

# Relationship Between Atherosclerosis and Late-Life Depression

## The Rotterdam Study

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**Context:** Depression in late life has been associated with vascular abnormalities. Several studies have demonstrated that persons with brain infarcts are more likely to have depressive disorders. Furthermore, depression is related to the subsequent development of ischemic heart disease.

**Objective:** To investigate the relationship between atherosclerosis at different locations and depression in the general population.

**Design:** Cross-sectional population-based study.

**Setting:** The Rotterdam Study, a population-based cohort study.

**Participants:** In 4019 men and women 60 years and older, we assessed atherosclerosis at different locations, including common carotid intima-media thickness, plaques in the carotid arteries, the ankle-brachial blood pressure index, and aortic atherosclerosis. An overall measure of extracoronary atherosclerosis was obtained in 3747 persons by computing the principal component of these extracoronary atherosclerosis measures. In a subgroup

of 1986 persons, we additionally measured coronary calcifications.

**Main Outcome Measure:** All subjects were screened for depressive symptoms. Screen-positive subjects had a psychiatric interview to diagnose depressive disorder.

**Results:** More severe extracoronary atherosclerosis was associated with a higher prevalence of depressive disorders. For every 1–standard deviation increase, the prevalence increased by 30%. Furthermore, we found a strong relationship of severe coronary and aortic calcifications with depressive disorders (odds ratio, 3.89; 95% confidence interval, 1.55–9.77; and odds ratio, 2.00; 95% confidence interval, 1.02–3.96, respectively).

**Conclusions:** Atherosclerosis and depression are associated in the elderly. This finding is compatible with the vascular depression hypothesis. However, the cross-sectional nature of the study does not allow causal inferences. In particular, earlier depressive episodes may have contributed to the development of atherosclerosis.

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SEVERAL LINES OF EVIDENCE suggest that there is a relationship between vascular factors and late-life depression. Both symptomatic and silent brain infarcts are associated with subsequent depression.<sup>1</sup> Furthermore, subtle white-matter and deep gray-matter abnormalities were found more frequently in depressed than in nondepressed persons.<sup>2</sup> A vascular depression hypothesis has been proposed. It postulates that structural changes in the brain due to atherosclerosis are of primary importance in late-life depression.<sup>3,4</sup>

On the other hand, depressive symptoms are also related to subsequent cardiovascular disease. Several prospective population-based studies of depressed persons showed an increased risk of myocardial in-

farct.<sup>5-8</sup> Possibly, depression contributes to the development of atherosclerosis or increases the risk of cardiovascular events in individuals who developed atherosclerosis unrelated to depression. However, none of these studies included any physiological measurements such as assessment of atherosclerosis or neuroendocrine function. Thus, it remains unclear which pathophysiological mechanisms could explain the observed association between depression and incident myocardial infarct. Numerous clinical studies on the cardiovascular risk associated with depressive symptoms investigated the excess morbidity and mortality in patients with established coronary heart disease.<sup>9</sup> Most studies did not assess the degree of atherosclerosis but rather focused on other measures like platelet function or heart rate variability.<sup>10-12</sup> Epi-

demographic evidence of an association between atherosclerosis and depression in the general population is lacking. Moreover, the vascular depression hypothesis is mainly supported by neuroimaging studies, which demonstrated hyperintensities. Although assumed to be vascular, the pathological basis of the hyperintensities in people with depression has not been determined.<sup>13</sup>

We examined the association between atherosclerosis at different locations in the body and depression in the Rotterdam Study, a large, prospective, community-based study. The aim of the Rotterdam Study is to investigate determinants of chronic and disabling diseases. The study started in 1990, when all inhabitants 55 years or older of Ommoord, a district of Rotterdam, the Netherlands, were invited to participate. A total of 7983 men and women entered the study (78% of those eligible). A first follow-up survey was done in 1993 to 1994, and a second follow-up survey in 1997 to 1999. In addition to follow-up surveys, the total cohort is continuously being monitored for major morbidity and mortality through linkage of general practitioner and municipality records.

## METHODS

### SUBJECTS

The study was conducted as part of the second follow-up examination (1997 to 1999) in the Rotterdam Study. The Medical Ethics Committee of Erasmus University approved the study, and written informed consent was obtained from all participants. In this survey, we added assessment of depressive symptoms to the study protocol. Of the 5901 subjects invited, 4730 persons (response rate, 80.2%) participated in the home interview. Of these, 4019 came to the research center for noninvasive assessments of atherosclerosis. The 711 subjects with no assessment of atherosclerosis were on average older (78 vs 72 years), were more likely to be female (69.4% vs 57.9%), and had more depressive symptoms (11.8% vs 6.9%; overall prevalence, 7.8%).

In addition, noninstitutionalized participants younger than 85 years who had completed the third survey were invited for a coronary atherosclerosis scan at a second research site. Of the 3371 eligible subjects, 2263 agreed to undergo electron-beam computed tomography (CT). Participation rate (67.1%) was only moderate, because the examination was performed in another part of the city and scheduled as an additional visit. Nonparticipants were more likely to be female (62.9% vs 53.3%) and to be depressed (9.0% vs 5.8%). Because of archiving problems, the scores of 277 participants were lost and electron-beam CT scores of only 1986 persons were available for analysis.

### ASSESSMENT OF DEPRESSION

Depressive disorders were assessed by a 2-step procedure. First, participants completed the Dutch version of the original Center for Epidemiological Studies Depression Scale (CES-D) during the home interview. The CES-D is a 20-item self-reported measure of symptoms scored on a scale of 0 to 3 points.<sup>14</sup> We used a score of 16 as a cutoff to indicate depressive symptoms. This cutoff had a very high sensitivity for major depression in a random sample of older subjects in the Netherlands.<sup>15</sup> Previous studies have verified that a score of 16 and above on the CES-D represents clinically significant depressive symp-

oms.<sup>16</sup> In a second step, screen-positive subjects had a psychiatric workup. They were studied with the Dutch version of the Present State Examination, a semistructured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry.<sup>17</sup> All interviews were conducted by one of 2 experienced clinicians, a psychiatrist and a clinical psychologist. Psychiatric disorders were classified according to the DSM-IV criteria with an algorithm based on the Present State Examination scores. The diagnostic criteria include minor depression as defined in the appendix of the DSM-IV.

Of the 4019 subjects included in the analyses, 285 (7.1%) screened positive for depressive symptoms as measured by the CES-D. Demented persons with depressive symptoms were excluded (n=10). A psychiatric workup was performed in 259 (94.2%) of the 275 remaining participants. Twelve subjects refused to participate in this evaluation; 4 screen-positive subjects could not be reached. A depressive disorder as defined by the DSM-IV criteria was established in 119 cases (56 persons with major depression, 47 with minor depression, and 16 with dysthymia). The remaining subjects either were classified as having anxiety disorders or other psychiatric diseases (n=22) or did not meet the criteria for an Axis I psychiatric disorder (n=118, subthreshold depressive symptoms).

To define late-onset depression, we used data from the baseline interview with a physician. All persons in the present analyses responded to the questions about psychiatric history. Participants who reported a history of depression before age 55 years were considered to have had early-onset depression.

### ASSESSMENT OF ATHEROSCLEROSIS

We measured atherosclerosis noninvasively with 4 established methods, ie, the ankle-brachial blood pressure index, intima-media thickness in the common carotid arteries, the presence of plaques in the carotid arteries, and aortic atherosclerosis. These 4 measures assess extracoronary atherosclerosis at different locations in the body. Furthermore, in a subgroup of participants, we measured coronary atherosclerosis. All measures are strongly associated with incident cerebrovascular and coronary artery disease.<sup>18-21</sup>

Ankle-brachial blood pressure index is an indicator of peripheral arterial disease.<sup>22</sup> Systolic blood pressure at the right brachial artery was calculated as the mean of 2 consecutive measurements with a random-zero sphygmomanometer. A single systolic blood pressure reading was taken at both the left and the right posterior tibial arteries with a Doppler ultrasound 8-MHz transducer (Huntleigh 500 D; Huntleigh Technology PLC, Bedfordshire, England) while the subject was in the supine position. In agreement with the approach followed by Fowkes et al,<sup>22</sup> peripheral arterial disease was considered present when the ankle-brachial blood pressure index was lower than 0.90 in at least 1 leg. The sensitivity and the specificity of this cutoff are 90% and 98%, respectively, for an angiographically defined stenosis of 50% or more in a major leg artery.<sup>23</sup>

Intima-media thickness was measured by recording ultrasonographic images of both the left and right carotid arteries, using a 7.5-MHz linear-array transducer (ATL Ultra-Mark IV; Advanced Technology Laboratories, Bethel, Wash).<sup>24</sup> The lumen-intima interface and the media-adventitia interface of the distal common carotid artery were measured offline. The common carotid intima-media thickness was determined as the average of near and far wall measurements of both left and right sides.

The presence of plaques in the carotid artery was assessed by evaluating the ultrasonographic images of the common, internal, and bifurcation sites of the carotid artery for the presence of atherosclerotic lesions.<sup>25</sup> Plaques were defined as a focal widening relative to adjacent segments and composed

of calcified or noncalcified components. The total carotid plaque score of each subject was defined by summation of the presence of plaques at far and near walls of left and right sides at 3 locations. For the analyses we used 4 categories of plaque scores (no plaques and 1, 2-3, and 4 or more plaques). Results from a reproducibility study of plaque and intima-media thickness of the carotid artery among 80 participants in the Rotterdam Study who underwent a second ultrasound have been described elsewhere. In short, between paired measurements, a  $\kappa$  of 0.67 was found for plaques and of 0.74 for intima-media thickness.<sup>26</sup>

Atherosclerosis of the abdominal aorta was determined with a lateral x-ray of the lumbar spine. Calcified plaques were considered present when linear densities were clearly visible in an area parallel and anterior to the lumbar spine.<sup>18</sup> Values for the extent of calcification were scored according to the length of the involved area (<1 cm, 1-2.5 cm, >2.5-5 cm, and >5 cm). Radiographic assessment of aortic atherosclerosis was shown to be highly specific and in most cases represents advanced intimal atherosclerosis as determined at autopsy. A comparison study with CT was performed in our department. In 56 unselected patients, abdominal radiography showed calcifications in 32; all but 1 were confirmed by CT.<sup>27</sup>

We used coronary calcifications as a measure of coronary atherosclerosis. Imaging of the epicardial coronary arteries was performed with an electron-beam CT scan (C-150; Imatron, San Francisco, Calif). From the root of the aorta through the heart, 38 images were obtained with 3-mm slice thickness. With the method of Agatston et al,<sup>28</sup> a calcium score was obtained by multiplying each area of interest with a factor indicating peak density within the area. We summed the scores for the calcifications to obtain a score for the entire epicardial system.

#### OTHER MEASUREMENTS

Age, sex, cognitive function, education, antidepressant medication, cigarette smoking, total cholesterol level, body mass index, blood pressure, diabetes mellitus, history of myocardial infarction, and stroke were considered as possible confounders. Cognitive function was assessed by the Mini-Mental State Examination. Education was measured on an ordinal scale and later dichotomized into low (primary education only) and high education. Information on current antidepressant medication was obtained during the home interview, which included a cabinet check. Cigarette smoking was coded as pack-years ([number of cigarettes per day/20] × years) and in categories of current, former, and never smoker. Quetelet body mass index (calculated as weight in kilograms divided by the square of height in meters) was assessed at the research center. Diabetes mellitus was defined as use of insulin or oral blood glucose-lowering drugs or serum glucose levels higher than 198 mg/dL (11.0 mmol/L). Fasting blood samples were obtained from all subjects in this analysis, and serum total cholesterol level was determined by an automatic enzymatic procedure. Histories of myocardial infarction and stroke were obtained by direct questioning and computerized linkage with general practitioner medical records. History was considered positive when verified by a physician.

#### STATISTICAL ANALYSIS

The association of atherosclerosis with depression was analyzed in 2 ways. First, we assessed the relationship of individual atherosclerosis measures with subthreshold depressive symptoms and depressive disorders by means of logistic regression. Intima-media thickness was entered into the model as a continuous variable divided by 1 SD. Ankle-brachial blood pressure index, carotid plaques, and aortic calcifications were analyzed in the categories defined earlier. For the coronary cal-

cifications, 3 calcium score categories were defined as described previously: 0 to 100, 101 to 500, and above 500.<sup>29</sup>

Second, we used the different extracoronary atherosclerosis measures to obtain an overall atherosclerosis score. A principal component analysis was performed. This is a standard procedure to combine related measures.<sup>30</sup> Original variables were replaced with linear combinations of these variables. For this aim, we used the continuous measure ankle-brachial blood pressure index, intima-media thickness, plaques in the carotid arteries, and aortic atherosclerosis. We were able to reduce the 4 measures in our original data set to 1 principal component. The association with extracoronary atherosclerosis was studied by regressing depressive disorders and subthreshold depressive symptoms on this continuous measure divided by its standard deviation. A principal component analysis increases the power to reveal relationships. Unlike other methods, such as the construction of a composite score, it does not rely on arbitrary cut-off points (categorizations). To investigate a possible dose-response relationship, we repeated the analyses including cases with major depression only.

To control for confounding, we added the potential confounders into the basic model, which already contained age (continuous) and sex. The analyses were run with and without exclusion of persons with a history of stroke and myocardial infarction. On the one hand, these conditions can be seen as an intermediate in the relationship between atherosclerosis and depressive disorders and should not be excluded. On the other hand, an analysis in a subset free of overt cardiovascular disease gives additional information. It indicates whether the relationship of depression with atherosclerosis is due to a psychological reaction after manifestation of disease. We also checked whether the associations found were different in men and women by performing stratified analyses. Furthermore, we reran the analysis excluding all persons who had had an early-onset depression. The background of this secondary analysis is the vascular depression hypothesis, which posits that atherosclerosis contributed to the onset of depression. Episodes of depression at younger ages may indicate a vulnerability to other factors than vascular ones.

In addition to the analyses described, which rely on a categorical classification, we used the CES-D scores as a continuous variable in an analysis including all persons with an overall atherosclerosis score. Of the 3747 subjects who had at least 3 measures of atherosclerosis performed, 742 had a missing value on the fourth measure. To decrease possible bias, these missing atherosclerosis values can be filled in (imputed) by the multiple imputation method.<sup>31</sup> Imputation is based on the correlation between the missing variable and other variables including the atherosclerosis measures. This correlation can be estimated by using the subjects in whom the measurement was performed. We followed the method described by van Buuren et al,<sup>32</sup> which accounts for the uncertainty around estimated values. Imputations were performed with the Multivariate Imputations by Chained Equations statistical package (TNO Prevention and Health, Leiden, the Netherlands). For the present analyses, imputed values were used for the principal component analyses only.

#### RESULTS

**Table 1** presents characteristics of the reference subjects who scored below the CES-D cutoff and the cases with subthreshold depressive symptoms or depressive disorders. Persons with depressive disorders were slightly older (74 years vs 72 years), more likely to be female (72% vs 57%), and more likely to have had a stroke (8% vs 3%) than the persons in the reference group.

**Table 1. Characteristics of the Study Subjects**

Characteristic	Below CES-D Cutoff* (n = 3734)	Subthreshold Depressive Symptoms* (n = 118)	Depressive Disorders* (n = 119)
Age, mean (range), y	72.2 (61-97)	74.1† (62-93)	74.3† (61-87)
Sex, % F	56.7	77.4‡	72.3‡
Primary education only, %	47.5	58.1	57.1
MMSE score, mean (SD)	27.7 (2.0)	27.2† (2.1)	26.5‡ (3.4)
History of stroke, %	2.8	7.3†	8.4†
History of MI, %	11.3	7.3	15.1
Smoking			
Current smoker, %	15.9	18.5	19.3
Ex-smoker, %	50.4	45.2	39.5
Pack-years§	16.0 (0-146)	13.6 (0-126)	16.2 (0-160)
Antidepressant medication, %	2.4	7.3	14.3
Blood pressure, mean (SD), mm Hg			
Diastolic	75 (11)	72.5 (11)	73 (12)
Systolic	144 (21)	143 (22)	139   (24)
Total cholesterol, mean (SD), mg/dL	224 (38.7)	228 (30.9)	224 (38.7)
Body mass index, mean (SD)	26.8 (4.0)	27.1 (4.2)	26.6 (3.9)
Diabetes mellitus, %	9.7	10.5	12.5
Common carotid intima-media thickness, mean (SD), mm	0.87 (0.15)	0.89 (0.14)	0.90 (0.16)
Peripheral arterial disease, %¶	16.8	21.0	21.8
Carotid plaques, %			
None	30	31	27
Mild	19	17	20
Moderate	33	32	31
Severe	18	20	22
Aortic calcifications, %			
None	22	17	17
Mild	36	25	34
Moderate	22	32	15
Severe	20	26	34
Coronary calcifications, %#			
0-100	47	44	25
101-500	25	29	31
>500	28	27	44

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; MI, myocardial infarction; MMSE, Mini-Mental State Examination. SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

\*"Below CES-D cutoff" includes all persons who had a depressive symptom score below 16, which indicates clinically relevant symptoms. "Subthreshold depressive symptoms" includes all persons above the threshold who did not fulfill the criteria for a *DSM-IV* disorder. "Depressive disorders" includes those with major or minor depression and dysthymia. Screen-positive subjects with other psychiatric disorders or without a psychiatric workup were excluded.

† $P < .01$  vs reference group. Continuous variables were analyzed by analysis of covariance and categorical variables by logistic regression, adjusted for age and sex where appropriate.

‡ $P < .001$ .

§Calculated as follows: (number of cigarettes per day/20)  $\times$  years.

|| $P < .05$ .

¶Defined as an ankle-brachial blood pressure index below 0.9.

#Numbers for coronary calcifications were 1871, 45, and 36 in nondepressed, subthreshold depressive symptoms, and depressive disorders groups, respectively. Analysis of coronary calcifications was available in 1986 persons; however, data for 34 persons with depressive symptoms were excluded.

**Table 2** shows the associations of the extracoronary atherosclerosis measures with subthreshold depressive symptoms and depressive disorders. There was no substantial relationship between individual measures of atherosclerosis and subthreshold depressive symptoms. A consistent pattern was found for depressive disorders across the 4 locations at which atherosclerosis was measured. The persons with a more severe disease process were more likely to have a depressive disorder. For intima-media thickness and severe aortic calcifications, the relationship reached statistical significance.

**Table 3** shows that subjects with higher levels of coronary calcifications had substantially more depressive disorders but no more subthreshold depressive symptoms than subjects without coronary calcifications.

**Table 4** presents the results based on the overall measure of atherosclerosis. Extracoronary atherosclerosis was related to depressive disorders. Furthermore, the results suggest a dose-response relationship between extracoronary atherosclerosis and depression. The highest odds ratios were observed when only persons with major depressive episodes were included as cases. However, the association was no longer significant because of the smaller number of cases.

The findings were very similar when imputed data from subjects with a missing atherosclerosis measurement were included. The odds ratio for this all-case analysis was 1.27 (95% confidence interval, 1.01-1.56;  $P = .04$ , with 102 cases with depressive disorders and 3491 persons who scored below the CES-D cutoff). Exclusion of

**Table 2. Relationship Between Different Extracoronary Measures of Atherosclerosis and Depression Expressed as Odds Ratios\***

Atherosclerosis Measure	Controls,† No.	Subthreshold Depressive Symptoms†			Depressive Disorders†		
		No.	Odds Ratio	95% CI	No.	Odds Ratio	95% CI
Intima-media thickness (per 1-SD increase)	3588	110	1.07	0.87-1.32	102	1.24	1.02-1.51
Peripheral arterial disease‡	3580	116	1.18	0.74-1.90	110	1.13	0.68-1.88
Carotid plaques							
None	1037	35	1.0	Reference	25	1.0	Reference
Mild	646	19	0.85	0.48-1.52	19	1.20	0.65-2.21
Moderate	1137	37	0.93	0.57-1.52	29	1.19	0.69-2.04
Severe	661	23	0.96	0.53-1.72	21	1.51	0.82-2.81
Aortic calcifications							
None	686	18	1.0	Reference	15	1.0	Reference
Mild	1112	26	0.85	0.46-1.59	29	1.19	0.62-2.27
Moderate	699	34	1.69	0.92-3.12	13	0.85	0.40-1.86
Severe	635	27	1.35	0.71-2.59	29	2.00	1.02-3.96

Abbreviation: CI, confidence interval.

\*Odds ratios were calculated with logistic regression adjusted for age, sex, total cholesterol level, blood pressure, cognitive score, antidepressant medication, smoking, diabetes mellitus, body mass index, history of stroke, and myocardial infarction. To test statistical significance of the categorical variables, we calculated overall *P* values for depressive disorders with a test for trend. For carotid plaques, we obtained *P* = .22; for aortic calcifications, *P* = .06.

†The control group consists of all persons who scored below the cutoff of 16 for clinically relevant depressive symptoms on the Center for Epidemiological Studies Depression Scale. The category "subthreshold depressive symptoms" includes all persons who scored above this cutoff and did not fulfill the criteria for a *DSM-IV* disorder. The category "depressive disorders" includes persons with major or minor depression and dysthymia. Screen-positive subjects with other psychiatric disorders or without a psychiatric workup were excluded.

‡Peripheral arterial disease was defined as an ankle-brachial index less than 0.90.

**Table 3. Relationship Between Coronary Calcifications and Depression Expressed as Odds Ratio\***

Atherosclerosis Measure	Controls,† No.	Subthreshold Depressive Symptoms†			Depressive Disorders†		
		No.	Odds Ratio	95% CI	No.	Odds Ratio	95% CI
Coronary calcification							
0-100	865	20	1.0	Reference	9	1.0	Reference
101-500	463	13	1.10	0.53-2.30	11	2.45	0.98-6.13
>500	511	12	0.96	0.43-2.16	16	3.89	1.55-9.77

Abbreviation: CI, confidence interval.

\*Odds ratios were calculated with logistic regression adjusted for age, sex, total cholesterol level, cognitive score, blood pressure, diabetes mellitus, body mass index, smoking, antidepressant medication, history of stroke, and myocardial infarction. To test statistical significance of the association between coronary calcifications and depressive disorders, we calculated the overall *P* value with a test for trend; *P* = .004.

†See Table 2 for explanation.

persons with stroke and myocardial infarction substantially attenuated the association of atherosclerosis with subthreshold depressive symptoms but not with depressive disorders or major depression (Table 4). Furthermore, the findings were similar in men and women. However, sex was a strong confounder. The elderly women had less atherosclerosis but were more likely to be depressed.

Excluding participants who reported an early-onset depressive episode (17 persons with depressive disorders and 151 persons who scored below the cutoff) scarcely changed the association between atherosclerosis and depression. The odds ratio of depressive disorders was 1.33 (95% confidence interval, 0.97-1.81; *P* = .06) in the fully adjusted model.

The analysis using the CES-D scores as a continuous variable further supports the notion of a dose-response relationship between atherosclerosis and de-

pression. Persons with more severe atherosclerosis had higher scores on the CES-D: 0.3 point per standard deviation of overall atherosclerosis score (95% confidence interval, 0.02-0.55; *P* = .03).

#### COMMENT

In this population-based study, we found that subjects with atherosclerosis were more likely to be depressed. A combined measure of extracoronary atherosclerosis was related to depressive disorders, although at some of the different locations the association was only moderate and nonsignificant. A strong relationship was observed only between severe coronary and aortic calcifications and depressive disorders.

The strengths of this study are the large number of elderly people participating and its population-based design. Furthermore, the psychiatric workup in subjects who

**Table 4. Association Between Measures of Generalized Extracoronary Atherosclerosis and Depression**

Principal Component (per SD) of Extracoronary Atherosclerosis Measures	Controls,* No.	Subthreshold Depressive Symptoms*			Depressive Disorders*			Major Depression		
		No.	OR (95% CI)	P Value	No.	OR (95% CI)	P Value	No.	OR (95% CI)	P Value
Adjusted†	2798	95	1.19 (0.95-1.49)	.12	77	1.29 (1.01-1.68)	.046	39	1.35 (0.96-1.90)	.08
Adjusted, persons with stroke or myocardial infarction excluded	2446	83	1.09 (0.86-1.38)	.50	65	1.31 (1.00-1.77)	.05	34	1.34 (0.95-1.92)	.10

Abbreviations: CI, confidence interval; OR, odds ratio.

\*See Table 2 for explanation. In these complete case analyses, only subjects with all 4 measurements of atherosclerosis were included.

†Odds ratio and 95% CI were calculated with logistic regression adjusted for age, sex, total cholesterol level, cognitive score, antidepressant medication, systolic blood pressure, diabetes, body mass index, and smoking.

screened positive on the CES-D enabled us to determine in which group depressive symptoms were due to depressive disorders. A previous study in an elderly Dutch population reported a high sensitivity with the same cut-off point, and misclassification of disease is therefore unlikely to have influenced our results.<sup>15</sup>

Some methodologic issues of this study must be discussed. First, this is a cross-sectional study and cannot demonstrate the chronology of the observed relationship. Second, the prevalence of subjects with depressive symptoms in this study (7.1%) was relatively low. However, it is comparable to the community prevalence observed by Blazer et al<sup>16</sup> in the United States (9.0%), who also used the CES-D. Furthermore, the rate falls within the variable range recently reported in a review of depressive symptoms in the elderly (2.8%-35%).<sup>33</sup>

To our knowledge, the present study is the first to examine the relationship between measures of atherosclerosis and depressive disorders in community-dwelling subjects. Many clinical studies have been performed in patients with preexisting vascular disease.<sup>34-36</sup> These studies generally show a high risk of comorbid depression on survival after a cardiovascular event. So far, few studies have been conducted in community-dwelling subjects.<sup>37,38</sup> A recent study in US Army personnel with the use of electron-beam CT observed no correlation between psychological factors and coronary atherosclerosis.<sup>38</sup> We studied an elderly population that encompassed a very broad spectrum of the degree of atherosclerosis. This may help to detect an association not found in a homogeneous population of middle-aged men. Furthermore, the previous population-based research, which investigated potential pathophysiologic mechanisms, concentrated on personality traits rather than specific mood states.<sup>37-39</sup> It is not clear how far a single trait (eg, negative affectivity) can account for the associations of depressive disorders with increased cardiovascular morbidity. This makes it even more difficult to relate previous findings to the present study, which measured clinical depressive disorders. Moreover, personality traits are much more stable than specific mood states such as depression. Studying distinct diseases has been advocated to identify potential treatments.<sup>9,40</sup>

Several explanations for the results need to be discussed. First, our findings are compatible with the vascular depression hypothesis, which posits an etiologic role

of vascular factors in the onset of depression. There is evidence from mostly cross-sectional studies that cerebrovascular disease contributes to the development or persistence of depression.<sup>13</sup> These studies, few of which were population based, have used different neuroimaging techniques in depressed patients.<sup>2,4,41-44</sup> It is assumed that the observed neuroradiologic findings such as white-matter lesions are due to vascular disease.<sup>3</sup> Furthermore, depression is highly prevalent in patients with overt or silent stroke,<sup>45</sup> which also suggests that people with cerebrovascular disease are particularly vulnerable to depression.

Second, depression could be a risk factor for the development of atherosclerosis. Although in most participants in this study we have no evidence of earlier episodes of depression, many of the depressed elderly will have had a chronic and intermittent course of depression. Previously, longitudinal population-based studies associated depression with cardiovascular disease later in life. Depressive status at baseline was an independent risk factor for ischemic heart disease and death.<sup>5-7,46</sup> Numerous biological processes that have been associated with depression may underlie this increased cardiovascular risk: decreased myocardial perfusion, abnormalities in platelet reactivity, cardiac arrhythmia, inflammatory processes, and noradrenergic hyperactivity.<sup>47-50</sup> These pathophysiologic changes are generally accompanied by increased atherosclerosis. Even if behavioral factors such as difficulties in smoking cessation or poor adherence to medical treatment account for the relationship of depression with subsequent vascular disease, one would expect to find increased levels of atherosclerosis in a cross-sectional study of elderly depressed persons.

Of course, the explanations are not mutually exclusive. The causal pathway may be bidirectional.<sup>13</sup> Furthermore, both depression and atherosclerosis could be manifestations of a common pathological process.

The observed association was somewhat more marked for coronary calcifications. This should be interpreted carefully because electron-beam CT was not available in all subjects. Subjects who underwent electron-beam CT were less likely to be depressed. However, unless the depressed nonparticipants had less atherosclerosis than the depressed participants, this will not have introduced bias. Moreover, the strong association between coronary calcifications and depression may re-

flect the good assessment of atherosclerosis rather than indicating a specific cardiac process. A recent publication of the Cardiovascular Health Study showed that some subclinical atherosclerosis detected by electron-beam CT was missed by measures of peripheral arterial disease and intima-media thickness.<sup>51</sup>

In summary, our findings in this large study of community-dwelling elderly confirm the postulated link between vascular factors and depression. Furthermore, a dose-response relationship was observed: more severe atherosclerosis was associated with more severe depressive symptoms. The present study cannot establish a causal role of atherosclerosis, but provides evidence that a generalized atherosclerotic process accompanies late-life depression. It is premature to speculate about clinical implications. However, if substantiated through further research, this knowledge may allow the prevention of the physical consequences of depression or new treatment strategies for late-life depression.<sup>52</sup> Primarily, prospective studies are needed to further elucidate the pathophysiology underlying the association between depressive disorders and vascular disease. These studies should include different biological measures and psychiatric interviews.

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