ORIGINAL ARTICLE

Atherosclerosis and Incident Depression in Late Life

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Context: Depression is a prominent concern for older adults; therefore, it is important to identify causal mechanisms so that prevention and treatment strategies can be developed. The vascular depression hypothesis proposes that vascular factors precede the onset of depression in older adults. However, although cross-sectional associations have been established, owing to a lack of objective assessments and longitudinal data, the validity and temporal nature of this relationship is unclear.

Objective: To examine whether atherosclerosis, an asymptomatic subclinical indicator of vascular burden, increases the risk of developing depression in older adults.

Design: Prospective, population-based study.

Setting: Set within the Rotterdam study, participants were assessed on objective measures of generalized atherosclerosis at baseline (1997-1999) and followed up for an average of 6 years for incident depression.

Participants: The baseline sample consisted of 3564 participants (56% female) with a mean age of 72 years who initially did not have depression or dementia.

Main Outcome Measures: Depression was categorized into symptoms or syndromes and assessed in a multidimensional manner from physician and mental health specialist reports, pharmacy records (antidepressant usage), a clinical interview, and self-report.

Results: During 21 083 person-years, 429 incidents of depressive symptoms and 197 incidents of depressive syndromes occurred. Individual atherosclerotic measures and a composite measure were not predictive of incident depressive symptoms (composite measure hazard ratio, 0.93; 95% confidence interval, 0.83-1.05) or incident depressive syndromes (composite measure hazard ratio, 0.97; 95% confidence interval, 0.81-1.16). An a priori power analysis indicated a sufficient sample size ($\alpha = .05$; 0.95 power).

Conclusions: Atherosclerosis does not appear to increase the risk of incident depression in older adults. These findings do not support the vascular depression hypothesis and, alternatively, taking findings from prior studies into account, suggest either that depression contributes to vascular burden or that both result from an underlying biological substrate.

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THE VASCULAR DEPRESSION HYpothesis postulates that depression in older adults manifests as a result of vascular disease.[1,2] Vascular depression is proposed as an etiologically distinct subtype of depression that occurs with atypical clinical presentation (eg, greater cognitive impairment, psychomotor retardation) and in the absence of psychobiological vulnerability or family history.[3,4] The vascular depression hypothesis is clinically important, as identifying a mechanism of depression in older age would assist in developing clinical risk profiles and designing and implementing effective treatment and prevention strategies.

This hypothesis largely originates from brain imaging studies, which show increased cerebral white matter hyperintensities, gray matter lesions, and brain atrophy, indicators of cerebral vascular burden, in people with depression.[5-7] However, these studies have been largely cross-sectional,[5-7] and the pathological basis of the abnormalities shown in imaging has not been reliably determined.[8] Further, many older adults in the general population exhibit these imaging abnormalities, yet do not exhibit depressive symptoms or syndromes.[9] A distinct clinical profile for vascular depression is proposed from hospital-based studies[1]; however, studies in large nonclinical settings have failed to identify this distinct clinical profile.[10,11] Further, vascular risk factors are purportedly associated with depression; however, this association has not been reliably found in longitudinal studies, with some studies showing no link[10,12,13] and others showing that only a few vascular risk factors such as smoking and antihypertensive medication were predictive of depression.[14,15] If vascular disease caused

incident depression, a more consistent pattern in risk factors would be expected. Another line of evidence often cited in support of the vascular depression hypothesis is depression following overt vascular events such as stroke (poststroke depression).[16] However, a recent prospective study examining this reported that vascular risk factors could not account for the relation between stroke and depression.[17] This indicates that depression seen after stroke may not be vascular in origin and may alternatively result from the psychological effect of the brain damage induced by stroke. The psychological and/or biological cause of poststroke depression is widely debated and still largely unclear.[18]

Examining atherosclerosis in relation to depression provides an important validation of the vascular depression hypothesis. Atherosclerosis is the main cause of vascular disease and, as such, provides a unique marker of vascular burden. First, this is useful because measuring atherosclerosis provides a more sensitive preclinical indicator of vascular burden that is more accurate for detecting the presence of vascular disease than examining vascular risk factors or overt vascular events. Second, generalized atherosclerosis may be the mechanism through which vascular disease triggers depression.[1] Third, atherosclerosis is largely asymptomatic, which increases the potential that incident depression results from biological mechanisms rather than the psychological consequence of experiencing an overt disorder.

The first study to examine atherosclerosis within the context of the vascular depression hypothesis was a cross-sectional article showing that elderly people with severe levels of extracoronary atherosclerosis, aortic plaques, and coronary calcification were more likely to have depressive disorders.[19] While these results support the vascular depression hypothesis, the temporal nature of this association is unclear. A longitudinal examination of atherosclerosis and depression demonstrated that atherosclerosis did not increase the risk of incident depression over a 5-year period.[20] However, atherosclerosis in this study was derived from a subjective estimate score based on cardiovascular outcomes, which may not provide a sensitive approximation of atherosclerosis. Further, only depressive symptoms were evaluated; intermittent depressive episodes were not examined; and the sample was restricted to the extreme end of the lifespan (85 and older).

Therefore, the current study aimed to clarify the validity and causal nature of the vascular depression hypothesis by prospectively examining the association between atherosclerosis and incident depressive symptoms and syndromes in a broad age range of older adults. Atherosclerosis was objectively examined with criterion standard measures at 4 sites and with electron-beam computed tomographic scans. Depression was continuously assessed using multiple methods.

METHODS

STUDY SETTING AND DESIGN

This study was based in the Rotterdam Study, a prospective, population-based cohort designed to examine the occurrence and risk factors of chronic diseases.[21] The current study used the third examination round (1997-1999) as baseline, as thorough depression screening was introduced at this time. At this baseline examination, a home interview and research center visit were conducted. Additionally, during the follow-up period, an interim examination occurred (2002-2004). Follow-up data on incident depression was collected continuously from baseline until October 1, 2005. A flow diagram of the design and data collection is presented in the **Figure**.

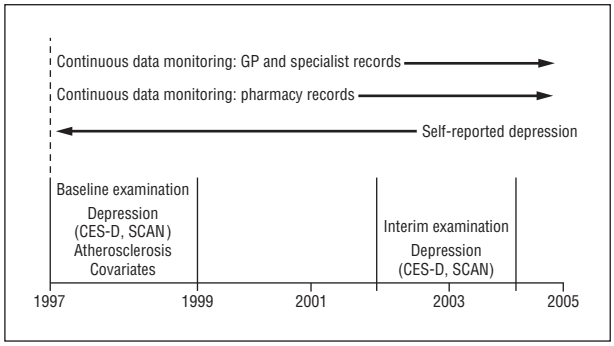

Figure. Assessment of depression (continuous monitoring, baseline, and interim examination). CES-D indicates center for Epidemiological Studies Depression scale; SCAN, Schedules for Clinical Assessment in Neuropsychiatry interview.

STUDY POPULATION

At the study baseline, 5990 residents were invited to attend and 4797 (80%) participated. Of these participants, 4597 (96%) had a valid screening for depression. Cases with depressive symptoms at baseline, as defined by a Centre for Epidemiological Studies Depression scale[22] score of 16 or more (n=362), and those scoring below the cutoff but with a positive indication for antidepressant usage (n=141) were excluded from analyses. Further, cases with a diagnosis of bipolar disorder (n=5) or dementia (n=122) at baseline were excluded.

Participants were included in analyses if they had at least 1 measurement of atherosclerosis. Participants with no atherosclerosis assessment were excluded (n=403). Atherosclerosis measures were therefore available for the following participants: carotid plaques, n=3014; aortic calcification, n=3026; peripheral arterial disease, n=3408; and intima-media thickness, n=3256. This provided an overall sample of 3564 participants (2005 women) for the current study. Participants who were excluded from the study were more likely to be female (71% vs 56%) and older (77 vs 72 years). A subset of community-dwelling participants younger than 85 years also participated in the Rotterdam Coronary Calcification Study, where they underwent a coronary atherosclerosis scan. Of the current study population, 1792 (50%) had available data on coronary calcification.

INCIDENT DEPRESSION ASSESSMENT

Incident depression was assessed with multiple sources to increase the validity of diagnosis and to capture more events. This is a form of best estimate diagnosis, which has been shown to be useful for psychiatric disorders.[23,24] Data on depression was collected continuously from baseline and during the baseline and interval examination rounds. This method has been described previously.[25]

Continuous Data

General practitioner and mental health specialist medical records were assessed continuously by trained research assistants

who relayed the information about a potential depression. Two research physicians independently assessed this information in accordance with a predefined protocol and discussed discordant assessments. Antidepressant use was determined from a cabinet check during the follow-up examination and continuously via digital pharmacy records from all pharmacies that serve the Ommoord area.

Examination Rounds: Baseline and Interval

The Centre for Epidemiological Studies Depression scale was completed during the home interview[22] of the third and fourth follow-up examinations. Participants with a positive depression score (≥16) were then invited for a subsequent assessment in which they completed the Schedules for Clinical Assessment in Neuropsychiatry with clinicians.[26] Self-reported history of depression was also recorded at each examination round. Standardized questions were used to determine if and when participants had experienced a depressive episode and if they sought treatment.

Incident depressive symptoms were recorded when clinically relevant depressive symptoms were reported that did not meet *DSM-IV* criteria for depression. This included participants who scored positive on the Centre for Epidemiological Studies Depression scale, were diagnosed with at least 1 core symptom of major depression in a medical record, self-reported depression when a physician or mental health professional was not consulted, or use of antidepressant drug treatments in the absence of medical records for depression.

Incident depressive syndromes included depressive syndromes recorded by a physician or self-reported depression for which a mental health specialist was consulted and *DSM*-defined minor and major depressive disorder and dysthymia reported by a mental health specialist or detected during the psychiatric Schedules for Clinical Assessment in Neuropsychiatry interview.

The date of onset of depressive symptoms or syndromes was set at the day of the first report of symptoms or the first prescription date of an antidepressant drug, whichever came first.

ATHEROSCLEROSIS MEASUREMENT

Extracoronary Atherosclerosis

Four measures were selected to assess extracoronary atherosclerosis at 5 sites in the body; they are strong predictors of vascular disease.[27-30] Carotid plaques were assessed by B-mode ultrasound at the common, internal, and bifurcation sites of the carotid artery for the presence of atherosclerotic lesions. A point was given for each positive location of atherosclerotic plaque (irrespective of plaque size).[31] This was categorized into 4 groups: 0 plaques, 1 plaque, 2 to 3 plaques, and 4 or more plaques. Aortic calcification of the posterior abdominal aortic wall was determined with a lateral x-ray of the lumbar spine (L1-L4). Calcification was considered present when linear densities were seen in an area parallel and anterior to the lumbar spine.[30] Aortic calcified plaques were scored according to the length of the involved area along the lumbar spine (L1-L4) and categorized into 4 groups: less than 1 cm, 1 to 2.5 cm, 2.5 to 5 cm, and more than 5 cm. Peripheral arterial disease was assessed with ankle-brachial blood pressure. Systolic blood pressure of the right brachial artery was measured twice by a trained research assistant with a random-0 sphygmomanometer after the subjects had rested for 5 minutes. For analyses, the mean of the 2 blood pressure measurements was calculated. Systolic blood pressure was also measured while in supine position in the left and right posterior tibial artery; the lowest reading was used for analyses (8-MHz continuous-wave Doppler probe; Huntleigh 500D; Huntleigh Technology, Bedfordshire, England). In agreement with the recommendation of the Ankle Brachial Index Collaboration,[29] peripheral arterial disease was considered present when the ankle-brachial blood pressure index was lower than 0.90. Intima-media thickness was measured as the mean of the far wall of both the right and left common carotid artery (millimeters). B-mode ultrasonography was conducted using a 7.5-MHz linear-array transducer (ATL Ultra-Mark IV; Advanced Technology Laboratories, Bethel, Washington).[32]

Coronary Calcification

In a subset of the population, coronary calcification was measured as an indication of coronary atherosclerosis. This has been shown to be a highly sensitive predictor of coronary artery disease.[33] A more detailed description of the Rotterdam Coronary Calcification Study is provided elsewhere.[34] An electron-beam computed tomographic scan (C-150; Imatron, San Francisco, California) was used and measured from the level of the root of the aorta. Thirty-eight images were obtained with 100-millisecond scan time and 3-mm slice thickness. A calcium score was then obtained using the Agatston et al method[35] in which the area (mm^2) of individual calcified lesions was multiplied by a factor based on the maximum density of the lesion. Calcium scores were divided into 4 categories: 0, more than 0 to 100, more than 100 to 400, and more than 400.[36]

COVARIATE ASSESSMENT

Age, sex, education, cognitive status, traditional cardiovascular risk factors, and history of overt vascular events were measured. Education was grouped according to the Standard Classification of Education and was rated from primary education (1) to university level (7). Cognitive status was measured with the Mini–Mental State Examination, which assesses 6 broad areas of daily cognitive functions.[37] Several cardiovascular risk factors were considered as covariates: body mass index, smoking status, systolic and diastolic blood pressure, antihypertensive medication use, total and high-density lipoprotein cholesterol, diabetes mellitus, and overt vascular events. Height (meters) and weight (kilograms) were measured and body mass index was calculated as weight in kilograms divided by height in meters squared. Smoking status was coded in categories as never, former, and current smoker. Antihypertensive use was verified during follow-up examination. A venipuncture was performed, and fasting blood samples were drawn and immediately frozen (–20°C). Cholesterol values were determined with an automated enzymatic procedure (Boehringer Mannheim System; Mannheim, Germany). Diabetes mellitus was determined by whether participants or pharmacy records reported using antidiabetic medication or if their fasting blood glucose concentrations were 200 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or higher. History of overt vascular events (cerebrovascular accident, myocardial infarction) was obtained continuously through automated linkage with general practitioners files and medical specialist discharge reports. For each reported event, additional information was collected (eg, hospital records, nursing home records). Two research physicians coded these events and, in the case of disagreement, a medical specialist was consulted. These covariates were selected, as they have been reported to be linked to both atherosclerosis and depression.

STATISTICAL ANALYSES

Participants contributed to the current study from baseline until their first incident depression, death, or the end of fol-

low-up (October 1, 2005). Intima-media thickness was used as a continuous variable and calculated so that an increase in hazard ratios reflected a 1-SD increase in the predictor. All other atherosclerotic measures were analyzed in their aforementioned categories to preserve their clinical meaning. However, they were also examined as continuous variables to assess for linear relations. The covariates of age, education, Mini–Mental State Examination, cholesterol, systolic and diastolic blood pressure, and cholesterol were examined as continuous variables. Sex, body mass index, smoking, and antihypertensive and antidepressant use were analyzed categorically. To increase the comparability of analyses and reduce bias, missing values on covariates used in analyses were imputed using single imputation with expectation maximization algorithm.[38] Variables were imputed using the entire baseline population (n=4797) and an array of variables available from the Rotterdam Study. Missing values on covariates were minimal (maximum, 8%).

An a priori power analysis was performed to detect the minimum number of participants required to detect a significant difference. The minimum number of participants required to detect a hazard ratio of 1.2 ($P < .05$) at a power of 0.9 was 2000 participants. This indicates that the present study was sufficiently powered to detect a reasonable difference.

To examine the overall predictive capacity of atherosclerotic measures, a composite score was created from the 4 extracoronary measures. A factor analysis was conducted to combine the measures, which is a standard procedure for combining related variables and provides an increased power to detect relationships.[39] The atherosclerosis measures were used in their continuous form, and a linear combination of these variables was used to construct a composite score. As participants with at least 1 measure of atherosclerosis were included in the study, some participants had missing values for 1 or more atherosclerosis measure. To ensure the composite score was representative of the entire sample, the missing values were imputed using the aforementioned expectation maximization algorithm.

The association between atherosclerosis and risk of incident depressive symptoms and incident depressive syndromes was examined using Cox regression analysis. Two models were conducted for each measure of atherosclerosis (4 extracoronary measures, composite score, and coronary calcification assessment). The first model examined atherosclerotic predictors of incident depressive symptoms and then incident depressive syndromes, controlling for age and sex. The second model assessed the same relationship but controlled for additional covariates and possible antecedents by using a multivariate model controlling for age, sex, education, Mini–Mental State Examination score, body mass index, smoking, total and high-density lipoprotein cholesterol, diabetes mellitus, systolic and diastolic blood pressure, and antihypertensive use. Proportional hazards assumptions were assessed with Schoenfeld residuals.

Secondary analyses were conducted to further examine the association. Analyses were first rerun in 3 subsets. The first was a subset of participants free from prevalent cardiovascular disease (n=3079). These cases were originally included because this could be in the pathway between atherosclerosis and depression; however, it important to analyze this subgroup to identify whether the depression is a psychological manifestation from an overt vascular event. Second, a subset of participants who were free from atherosclerosis 5 years prior to baseline, then developed atherosclerosis in the interim period, were evaluated. This enabled assessment of whether it is the development or the presence of atherosclerosis that is vital for vascular depression. Third, the associations were evaluated in a subset free from history of depression. They were initially included to allow for atherosclerosis prior to baseline creating vulnerability to depression. Participants self-reported whether they had sought professional treatment for depression in the 4 years prior to baseline (n=167). Additionally, analyses were run to evaluate sex × atherosclerosis interactions, as it is possible that a differential association between atherosclerosis and depression exists for men and women. Men have higher rates of atherosclerosis,[40] and women are more likely to be depressed.[41] Finally, it was evaluated whether atherosclerosis was a risk factor for incident *DSM-IV*–defined major depressive disorder (n=56).

Table 1. Baseline Characteristics of Study Participants 1997-1999 (n=3564)

Measures	
Demographics and background, mean (SD)	
Age, y	71.92 (6.81)
Sex female, No. (%)	2005 (56.30)
Education, range 1-7 y	3.78 (1.87)
Mini–Mental State Examination score	27.76 (1.83)
Cardiovascular risk factors and history[a]	
Smoking, No. (%)	
Never	1203 (33.80)
Former	1796 (50.40)
Current	565 (15.90)
Body mass index, mean (SD)[b]	26.81 (4.07)
Systolic blood pressure, mm Hg, mean (SD)	143.97 (21.17)
Diastolic blood pressure, mm Hg, mean (SD)	75.46 (11.08)
Receiving antihypertensive medication, No. (%)	1488 (41.80)
Total cholesterol, mg/dL, mean (SD)	5.82 (0.95)
HDL cholesterol, mg/dL, mean (SD)	1.39 (0.39)
Diabetes mellitus, No. (%)	219 (6.10)
Prevalent MI, No. (%)	397 (11.10)
Prevalent CVA, No. (%)	116 (3.30)
Extracoronary atherosclerosis, mean (SD)[c]	
Carotid plaques	1.25 (1.56)
Aortic calcification	2.13 (1.47)
Peripheral arterial disease, No. (%)[d]	598 (17.55)
Intima-media thickness, mm	0.87 (0.15)
Coronary atherosclerosis[c]	
Coronary calcification, mean (SD)	495.07 (950.76)

Abbreviations: CVA, cerebrovascular accident; HDL, high-density lipoprotein; MI, myocardial infarction.

SI conversion factors: To convert total and HDL cholesterol to millimoles per liter, multiply by 0.0259.

[a] Cardiovascular risk factors are based on imputed data (maximum, 8%).

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Atherosclerotic measures were available for the following participants: carotid plaques, n=3014; aortic calcification, n=3026; peripheral arterial disease, n=3408; intima-media thickness, n=3256.

[d] Peripheral arterial disease measured by ankle-brachial index (present, ≤0.900).

RESULTS

Participants had a mean (SD) age of 71.9 (6.81) years at baseline and were followed up for incident depressive events for a mean (SD) of 5.9 (2.1) years. Baseline characteristics of the sample are displayed in **Table 1**. During the study follow-up (21 083 person-years), 2938 participants (82.4%) experienced no incident depression, 429 (12.0%) experienced incident depressive symptoms, and 197 (5.5%) experienced incident depressive syndromes. Of the latter group, 56 (1.6%) were diagnosed with a *DSM-IV* major depressive disorder.

Higher levels on individual measures of extracoronary atherosclerosis and their composite measure score

Table 2. Association Between Extracoronary Measures of Atherosclerosis and Incident Depression (Age- and Sex-Adjusted Model)[a]

	Incident Depressive Symptoms				Incident Depressive Syndromes			
Variable	Total, No.	Cases, %	HR (95% CI)	*P* Value	Total, No.	Cases, %	HR (95% CI)	*P* Value
Carotid plaques								
Categorical								
None	865	14.1	1.00 [Reference]		809	8.2	1.00 [Reference]	
Mild	563	12.3	0.87 (0.65-1.17)	.36	522	5.4	0.70 (0.45-1.09)	.11
Moderate	938	11.8	0.86 (0.66-1.12)	.27	872	5.2	0.72 (0.49-1.06)	.10
Severe	484	13.2	1.02 (0.74-1.41)	.89	445	5.6	0.89 (0.55-1.44)	.63
P value for trend				.54				.26
Continuous per 1 unit	2850	12.8	1.00 (0.93-1.07)	.96	2648	6.2	0.96 (0.86-1.07)	.46
Aortic calcification								
Categorical								
None	870	12.9	1.00 [Reference]		811	6.5	1.00 [Reference]	
Mild	785	10.8	0.84 (0.63-1.11)	.22	742	5.7	0.94 (0.62-1.41)	.75
Moderate	636	15.3	1.19 (0.90-1.58)	.22	576	6.4	1.12 (0.73-1.73)	.60
Severe	567	14.8	1.13 (0.84-1.52)	.42	519	6.9	1.21 (0.77-1.88)	.40
P value for trend				.09				.69
Continuous per 1 unit	2858	13.2	1.07 (0.99-1.15)	.08	2648	6.3	1.05 (0.94-1.17)	.36
PAD								
None	2651	12.7	1.00 [Reference]		2473	6.4	1.00 [Reference]	
Present	566	13.8	1.05 (0.82-1.35)	.70	520	6.2	1.00 (0.68-1.47)	.99
IMT per 1-SD increase	3079	12.5	1.00 (0.89-1.12)	.95	2871	6.2	1.05 (0.89-1.25)	.56
Composite score per 1 SD[b]	3367	12.7	1.01 (0.91-1.12)	.88	3135	6.3	1.04 (0.89-1.22)	.63

Abbreviations: CI, confidence interval; HR, hazard ratio; IMT, intima-media thickness; PAD, peripheral arterial disease measured by ankle-brachial index (present, ≤0.90).

[a] Each measure was analyzed in a separate Cox regression multivariate model adjusted for age and sex.

[b] Composite score derived from the principal component analysis of the 4 extracoronary atherosclerotic measures (based on imputed data for missing values).

Table 3. Association Between Coronary Calcification and Incident Depression (Age- and Sex-Adjusted Model)

	Incident Depressive Symptoms				Incident Depressive Syndromes			
Coronary Calcification	Total, No.	Cases, %	HR (95% CI)	*P* Value	Total, No.	Cases, %	HR (95% CI)	*P* Value
Categorical								
None	157	12.1	1.00 [Reference]		146	5.5	1.00 [Reference]	
Mild	615	12.7	1.08 (0.65-1.79)	.78	581	7.6	1.54 (0.72-3.28)	.27
Moderate	381	11.8	1.06 (0.61-1.83)	.84	358	6.1	1.32 (0.58-3.00)	.51
Severe	537	11.7	1.12 (0.65-1.94)	.68	502	5.6	1.38 (0.60-3.15)	.45
P value for trend				.98				.71
Continuous per 1 unit	1690	12.1	0.96 (0.81-1.14)	.67	1587	6.4	1.09 (0.91-1.31)	.34

Abbreviations: CI, confidence interval; HR, hazard ratio.

did not increase the risk of incident depressive symptoms or syndromes after adjusting for age and sex (**Table 2**). This null relationship persisted after taking into account the effect of other potential depression and cardiovascular risk factors (results not shown, as they were highly comparable with unadjusted results). The only significant result from these models was the association between moderate carotid plaques and incident depressive syndromes, which became statistically significant (hazard ratio, 0.66; 95% confidence interval, 0.44-0.98; *P*=.04). However, it is notable that the predictive value of this hazard ratio is in an unexpected direction. Further, for this result to be meaningful within the vascular depression hypothesis, severe carotid plaques should match or increase this risk, while this was not the case in the current setting. Therefore, it is likely that this result is spurious. The proportional hazards assumption for a constant risk over time was met.

Within the subset of participants drawn from the Rotterdam Coronary Calcification Study, it was found that people with higher levels of coronary calcification did not have a greater risk of developing depressive symptoms or depressive syndromes. Age- and sex-adjusted models (**Table 3**) did not differ greatly from multivariate models (results not shown, as they were highly comparable with unadjusted results).

Secondary analyses conducted revealed comparable results (data not shown). The analyses outlined above were rerun in 3 subsets: (1) participants free from prevalent cardiovascular disease, (2) participants free from atherosclerosis 5 years prior to baseline but who went on to develop atherosclerosis in the time leading up to baseline, and (3) participants free from history of depression. The results did not differ greatly in these population subsamples when compared with the original sample. Additionally, it was evaluated whether a differential re-

lationship existed between atherosclerosis and depression in men and women by atherosclerosis measures interaction terms. No differential association was found between men and women (all interaction terms, $P > .05$). Finally, we sought to determine if atherosclerosis was a predictor of incident depression when depression was restricted to *DSM-IV*–defined major depressive disorder. This analysis did not reveal the existence of a dose-response relationship.

CONCLUSIONS

In this population-based prospective cohort study, atherosclerosis was not predictive of incident depression. None of our measures of extracoronary atherosclerosis were linked to either incident depressive symptoms or depressive syndromes. Similarly, a composite score of these variables was not predictive of incident depression. Coronary calcification, measured in a subsample of participants, was also not associated with incident depression in older adults.

The vascular depression hypothesis proposed in the 1990s by Alexolopoulos and Krishnan[1,2] suggests that vascular disease precedes depression in older adults. To date, support for the vascular depression hypothesis has been inconsistent with several methodological limitations impairing interpretation of findings. Atherosclerosis is the main cause of vascular disease and a sensitive asymptomatic marker of vascular disease. Thus, examining atherosclerosis in relation to depression provides an important validation of the vascular depression hypothesis. However, most investigations into this hypothesis have been cross-sectional[19] or in small clinical samples.[42,43] The only longitudinal study to examine this found that a subjective estimate of atherosclerosis was not predictive of incident depression.[20] However, this study had several limitations. We sought to reexamine this hypothesis using standardized objective measures of atherosclerosis, an expanded age range, and continuous assessment of incident depressive symptoms and syndromes, assessed from multiple sources. Interestingly, in support of the null association of the prior longitudinal study, yet in contrast to the prominent vascular depression hypothesis, we also found that atherosclerosis was not predictive of incident depression.

Reconciling these findings in this large body of literature does not provide strong support for the vascular depression hypothesis. However, the original cross-sectional investigation in the Rotterdam Study[19] and other cross-sectional research[42] established an association between atherosclerosis and depression. A plausible explanation for this is that a relation exists but such that depression contributes to the development of vascular disease. This proposition is supported by multiple population-based prospective studies showing that depression is prospectively linked to overt vascular events such as myocardial infarction,[44-46] stroke,[47] and cardiovascular-related mortality.[48] This has also been maintained by studies specifically on atherosclerosis; for example, in the Cardiovascular Health Study, which showed that in 3781 participants aged 65 years and older, depressive symptoms were related to the development of atherosclerosis during a 3-year period, even after excluding for prevalent vascular disease.[49] Depression has also been shown to predict the development of carotid plaques during a 10-year period.[50] An alternative plausible explanation is that both atherosclerosis and depression are clinical presentations of a shared biological substrate.

Most support for the vascular depression hypothesis has been derived from clinical studies, while most community-based studies such as the current study fail to support the hypothesis. This could reflect that vascular factors are not specifically causative for depression but additionally for other symptoms or disorders. However, caution should also be taken when replicating clinical study findings within large cohort studies. Although this has many advantages, such as increased sample size, to detect findings, standardized assessments, and generalizability, it also can have drawbacks such as missing interim events and less specific symptom assessment.

The current study has several strengths of design that enhance the validity of the presented null results. The study had an adequate sample size with a large amount of cases, both for incident depressive symptoms (n=429) and incident depressive syndromes (n=197). This number of cases provides adequate power for the analyses conducted and allows for a large number of covariates.[51] The study was also based in the general population, thus increasing the external validity and decreasing potential selection bias. Further, the range of atherosclerosis was heterogeneous, which may increase the chance of finding an association across all levels of atherosclerosis. The measurement of atherosclerosis was also objective, and well-validated assessment techniques were used.[27-30,33] Additionally, we took into account cardiovascular risk factors and variables that are important in aging and psychiatric research, thus allowing us to conduct multivariate models. Finally, a unique approach to measuring incident depression was used that increases the chances of detecting events and increases the specificity.[25] We collated multiple sources of information to detect cases of depression both continuously and within a clinical interview setting. The multiple sources of information are valid and monitored continuously, and the clinical interview is a criterion standard for assessing clinical events. Further, this method allows us to differentiate between depressive symptoms and syndromes. This is important for predictive studies, as the degree of depression has been shown to present with a different clinical profile and potentially different underlying causal mechanisms.

Some limitations of the study should also be discussed. The current study included participants with at least 1 measure of atherosclerosis. Therefore, the main analyses were conducted on marginally different populations. However, the analysis of the composite score of these measures, which imputed missing values, revealed no difference in findings, suggesting this was not creating a large bias. This left only a small subsample of participants (n=422) for whom we had no measures of atherosclerosis. It is possible that the reasons for nonassessment may create a bias. This subgroup may have a marginally different depression and/or cardiovascular risk profile, as they were more likely to be female and older.

Similarly, the subsample analyzed from the Rotterdam Coronary Calcification Study was restricted to adults younger than 85 years. Nevertheless, the variation of atherosclerosis in this group was large, suggesting that if a differential association was present, it would have been detected.

Points pertinent to the assessment of depression in the current study should also be considered. Between the baseline and intervening assessment, it is possible that a differential attrition occurred for those with a high vascular burden and a depression. However, given the use of continuous data from medical and pharmaceutical records in the current study, it is likely that serious cases were detected. The current study did not specifically assess the clinical profile ascribed to vascular depression[3]; however, although this profile has not been consistently validated,[11] it is likely that the broad definition of depression in the current study captured the proposed clinical syndrome. It is also possible that vascular depression is more chronic and refractory in nature, thus examining first incident event may not capture this. As examining repeated events would require knowledge of the end date of each depressive episode and a longer follow-up period, we are unable to examine this in the current data set, but the concept could be better examined in a closely observed clinical setting. Further, it is important to note that any cohort study of older adults includes many individuals with preexisting vascular disease and past depression. Although these disease entities can be controlled for, only incident and recurrent depression can be linked in their temporal sequence to vascular disease.

A final issue to be considered is that the present study focused on measures of extracerebral atherosclerosis. Given that a large body of support for the vascular depression hypothesis derives from brain imaging studies of cerebral atherosclerosis,[5-7] it is consequently possible that only cerebral atherosclerosis increases the risk of incident depression. However, cerebral atherosclerosis, indirectly measured through the presence of white matter lesions and lacunar infarcts on brain magnetic resonance imaging, is highly associated with extracerebral atherosclerosis.[52,53] Therefore, it is likely that the relationship between these two locations of atherosclerosis to depression is similar. A recent investigation from the Rotterdam Study supports this notion.[54] In a subsample of 479 people, it was found that markers of vascular brain disease, detected by magnetic resonance imaging, were associated with depression cross-sectionally. However, in line with the findings from the current study, no relationship was detected between these markers and risk of depression longitudinally.

In summary, atherosclerosis did not increase the risk of depression in older adults. Given the strengths of the study, including a large sample, population-based setting, and criterion standard measurement, we are confident in the validity of these null findings. In light of this, the current study does not support the vascular depression hypothesis. Interpreting these results within the context of prior associational studies, which found a relationship between atherosclerosis and depression, and longitudinal studies showing depression as a predicator of vascular events may suggest that depression may contribute to, rather than result from, vascular burden in older adults.

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