ORIGINAL ARTICLE

Temporal Relationship Between Depression and Dementia

Findings From a Large Community-Based 15-Year Follow-up Study

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Context: Late-life depression is associated with increased risk of dementia, but the temporal relationship between depression and development of dementia remains unclear.

Objectives: To examine the association between risk of dementia and baseline depressive symptoms; history of depression, particularly early-life (<50 years) vs late-life depression (≥50 years); and individual domains of the Center for Epidemiologic Studies Depression Scale.

Design: A large cohort with initially nondemented participants was followed up biennially for up to 15 years. Baseline depressive symptoms were assessed using the 11-item version of the Center for Epidemiologic Studies Depression Scale; presence of significant depressive symptoms was defined as a score of 11 or greater. Self-reported history of depression was collected at the baseline interview. Cox proportional hazards regression was used to assess the association between depression and dementia risk.

Setting: Population-based cohort drawn from members of the Group Health Cooperative in Seattle, Washington.

Participants: A cohort of 3410 participants without dementia aged at least 65 years.

Results: During a mean of 7.1 years of follow-up, 658 participants (19.3%) developed dementia. At baseline, 9.4% of participants had presence of significant depressive symptoms, and 21.2% reported a history of depression. The adjusted hazard ratio for dementia associated with baseline depressive symptoms was 1.71 (95% confidence interval, 1.37-2.13), after adjusting for age at entry, sex, educational level, and wave of enrollment. Compared with participants without depression history, those with late-life depression were at increased dementia risk (adjusted hazard ratio, 1.46; 95% confidence interval, 1.16-1.84), but early-life depression had no association with dementia risk (1.10 [0.83-1.47]). Depressed mood (adjusted hazard ratio, 1.48; 95% confidence interval, 1.25-1.76) and perceived performance difficulty (1.39 [1.15-1.67]) were independently associated with dementia.

Conclusion: This study confirmed that late-life depression is associated with increased risk of dementia and supplied evidence that late-life depression may be an early manifestation of dementia rather than increasing risk for dementia.

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SEVERAL LARGE LONGITUDINAL studies have shown that depression is associated with increased risk of cognitive decline,[1,2] mild cognitive impairment,[3] dementia,[4] and Alzheimer disease (AD),[2,4-7] but other studies have not found these associations.[8-10] An important question to be addressed is the temporal relationship between depression and dementia, ie, whether depression increases the risk of developing dementia or is an early manifestation of dementia. The Rotterdam Scan Study showed that history of depression, especially history of early-life depression (age <60 years), was associated with risk of AD, but depressive symptoms measured later in life at the baseline evaluation for the study were not associated with increased risk of developing AD and were not associated with hippocampal or amygdalar volume, suggesting early-life depression may be a risk factor for AD but not an early manifestation of AD.[11] Other studies have suggested that depression may be an early symptom of dementia.[9,12,13] In 1 study,[9] depression had a cross-sectional association with cognitive impairment but did not increase risk of subsequent cognitive decline; newly incident depressive symptoms were associated with recent onset of dementia, suggesting that depression might reflect symptoms of incipient dementia. A case-control study of dementia used the Swedish National Hospital Discharge Reg-

istries and medical records to identify individuals with a history of depression. The investigators[13] found that individuals with *recent* registry-identified depression were 3.9 times more likely than those with no registry-identified depression history to have dementia, whereas registry-identified depression *earlier* in life was not associated with dementia risk.

There is increasing evidence that subjective perception of memory loss and cognitive failure in the absence of objective cognitive impairment commonly occurs before cognitive decline and dementia.[14,15] Perceived cognitive failure and symptoms of depression overlap.[16,17] For example, the Subjective Cognitive Failures Questionnaire used in the Rotterdam Scan Study includes such questions as "Do you think or act more slowly than you used to?," "Do you feel more exhausted than you used to?," and "Do you have concentration problems?," which are similar in content to the items "You could not get 'going,'" "You felt that everything you did was an effort," and "You had trouble keeping your mind on what you were doing," used in the Center for Epidemiologic Studies Depression scale (CES-D) for depression assessment. Whether the association between *depressed mood* (assessed by the CES-D) and risk of dementia is independent of or mediated by subjective perception of performance difficulty remains to be elucidated.

Using data from the Adult Changes in Thought study, a large community-based prospective study of initially nondemented participants with up to 15 years of follow-up, we examined the association between all-cause dementia and (1) depressive symptoms assessed at baseline using the CES-D; (2) self-reported history of depression, especially early-life (<50 years) vs late-life (≥50 years); and (3) individual domains of the CES-D (eg, depressed mood, positive attitude, performance difficulty, and somatic symptoms, including disturbance of sleep and appetite). Finally, we explored the relationship between depressive symptoms at baseline and risk of different types of dementia, including AD, vascular dementia, mixed dementia (dementia due to multiple etiologies), and dementia due to other causes. If late-onset depression (late-life depressive symptoms without early-life depression) is associated with dementia risk, this would be consistent with depressive symptoms as an early manifestation of dementia. If early-life depression is associated with dementia risk, this would be consistent with depression acting as a risk factor for dementia. Thus, this line of research has important implications for understanding the underlying biology and for providing information toward early identification of dementia.

METHODS

PARTICIPANTS

The Adult Changes in Thought study has been described elsewhere.[18] Briefly, this community-based prospective cohort study drew participants from Seattle area members of the Group Health Cooperative health maintenance organization. This study had 3 waves of enrollment: 2581 participants aged 65 years and older were enrolled in 1994-1996 (original cohort), 811 participants were enrolled in 2000-2002 (expansion cohort), and 709 have been enrolled continuously since 2004 (replacement cohort) to maintain a cohort of more than 2000 subjects at risk for dementia outcomes in each calendar year. As of March 31, 2009, there were 4101 participants who had been enrolled in the Adult Changes in Thought study. The criterion for enrollment was either a score of at least 86 of 100 on the Cognitive Abilities Screening Instrument[19] (CASI, a brief cognitive screen test) or the absence of evidence of dementia after additional examination. Demographic characteristics, medical history, and suspected AD risk factors were obtained at the time of entry to the study. Of 4101 individuals who were enrolled in the Adult Changes in Thought study, 3410 partcipants having at least 1 follow-up visit and a valid baseline CES-D (83.2%) were included in this study. Of the 691 participants who were excluded from the analysis, most (675 [97.7%]) did not have a follow-up visit (204 died before follow-up, 113 withdrew from the study, and 358 had not yet been scheduled for their first follow-up), and 16 (2.3%) had no valid baseline 11-item CES-D (CES-D–11). For those excluded vs those included, comparisons of the mean age at entry (75.3 vs 74.9 years), baseline CES-D–11 score (4.2 for both), baseline CASI score (93.5 vs 93.1), and proportion of participants who were women (56% vs 60%) did not show significant differences ($P > .05$ for all). The study followed appropriate informed consent and local approval from the institutional review board.

OUTCOME ASSESSMENT

After enrollment, participants were rescreened every 2 years with the CASI. Those participants whose CASI scores were less than 86 underwent a standardized dementia diagnostic evaluation that included examination by a study physician (W.M., J.D.B., or E.B.L.) and neuropsychologic tests. Relevant laboratory tests and neuroimaging studies were performed or results were obtained from the Group Health Cooperative records. Dementia diagnoses were assigned at consensus diagnostic conferences using the *DSM-IV*,[20] and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association criteria for AD.[21] Our primary outcome was all-cause dementia defined by the *DSM-IV*. Secondary outcomes included dementia subtypes based on *DSM-IV* diagnostic criteria, categorized into AD, vascular dementia, dementia due to multiple etiologies (mixed type), and dementia due to other general medical conditions, such as Parkinson disease, substance-induced persisting dementia, and dementia not otherwise specified (other). Those participants with newly diagnosed dementia underwent at least 1 annual follow-up examination to confirm dementia status and subtype. Dementia onset was defined by convention as halfway between the date of diagnosis and the date of the prior Adult Changes in Thought study examination that showed no dementia.

ASSESSMENT OF DEPRESSIVE SYMPTOMS AND HISTORY OF DEPRESSION

Depressive symptoms were assessed using the CES-D at baseline. The CES-D is a short, structured self-report measure of depressive symptoms in the general population. It has been widely used during the past 30 years for epidemiologic studies of depression in general populations of all ages, including the elderly.[22-25] The original CES-D has 20 questions assessing depressive symptoms in the previous week, and each symptom is rated from 0 to 3 on the basis of frequency and severity. The total score ranges from 0 to 60. The CES-D was not designed to diagnose depression, but a cut-off score of 16 or higher discriminated well between psychiatric inpatients and general popu-

lations.[26] A score of 16 or higher on the CES-D is considered indicative of a depressive disorder in the elderly.[27]

In the initial baseline visit in 1994-1996, a short version of the CES-D that contained 11 of 20 items (CES-D–11) was administered in our study. However, during subsequent follow-up visits, the full 20-item version was used. To determine which CES-D–11 cut-off to use to identify significant depressive symptoms, we considered our first follow-up visit when the full CES-D (20 items) was obtained. We used the standard score of 16 or higher in the full CES-D as the criterion standard for significant depressive symptom classification and found that a CES-D–11 score of 11 or more had low misclassification error (3.0%), and adequate sensitivity (84.3%) and specificity (98.1%), relative to this criterion standard. We therefore defined those with a CES-D–11 score of at least 11 and those with a CES-D–11 score of less than 11 as being with and without *significant* depressive symptoms (which we refer to as depressive symptoms) in this study.

The original CES-D has 4 highly related components: depressed affect, positive attitude, somatic and retarded activities, and interpersonal problems,[26] and it was further validated in a large meta-analysis.[28] The 11 items of the CES-D–11 include 3 of the 4 components: depressed affect (3 mood items: felt depressed, felt fearful, and felt lonely; score 0-9; named depressed mood), positive attitude (2 items: felt hopeful and felt happy; score 0-6), and somatic and retarded activities. Because somatic symptoms and poor concentration/psychomotor retardation may have different associations with dementia risk, we considered somatic symptoms (2 items: poor appetite and restless sleep; score 0-6) separately from perceived performance difficulty (4 items: bothered by things, can't keep mind on tasks, everything is an effort, and could not get going; score 0-12).

History of depression was ascertained at baseline with the question "Have you ever had episodes of depression (feeling sad, blue, hopeless, or down in the dumps) lasting longer than 2 weeks?" If a depression episode was endorsed, information on age at onset, severity of depression (Did these episodes limit your ability to work or perform daily tasks?), and type of treatment received was collected. Depression history was further divided into early-life (onset age, <50 years) and late-life (onset age, ≥50 years).

STATISTICAL ANALYSIS

Comparisons of study characteristics by baseline CES-D–11 assessment (presence/absence of depressive symptoms) or by dementia diagnosis were summarized using means and SDs and tested by either 2-sample *t* tests (continuous data) or χ^2 tests (categorical data). Kaplan-Meier cumulative risk curves (for the event all-cause dementia) were compared for participants with and without baseline depressive symptoms. The log-rank test provided an initial assessment of whether the survival curves for all-cause dementia differed in those with and without baseline depressive symptoms. Hazard ratios (HRs) for dementia by depressive symptom status at baseline and depression history (either present vs absent or further divided into early-life, late-life, or unknown onset vs absent) in separate models and in combination were estimated using Cox proportional hazards regression with age as the time scale and delayed entry. Sensitivity analyses were performed assigning participants with unknown age of depression onset to both early-onset and late-onset depression in separate models. Secondary analyses estimated HRs for dementia by CES-D–11 subscales and HRs for dementia subtypes by baseline depressive symptom status. The null hypothesis that an HR was equal to 1 was assessed using likelihood ratio tests. Confidence intervals used Wald-based standard errors and the assumption of asymptotic normality. Models were fitted without any other covariates (crude HR estimates) and were adjusted for covariates (adjusted HR [aHR] estimates), which included categorical age at entry, sex, attainment of a college education, and enrollment cohort. The covariates were specified a priori on the basis of the literature and our understanding of the content area. Proportional hazards assumptions for each covariate were assessed graphically and using the test for proportional hazards based on Schoenfeld residuals.[29] To test robustness of the results to the chosen categorization of the CES-D–11 score, analyses were also performed defining the presence or absence of depressive symptoms at baseline using a CES-D–11 score of at least 10 as a cut-off. To facilitate comparisons with the Rotterdam Scan Study, we performed additional analyses in which we defined late-life depression as onset at age 60 or later. Analyses were performed using R, version 2.9.1 (R Foundation for Statistical Computing, Vienna, Austria), with statistical significance defined as $P < .05$.

RESULTS

The distribution of CES-D–11 scores was skewed, with a median of 3.0 (range, 0-33) and a mean (SD) of 4.2 (4.4). Of all participants, 321 (9.4%) had significant depressive symptoms (CES-D–11 score of ≥11). History of depression was reported in 723 participants (21.2%). Of these, 331 (45.8%) reported onset in early life (age <50 years), 342 (47.3%) reported onset in late life (age ≥50 years), and 50 (6.9%) had unknown onset. There were no differences between those with early-life and late-life depression in severity as measured by function limitation as a result of depression (39.5% early-life vs 41.3% late-life; $P = .69$), by requirement of any treatment (72.4% vs 74.3%; $P = .65$), and by requirement of antidepressants (53.4% vs 56.2%; $P = .51$). For a small number of participants, self-reported depression was severe enough to require hospitalization (7.1%) or electroconvulsive therapy (2.4%). This severe depression was more common in early-life (11.8% hospitalized, and 4.5% had electroconvulsive therapy) than in late-life depression (2.3% and 0.6%) ($P < .001$ for both). As shown in **Table 1**, participants with depressive symptoms (CES-D–11 score of ≥11) at baseline were older at enrollment, had slightly shorter follow-up time, were more likely to be female, and were less likely to have a college education. As expected, those with depressive symptoms at baseline had a higher rate of a self-reported history of depression.

During a mean of 7.1 years of follow-up (range, 1-15 years) of 3410 participants with 24 309 person-years, 658 participants developed dementia (19.3%). Mean (SD) age at onset was 83.3 (5.9) years. Of those who developed dementia, there were 386 (58.7%) with AD, 89 (13.5%) with vascular dementia, 113 (17.2%) with mixed dementia, and 70 (10.6%) with other forms of dementia. Of the 70 cases of dementia due to other causes, 11 were substance-induced persisting dementia, 36 were due to other general medical conditions (of which 17 were related to Parkinson disease), and 23 were due to other etiologies, such as head injury.

BASELINE DEPRESSIVE SYMPTOMS AND RISK OF DEMENTIA

The estimated cumulative risk of developing all-cause dementia by age was higher for those with baseline depres-

Table 1. Characteristics of Participants by Baseline Depressive Symptoms Status Based on CES-D–11 Assessment and Dementia Outcome[a]

Characteristic	Baseline CES-D–11 Assessment		Study Outcome	
	No Depressive Sxs (n=3089)	Significant Depressive Sxs (n=321)	Nondemented (n=2752)	Demented (n=658)
Age at entry or age at first CES-D, y	74.8 (6.2)	75.8 (6.2)[b]	74.3 (6.1)	77.5 (6.1)[c]
Age at onset of dementia or censor, y	82.1 (6.3)	82.0 (6.2)	81.8 (6.3)	83.3 (5.9)[c]
Follow-up duration, y	7.2 (4.0)	6.2 (3.8)[b]	7.4 (4.1)	5.8 (3.4)[c]
Baseline CASI score (0-100)	93.3 (4.9)	91.2 (5.8)[b]	93.7 (4.6)	90.5 (5.8)[c]
No. (% of row category)				
Male	1263 (92.3)	105 (7.7)	1118 (81.7)	250 (18.3)
Female	1826 (89.4)	216 (10.6)[b]	1634 (80.0)	408 (20.0)
Attainment of college degree	2007 (92.2)	170 (7.8)[b]	1819 (83.6)	358 (16.4)[c]
No	1082 (87.8)	151 (12.2)	933 (75.7)	300 (24.3)
Yes	2007 (92.2)	170 (7.8)[b]	1819 (83.6)	358 (16.4)[c]
Enrollment cohort				
Original (n=2581)	2128 (90.4)	226 (9.6)	1800 (76.5)	554 (23.5)[c]
Expansion (n=811)	682 (90.9)	68 (9.1)	655 (87.3)	95 (12.7)
Replacement (n=709)	279 (91.2)	27 (8.8)	297 (97.1)	9 (2.9)
Depression history[d]				
None	2526 (94.3)	154 (5.7)[b]	2161 (80.6)	519 (19.4)[c]
Before age 50	270 (81.6)	61 (18.4)	277 (83.7)	54 (16.3)
After age 50	250 (73.1)	92 (26.9)	258 (75.4)	84 (24.6)
Unknown onset age	36 (72.0)	14 (28.0)	49 (98.0)	1 (2.0)

Abbreviations: CASI, Cognitive Abilities Screening Instrument; CES-D–11, 11-item version of the Center for Epidemiologic Studies Depression Scale; Sxs, symptoms.

[a] Data are given as mean (SD) unless otherwise indicated.

[b] $P<.05$ between no baseline depression and depression in either t test or χ^2 test.

[c] $P<.05$ between nondemented and demented in either t test or χ^2 test.

[d] Seven cases were missing information on history of depression.

sive symptoms than for those without (**Figure 1**) with the log-rank test statistic $\chi^2=24.0$ ($P<.001$). After adjusting for age at entry, sex, educational level, and cohort, the risk of developing all-cause dementia remained higher in those with depressive symptoms (aHR, 1.71; 95% confidence interval [CI], 1.37- 2.13) (**Table 2**). This association remained after further adjustment for baseline CASI score (aHR, 1.61; 95% CI, 1.29-2.01). In these analyses and those reported next, there was no evidence of nonproportional hazards.

HISTORY OF DEPRESSION AND RISK OF DEMENTIA

Compared with participants who had no self-reported history of depression, those with a history of depression had increased risk of all-cause dementia (aHR, 1.29; 95% CI, 1.06-1.55) after adjustment for age at entry, sex, educational level, and cohort. In particular, late-life depression (age ≥50 years) but not early-life depression (age <50 years) was associated with increased risk of all-cause dementia (Table 2). In a model with both baseline depressive symptom status (based on the CES-D–11) and self-reported history of early-life depression, we found that, compared with those without depressive symptoms at baseline and with no history of early-life depression, those who had depressive symptoms at baseline and who had no history of early-life depression had the highest hazard for dementia (aHR, 1.77; 95% CI, 1.39-2.25) (Table 2). In sensitivity analyses, the associations between early- or late-life depression and dementia risk were essentially unchanged when defining late-life depression onset as at least age 60 instead of at least age 50, when defining baseline depression as CES-D–11 score of at least 10 instead of at least 11, or when imputing those with missing age of depression onset into early- or late-life depression.

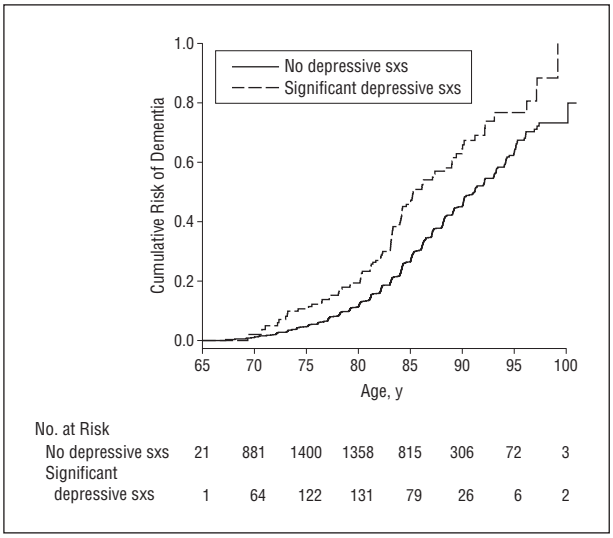

Figure 1. Kaplan-Meier cumulative risk curves for dementia by baseline depressive symptoms (sxs) status based on the 11-item version of the Center for Epidemiologic Studies Depression Scale score.

Table 2. HRs for All-Cause Dementia by Baseline Depressive Symptoms and Self-Reported History of Depression

Variable	No. With Dementia/ Person-Years	Crude HR (95% CI)	aHR (95% CI)[a]
Baseline CES-D–11 assessment			
No depressive sxs	566/22 329	1.0 [Reference]	1.0 [Reference]
Significant depressive sxs	92/1979	1.72 (1.38-2.15)	1.71 (1.37-2.13)
Self-reported history of depression			
No history of depression	519/19 340	1.0 [Reference]	1.0 [Reference]
Any history of depression	139/4948	1.26 (1.04-1.52)	1.29 (1.06-1.55)
Early- or late-life depression by history			
No history of depression[b]	519/19 340	1.0 [Reference]	1.0 [Reference]
Early-life depression	54/2431	1.08 (0.81-1.43)	1.10 (0.83-1.47)
Late-life depression	84/2386	1.44 (1.14-1.81)	1.46 (1.16-1.84)
Baseline depression with or without history of early-life depression			
No depressive sxs, no early-life depression	526/20 272	1.0 [Reference]	1.0 [Reference]
No depressive sxs, early-life depression	40/2037	1.01 (0.73-1.40)	1.03 (0.74-1.42)
Significant depressive sxs, no early-life depression	78/1585	1.79 (1.41-2.27)	1.77 (1.39-2.25)
Significant depressive sxs, early-life depression	14/394	1.42 (0.84-2.42)	1.46 (0.86-2.49)

Abbreviations: aHR, adjusted hazard ratio; CES-D-11, 11-item version of the Center for Epidemiologic Studies Depression Scale; CI, confidence interval; HR, hazard ratio; sxs, symptoms.

[a] Adjusted for categorical age at entry, sex, attainment of college degree, and study cohort.

[b] There were 50 participants with missing information on age of depression onset.

CES-D–11 DOMAINS AND RISK OF DEMENTIA

Most participants reported either no symptoms of depressed mood (66.0%) or lack of positive attitude (66.7%). Less than half of participants (39.9%) had no perceived performance difficulty. Any difficulties reported tended to be mild (total score of 1-2, 33.4%). Approximately half (51.2%) reported problems with either appetite or sleep disturbance. Compared with those who had no depressed mood, any depressed mood (score >0) was associated with an elevated risk of dementia (aHR, 1.56; 95% CI, 1.34-1.83) after adjusting for age at entry, sex, educational level, and cohort. Compared with no perceived performance difficulty, perceived performance difficulty (score >0) was associated with increased risk of all-cause dementia (aHR, 1.48; 95% CI, 1.25-1.75). The association between lack of positive attitude and risk of dementia was much weaker (score 0 vs >0: aHR, 1.18; (95% CI, 1.01-1.39). There was no association between the somatic symptoms of poor appetite and sleep and risk of dementia (score 0 vs >0: aHR, 0.96; 95% CI, 0.82-1.12). To examine whether the associations of depressed mood or perceived performance difficulty with dementia risk were independent of other domains, each of the 4 domains was included as a covariate in a single Cox proportional hazards regression model. Both depressed mood (aHR, 1.48; 95% CI, 1.25-1.76) and perceived performance difficulty (1.39; 1.15-1.67), but not the lack of positive attitude (0.98; 0.83-1.17), were independently associated with all-cause dementia.

DEPRESSION AND SUBTYPE OF DEMENTIA

The Kaplan-Meier cumulative risk curves presented in **Figure 2** illustrate that baseline depression status was associated with increased dementia risk across all dementia subtypes. The aHR (95% CI) comparing those with and without baseline depressive symptoms for each dementia subtype was as follows: AD, 1.43 (1.05-1.94); vascular dementia, 1.78 (0.98-3.22); mixed dementia, 2.24 (1.36-3.69); and other dementia, 2.52 (1.38-4.64)—after adjusting for age at entry, sex, educational level, and cohort. Self-reported history of depression was associated only with the other dementia subtype (aHR, 1.80; 95% CI, 1.06-3.08) but not with AD, vascular dementia, or mixed dementia.

COMMENT

This community-based prospective study of 3410 participants initially without dementia confirmed previous observations of an association between depression and increased risk of developing dementia and provided additional evidence of a temporal relationship between depression and dementia. Our finding that dementia risk was associated with depressive symptoms assessed at baseline and with self-reported history of late-life depression (age ≥50), but not early-life depression, suggests that depression may be less likely to be a causal factor of dementia. Rather, late-life depressive symptoms may be early manifestations of dementia. Both depressed mood and perception of performance difficulties assessed by the CES-D–11 subscales were independently associated with risk of dementia. The depressive symptoms did not appear specific to individual subtypes of dementia, eg, AD, vascular dementia, dementia due to multiple etiologies, or dementia due to other medical conditions.

Our finding of an association between depressive symptoms and increased risk of dementia is consistent with most cohort studies.[2-7,12] The aHR of baseline depressive symptoms for dementia of 1.71 (95% CI, 1.37-2.13) is similar to a recent report (1.72; 1.04-2.84) from the Framingham Heart Study.[6] However, the Rotterdam Scan Study[11] and other studies[8,10] did not show the same association between late-life depression and risk of devel-

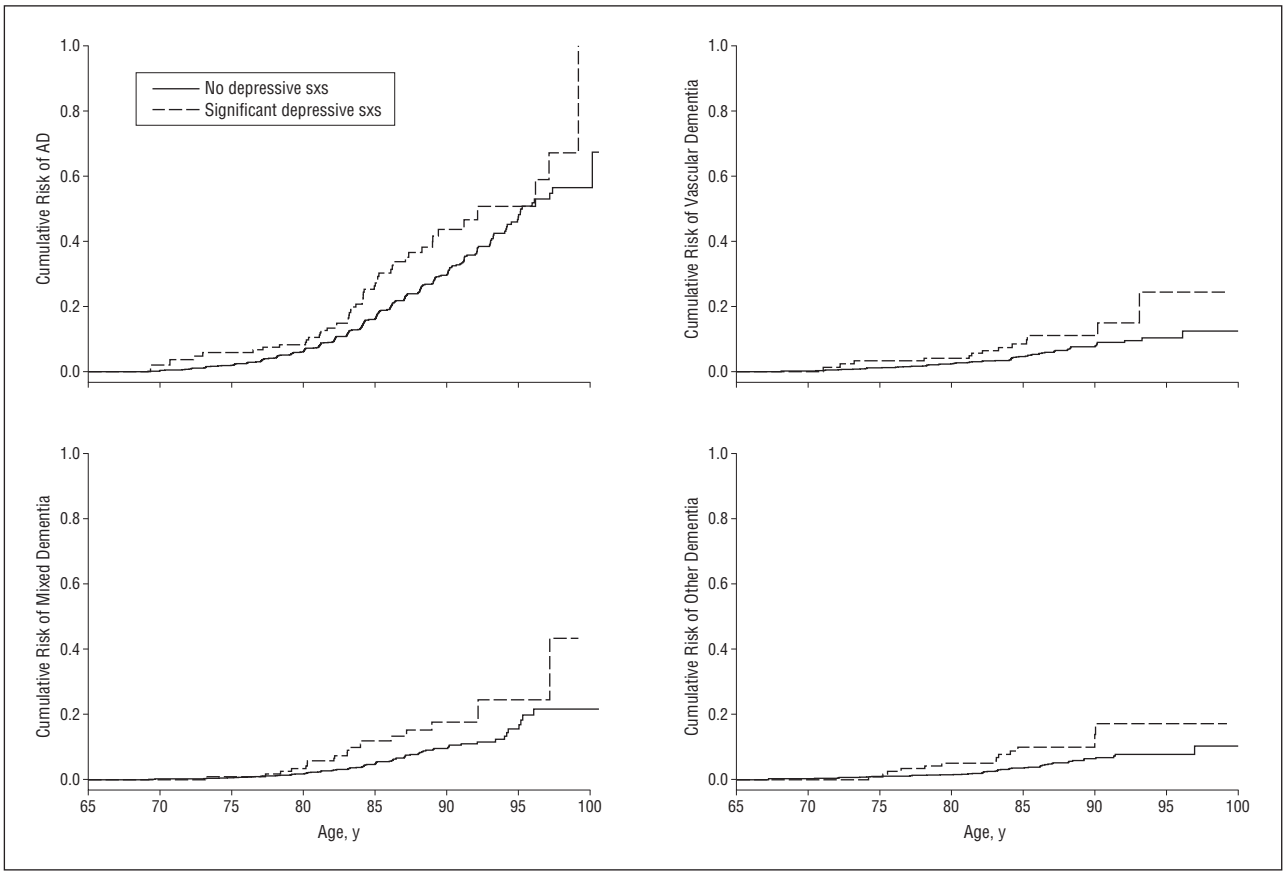

Figure 2. Kaplan-Meier cumulative risk curves for each type of dementia by baseline depressive symptoms (sxs) status based on the 11-item version of the Center for Epidemiologic Studies Depression Scale score. AD indicates Alzheimer disease.

oping dementia. The Rotterdam Scan Study is a population-based prospective study of 503 nondemented persons aged 60 to 90 years. Similar to our study, the CES-D was used to assess depressive symptoms at baseline, and history of depression was obtained on the basis of self-report. In addition, a brain magnetic resonance image was obtained at baseline. In contrast to our findings, this study found that history of early-life depression, but not presence of depressive symptoms at baseline, increased the risk for AD. The discrepancy in findings between these 2 studies was not due to differences in the definition of early- vs late-life depression history because our results were unchanged when we used age 60 as the cut-off. A possibility is the potential lack of statistical power to detect modest associations between clinical depression at baseline or history of late-life depression and risk of dementia or AD in the Rotterdam Scan Study because there were only 8 dementia cases (6 with AD) with baseline depression.[11] The point estimate of the aHR (95% CI) of baseline depressive symptoms for dementia in the Rotterdam Scan Study is 1.35 (0.55-3.30) compared with 1.71 (1.37-2.13) in our study.

It is not possible to conduct a randomized study of the association between depression and dementia, and hence conclusions must be based on observational studies. Although causality cannot be established from this single observational study, our finding of an association between late-life depression, but not early-life depression, and increased risk of dementia does not support a causal association between depression and the development of AD pathologic characteristics that appear to develop years and even decades before clinical diagnosis. However, the possibility that early-life depression causes dementia cannot be ruled out: left truncation in our study design means that a person with early-onset (before age 65) dementia caused by depression could have been missed in this study because of ineligibility. Hypersecretion of glucocorticoids associated with episodes of severe major depression has been hypothesized to cause hippocampal atrophy and cognitive impairment.[30] Despite the finding by the Rotterdam Scan Study that early-life depression was associated with increased risk of AD, this association was not mediated by smaller hippocampal volumes,[11] which does not support the glucocorticoid cascade hypothesis. Although depressed mood could be simply an early reaction to perceived cognitive decline and performance difficulty, it is also possible that depressive symptoms and dementia share the same underlying brain pathologic features, such as neurodegenerative changes of AD and Lewy body disease and/or cerebrovascular disease. The vascular depression concept, proposed more than 10 years ago, hypothesizes that cerebrovascular disease can predispose, precipitate, or perpetuate a depressive syndrome in older adults.[31] Cliniconeuropathologic studies have shown that people with histories of dementia and major depressive disorders had more degenerative changes in the locus ceruleus and substantia nigra than those with histories of dementia with-

out major depressive disorders[32] and that brains of patients with AD and comorbid depression had higher levels of cortical neurofibrillary tangles than brains of patients with AD but without depression,[33,34] suggesting clinical symptoms of depression may be associated with neurodegenerative changes as well. Furthermore, studies of late-life depression suggest that mild cognitive impairments co-occur frequently with depression[35] and persist as depressive symptoms resolve with treatment.[36,37] Depressive symptoms observed in the preclinical stages of dementia may be manifestations of underlying pathologic conditions in the brain and thus may serve as an early indicator of dementia.

Neurodegenerative changes in AD or Lewy body disease as well as cerebral vascular damage likely affect multiple brain functions, including mood and affect, executive function, and other cognitive functions, in addition to memory. The association between depression and risk of dementia observed in this study was independent of the contribution of subtle objective cognitive impairment measured by baseline CASI. There is increased evidence that subjective perception of cognitive impairment is associated with future development of dementia.[14,16,25,38] It is not surprising that self-reported difficulties in concentration and performance, and loss of interest and motivation assessed by the CES-D, may be early manifestations of brain dysfunction. The PAQUID study, a longitudinal study of the elderly in France,[25] demonstrated multidimensional changes during the decade before dementia diagnosis (the prodromal stage), including declines in memory and cognitive function, depression, and subjective memory complaints.

Several methodologic issues should be considered when interpreting our findings. First, significant depressive symptoms assessed by the CES-D are based on self-reported symptoms during the previous 2 weeks rather than depression diagnosed by a physician on the basis of diagnostic criteria. Caution is advised when generalizing this finding to major depressive disorders seen in the clinical setting. The CES-D as a screening tool (CES-D $\geq$16) for major depression had excellent sensitivity of 100% with a specificity of 88% in a community-based population aged 55 to 85 years.[27] However, in further analysis of those with a CES-D score of at least 16, most participants (75%) had subthreshold depression that did not meet the criteria for major depressive disorder, dysthymic disorder, or "double depression" (major depressive disorder plus dysthymic disorder) on the basis of the Diagnostic Interview Schedule, but they had a poor prognosis.[23] Second, depressive symptoms assessed through CES-D–11 at baseline could be transitory. However, a large longitudinal study shows a baseline CES-D score of at least 16 remained elevated in more than three-quarters of elderly individuals during 6 years of follow-up.[23] Third, history of depression was obtained through self-report. Underreporting of depression history in those with mild memory loss and at higher risk of developing dementia may bias the association toward the null. Although the overall severity of self-reported depression was not significantly different between early- and late-life depression, severe depression that required hospitalization or electroconvulsive therapy was more common in early-life depression than in late-life depression. If severe depression is more likely to cause dementia, we would be more likely to find an association of early-life depression with dementia, whereas our findings were that late-life but not early-life depression was associated with dementia risk. Finally, our study outcome of dementia was identified through a 2-stage procedure and met standard diagnostic criteria of dementia. People with the preclinical stage of dementia, such as those with mild cognitive impairment or those with a significant decline in CASI score but higher than our screening criterion for dementia, were not captured in this study. Further research is needed to determine the relationship between depressive symptoms and this preclinical stage of dementia.

Despite these limitations, this study has important strengths. Depressive symptoms were assessed at baseline using a standardized tool in a large community-based elderly population. Dementia was evaluated longitudinally with up to 15 years of follow-up, which enables the examination of the temporal relationship between depression and dementia. This study provides evidence that depressive symptoms, including depressed mood, lack of motivation, and the perception of performance difficulty, is associated with future development of dementia and should be considered as elements of early detection of dementia. Whether efforts to treat depression might delay clinical onset of dementia is unknown, but our results suggest this is an issue worth exploring.

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