need to be considered among elderly individuals with subclinical atherosclerosis and arteriosclerosis.17,18

**Strengths and Limitations**

This study has several strengths, including the length of follow-up with repeated assessments of study participants, the standardized measurement of CPP and CCA-IMT, the use of a validated instrument to evaluate depressive symptoms, and the adjustment for many potential confounding factors. Among study limitations, we note that measures of CPP and CCA-IMT at a single point in time disregard the dynamic nature of vascular remodeling. We, therefore, cannot exclude the possibility of regression dilution bias attenuating the findings toward the null result. Furthermore, we lacked qualitative (echolucency and calcification) and quantitative (surface area and volume) data with regard to carotid plaque. Finally, no data were available on clinical depressive disorders using a formal diagnostic evaluation. However, in the Rotterdam Study mentioned above, extracoronary atherosclerosis was not significantly related to incident clinical depressive disorders.

**Conclusions**

Among community-dwelling elderly, carotid plaque was associated with increments in CES-D score and the occurrence of HLDS in men during a period of 10 years, whereas carotid intima-media thickness was associated with increments in CES-D score in women and men. These results lend support to the hypothesis that vascular disease may contribute to the pathogenesis of depression in late life.

**Sources of Funding**

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Disclosures
Dr Helmer reports financial relationships with Ipsen and Schwab, outside the submitted work. The other authors report no conflicts.

References

Significance
This is the first study to show that subclinical vascular disease is associated with future depressive symptoms in the elderly. During a period of 10 years, subclinical vascular disease was related to the progression of depressive symptoms in men and women and the occurrence of high level of depressive symptoms in men. As postulated in the vascular depression hypothesis, vascular disease may thus be on the pathophysiological pathway to depression in late life. Our findings raise the question whether intervening on vascular risk at the stage of subclinical vascular disease and its risk factors may prevent depression in late life. Given the high prevalence of late life depression and the increased cardiovascular risk associated with depression, this is of utmost significance. Randomized controlled studies may thus investigate whether such interventions will lower the incidence of late life depression.
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SUPPLEMENTAL MATERIAL

LONGITUDINAL ASSOCIATION OF CAROTID PLAQUE PRESENCE AND INTIMA-MEDIA THICKNESS WITH DEPRESSIVE SYMPTOMS IN THE ELDERLY: THE THREE-CITY STUDY

Christof Prugger, Ophelia Godin, Marie-Cécile Perier, Karen Ritchie, Catherine Helmer, Jean-Philippe Empana, Christophe Tzourio, Carole Dufouil

MATERIALS AND METHODS

Study design
The Three-City Study is a cohort of community-dwelling adults 65 years of age and older who were recruited from the electoral rolls of 3 cities in France - Bordeaux, Dijon, Montpellier - between 1999 and 2001. Ethical approval was obtained from the ethics committee of the Kremlin-Bicêtre University Hospital. Study participants provided written informed consent.

Data collection
A detailed description of the data collection has been published elsewhere.\(^1\) Data sought from all study participants at baseline comprised information on socio-demographic characteristics, cardiovascular risk factors, medication use, cognitive functioning, major depressive episodes, and depressive symptoms. Study participants 65-85 years of age were additionally offered an ultrasound examination of the carotid arteries, except for the last 4 months of the baseline examination phase. Individuals were followed up approximately 2, 4, 7 and 10 years later for interview and examination.

Carotid plaque and intima-media thickness measurement
Ultrasound imaging of the carotid arteries was performed at baseline examination using the B-mode system (Ultramark 9 High Definition Imaging) with a 5- to 10-MHz sounding in each study center followed by centralized evaluation at the Reference Reading Center (Hospital Broussais, Paris) by one reader.\(^2\) To ensure reliability and validity of measurements, programs of centralized training and regular quality control were implemented for sonographers (N=7) and the reader.

The examination involved scanning of the common carotid arteries, the carotid bifurcations and the origin of the internal carotid arteries. The near and far walls of these arterial segments were scanned longitudinally and transversally to assess carotid plaque presence (CPP) defined as localized echo structures encroaching into the vessel lumen for which the distance between the media-adventitia interface and the internal side of the lesion was ≥1 mm.\(^3\)

For the measurement of intima-media thickness, the near and far walls of the right and left common carotid arteries 2 to 3 cm of proximal to the bifurcation were imaged and frozen in end-diastole by electrocardiogram R-triggering. All frozen images were transferred to a computer system and digitized into 640×580 peak cells with 256 grey levels.\(^4\) They were stored on CD-ROMs that were sent to the reference center weekly. Common carotid artery intima-media thickness (CCA-IMT) was measured at sites free of any discrete plaque along a 10 mm long segment of the far wall and
defined as the distance between the lumen-intima interface and the media-adventitia interface using an automated edge-detection algorithm. Overall, an average of 75 measurements was automatically performed on each image and on each side.

A reproducibility study was conducted on 114 individuals. For CPP, the correlation coefficient for agreement between 2 examinations was 0.78, whereas the mean absolute difference and correlation coefficient between repeated measurements of CCA-IMT were 0.060 mm and 0.71, respectively. These results are very consistent with those reported in the Cardiovascular Health Study and in the Rotterdam Study.\textsuperscript{5,6}

**Depressive symptoms, antidepressant use and major depressive episodes**

At baseline and follow-up examinations, depressive symptoms were evaluated using the Center for Epidemiologic Studies Depression Scale (CES-D).\textsuperscript{7} The CES-D is a 20-item Likert-type scale designed to evaluate depressive symptoms in community individuals. Respondents are assigned a CES-D score between 0 and 60 points, with higher numbers indicating a higher depressive symptom level. Significant depressive symptoms were defined as a CES-D score \(>16\) in men and \(>22\) in women, cut-offs previously validated among populations in France,\textsuperscript{8} and will in the following be referred to as high level of depressive symptoms (HLDS). Antidepressant use at baseline and follow-up examinations was assessed through an inventory of all prescribed medications during the preceding month which were coded according to the Anatomical Therapeutic Chemical Classification System. The Major Depressive Episode module of the Mini-International Neuropsychiatric Interview (French version 5.00) was applied at baseline examination to identify study participants with current (within the last two weeks) and past (during lifetime) major depressive episodes.

**Cognitive performance and dementia diagnosis**

Global cognitive performance at baseline was assessed using the Mini-Mental State Examination.\textsuperscript{9} At follow-up examinations, screening for possible dementia followed an algorithm relying on the scores of the Mini-Mental State Examination and the Isaacs Set Test as reported previously.\textsuperscript{10,11} All possible cases of dementia were reviewed and ascertained by an independent committee of neurologists using DSM-IV criteria and the Clinical Dementia Rating scale.\textsuperscript{12,13}

**Cardiovascular disease history and events**

History of cardiovascular disease at baseline was self-reported using a validated face-to-face questionnaire and defined as myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention or stroke. Incident coronary heart disease and stroke events during follow-up were adjudicated by an independent committee as reported elsewhere.\textsuperscript{14,15}

**Statistical analysis**

Baseline characteristics of men and women were compared using the chi-squared test, \(t\)-test and Wilcoxon test as appropriate. Associations with depressive symptoms were investigated modelling the latter both as a continuous (total CES-D score) and as a categorical (HLDS) outcome. First, the progression of CES-D score between baseline and follow-up examinations was estimated using linear mixed models with an unstructured correlation matrix. To examine the association of CPP and CCA-IMT (per standard deviation increase in the log-transformed variable) with CES-D score at follow-up examinations, separate linear mixed models were fitted that contained parameters for CPP or CCA-IMT, follow-up time and CPP \(\times\) time or CCA-
IMT×time interaction. Longitudinal associations of CPP and CCA-IMT were estimated by means of their interaction terms with time. Normality of residuals from linear mixed models was assessed graphically. Second, the likelihood of the occurrence of HLDS at follow-up examinations was estimated using generalized estimating equations with logit-link and unstructured correlation structure. To estimate odds ratios with 95% confidence intervals of HLDS, separate generalized estimating equations were fitted for CPP and per standard deviation increase in log-transformed CCA-IMT. In the primary analysis, models were firstly adjusted for age, study center (random effect), and antidepressant use at follow-up examinations and secondly for major cardiovascular risk factors at baseline. In sensitivity analysis, we evaluated possible confounding and robustness of study results. First, analyses were additionally adjusted for Mini-Mental State Examination score (<20 points) at baseline and incident dementia during follow-up. Second, we further adjusted the analyses for incident coronary heart disease and stroke events. Third, we repeated the analyses in the subset of individuals without a history of cardiovascular disease at baseline. Finally, interactions of CPP and CCA-IMT with sex were tested in pooled analyses combining data from men and women. All tests were two-tailed and an alpha level of 0.05 was chosen to indicate statistical significance. The statistical analysis was conducted using Statistical Analysis Software version 9.4 (SAS, Cary, NC).

**Eligible study participants**

Among 6,462 study participants with measures of CPP and CCA-IMT, 462 (7.2%) had missing information on CES-D score or on Mini-International Neuropsychiatric Interview at baseline examination. Participants with the following characteristics at baseline were excluded: those diagnosed with current or past major depressive episodes (N=779), those with HLDS (N=560) and those with antidepressant use (N=183), since we investigated incident HLDS; those with dementia diagnosis (N=44), since evaluation of depressive symptoms (self-reported) could be unreliable in these subjects. A total of 4,434 study participants at baseline were thus eligible for the present analysis.
References

SUPPLEMENTAL MATERIAL

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INTIMA-MEDIA THICKNESS WITH DEPRESSIVE SYMPTOMS IN THE ELDERLY:
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SUPPLEMENTAL TABLES

**Supplemental Table I**: Center for Epidemiologic Studies Depression Scale score, high level of depressive symptoms, and antidepressant use at baseline and follow-up, by sex (N=4,125)

**Supplemental Table II**: Associations of carotid plaque presence and common carotid artery intima-media thickness with Centre for Epidemiologic Studies Depression Scale score over 10 years, by sex (N=4,125)
**Supplemental Table I**: Mean Center for Epidemiologic Studies Depression Scale score and frequency of high level of depressive symptoms and antidepressant use at baseline and follow-up, by sex (N=4,125)

<table>
<thead>
<tr>
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<th>Men</th>
<th>Women</th>
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<td>7 years</td>
<td>1202</td>
<td>6.17 (6.66)</td>
<td>98 (8.15)</td>
<td>58</td>
<td>9.11 (7.89)</td>
<td>136 (7.66)</td>
<td>140</td>
<td>142 (5.63)</td>
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</tr>
<tr>
<td>10 years</td>
<td>956</td>
<td>5.66 (6.03)</td>
<td>60 (6.24)</td>
<td>44</td>
<td>8.62 (7.80)</td>
<td>116 (7.85)</td>
<td>142</td>
<td>142 (5.63)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beta</td>
<td>-</td>
<td>0.083 &lt;0.001</td>
<td>0.368 &lt;0.001</td>
<td>1.668 -</td>
<td>0.140 0.359</td>
<td>0.984</td>
<td>0.002 &lt;0.001</td>
<td>0.001 &lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>-</td>
<td>0.066 &lt;0.001</td>
<td>0.368 &lt;0.001</td>
<td>1.668 -</td>
<td>0.140 0.359</td>
<td>0.984</td>
<td>0.002 &lt;0.001</td>
<td>0.001 &lt;0.001</td>
<td></td>
<td></td>
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</tr>
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</table>

High level of depressive symptoms was defined as CES-D score >16 among men and >22 among women.

Beta coefficients and p-values for the comparison between baseline and follow-up examinations from linear mixed models (CES-D score) and generalized estimating equations (high level of depressive symptoms, antidepressant use) adjusted for age, study center and antidepressant use during follow-up.

ADU: antidepressant use; CES-D: Center for Epidemiologic Studies Depression Scale; HLDS: high level of depressive symptoms; SD: standard deviation
Supplemental Table II: Associations of carotid plaque presence and common carotid artery intima-media thickness with Centre for Epidemiologic Studies Depression Scale score over 10 years, by sex (N=4,125)

<table>
<thead>
<tr>
<th></th>
<th>2 years</th>
<th></th>
<th>4 years</th>
<th></th>
<th>7 years</th>
<th></th>
<th>10 years</th>
<th></th>
<th>Overall</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Beta ± SE</td>
<td>P-value</td>
<td>Beta ± SE</td>
<td>P-value</td>
<td>Beta ± SE</td>
<td>P-value</td>
<td>Beta ± SE</td>
<td>P-value</td>
<td>Beta ± SE</td>
<td>P-value</td>
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<td>CPP</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Model 1 Men</td>
<td>0.67 ± 0.26</td>
<td>0.009</td>
<td>0.83 ± 0.28</td>
<td>0.003</td>
<td>1.57 ± 0.37</td>
<td>&lt;0.001</td>
<td>1.41 ± 0.38</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.36 ± 0.29</td>
<td>0.212</td>
<td>0.37 ± 0.31</td>
<td>0.245</td>
<td>1.03 ± 0.36</td>
<td>0.004</td>
<td>0.58 ± 0.40</td>
<td>0.153</td>
<td>0.075</td>
<td></td>
</tr>
<tr>
<td>Model 2 Men</td>
<td>0.71 ± 0.26</td>
<td>0.006</td>
<td>0.80 ± 0.28</td>
<td>0.005</td>
<td>1.65 ± 0.37</td>
<td>&lt;0.001</td>
<td>1.46 ± 0.38</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Women</td>
<td>0.37 ± 0.29</td>
<td>0.203</td>
<td>0.43 ± 0.32</td>
<td>0.170</td>
<td>1.09 ± 0.36</td>
<td>0.002</td>
<td>0.66 ± 0.41</td>
<td>0.108</td>
<td>0.054</td>
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</tr>
<tr>
<td>Model 3 Men</td>
<td>0.69 ± 0.26</td>
<td>0.008</td>
<td>0.79 ± 0.28</td>
<td>0.005</td>
<td>1.61 ± 0.37</td>
<td>&lt;0.001</td>
<td>1.42 ± 0.38</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.37 ± 0.29</td>
<td>0.201</td>
<td>0.45 ± 0.32</td>
<td>0.152</td>
<td>1.10 ± 0.36</td>
<td>0.002</td>
<td>0.66 ± 0.41</td>
<td>0.104</td>
<td>0.053</td>
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</tr>
<tr>
<td>Model 4 Men</td>
<td>0.67 ± 0.26</td>
<td>0.009</td>
<td>0.77 ± 0.28</td>
<td>0.006</td>
<td>1.59 ± 0.37</td>
<td>&lt;0.001</td>
<td>1.37 ± 0.38</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.36 ± 0.29</td>
<td>0.213</td>
<td>0.42 ± 0.32</td>
<td>0.181</td>
<td>1.04 ± 0.36</td>
<td>0.004</td>
<td>0.65 ± 0.41</td>
<td>0.114</td>
<td>0.077</td>
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</tr>
<tr>
<td>Model 5 Men</td>
<td>0.74 ± 0.27</td>
<td>0.007</td>
<td>0.96 ± 0.30</td>
<td>0.001</td>
<td>1.78 ± 0.40</td>
<td>&lt;0.001</td>
<td>1.45 ± 0.40</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.41 ± 0.30</td>
<td>0.170</td>
<td>0.47 ± 0.32</td>
<td>0.143</td>
<td>1.06 ± 0.37</td>
<td>0.004</td>
<td>0.61 ± 0.42</td>
<td>0.142</td>
<td>0.075</td>
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</tr>
<tr>
<td>CCA-IMT</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Model 1 Men</td>
<td>0.19 ± 0.13</td>
<td>0.136</td>
<td>0.31 ± 0.14</td>
<td>0.029</td>
<td>0.50 ± 0.19</td>
<td>0.007</td>
<td>0.38 ± 0.19</td>
<td>0.050</td>
<td>0.068</td>
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<tr>
<td>Women</td>
<td>0.44 ± 0.14</td>
<td>0.002</td>
<td>0.33 ± 0.16</td>
<td>0.034</td>
<td>0.41 ± 0.18</td>
<td>0.022</td>
<td>0.58 ± 0.20</td>
<td>0.004</td>
<td>0.010</td>
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</tr>
<tr>
<td>Model 2 Men</td>
<td>0.19 ± 0.13</td>
<td>0.132</td>
<td>0.33 ± 0.14</td>
<td>0.021</td>
<td>0.51 ± 0.19</td>
<td>0.006</td>
<td>0.40 ± 0.19</td>
<td>0.037</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.44 ± 0.14</td>
<td>0.002</td>
<td>0.32 ± 0.16</td>
<td>0.038</td>
<td>0.38 ± 0.18</td>
<td>0.033</td>
<td>0.55 ± 0.20</td>
<td>0.006</td>
<td>0.012</td>
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<tr>
<td>Model 3 Men</td>
<td>0.19 ± 0.13</td>
<td>0.144</td>
<td>0.32 ± 0.14</td>
<td>0.025</td>
<td>0.49 ± 0.19</td>
<td>0.008</td>
<td>0.37 ± 0.19</td>
<td>0.052</td>
<td>0.069</td>
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</tr>
<tr>
<td>Women</td>
<td>0.43 ± 0.14</td>
<td>0.003</td>
<td>0.33 ± 0.16</td>
<td>0.034</td>
<td>0.38 ± 0.18</td>
<td>0.034</td>
<td>0.55 ± 0.20</td>
<td>0.007</td>
<td>0.013</td>
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<tr>
<td>Model 4 Men</td>
<td>0.18 ± 0.13</td>
<td>0.152</td>
<td>0.31 ± 0.14</td>
<td>0.028</td>
<td>0.49 ± 0.19</td>
<td>0.009</td>
<td>0.36 ± 0.19</td>
<td>0.061</td>
<td>0.077</td>
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<tr>
<td>Women</td>
<td>0.44 ± 0.14</td>
<td>0.002</td>
<td>0.32 ± 0.16</td>
<td>0.037</td>
<td>0.35 ± 0.18</td>
<td>0.048</td>
<td>0.52 ± 0.20</td>
<td>0.011</td>
<td>0.017</td>
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<tr>
<td>Model 5 Men</td>
<td>0.20 ± 0.14</td>
<td>0.147</td>
<td>0.27 ± 0.15</td>
<td>0.070</td>
<td>0.49 ± 0.20</td>
<td>0.014</td>
<td>0.47 ± 0.20</td>
<td>0.018</td>
<td>0.103</td>
<td></td>
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<tr>
<td>Women</td>
<td>0.42 ± 0.15</td>
<td>0.005</td>
<td>0.33 ± 0.16</td>
<td>0.040</td>
<td>0.35 ± 0.18</td>
<td>0.052</td>
<td>0.50 ± 0.21</td>
<td>0.015</td>
<td>0.028</td>
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</tbody>
</table>

Beta coefficients, standard errors and p-values from linear mixed models.
Model 1 was adjusted for age, study centre, and antidepressant use during follow-up.
Model 2 was additionally adjusted for smoking status, systolic blood pressure, total cholesterol, body mass index, diabetes mellitus, and educational level.
Model 3 was additionally adjusted for Mini-Mental State Examination score at baseline and incident dementia (n=52 in men, n=55 in women) during follow-up. Model 4 was additionally adjusted for incident coronary heart disease (n=142 in men, n=80 in women) and stroke (n=50 in men, n=49 in women) during follow-up. Model 5 was adjusted for all variables in Model 4 and restricted to individuals without a history of cardiovascular disease at baseline. Estimates for CCA-IMT are expressed per standard deviation increase in the log-transformed variable. CES-D: Centre for Epidemiologic Studies Depression Scale; CCA-IMT: common carotid artery intima-media thickness; CPP: carotid plaque presence; SE: standard error