ORIGINAL ARTICLE

Change in Depressive Symptoms During the Prodromal Phase of Alzheimer Disease

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Context: Prospective studies have established an association between depressive symptoms and risk of dementia, but how depressive symptoms change during the evolution of dementia is uncertain.

Objective: To test the hypothesis that depressive symptoms increase during the prodromal phase of Alzheimer disease (AD).

Design: Prospective cohort study.

Participants and Setting: For up to 13 years, 917 older Catholic nuns, priests, and monks without dementia at study onset completed annual clinical evaluations that included administration of the 10-item Center for Epidemiologic Studies Depression Scale and clinical classification of mild cognitive impairment and AD.

Main Outcome Measure: Change in depressive symptoms reported on the Center for Epidemiologic Studies Depression Scale.

Results: At baseline, participants reported a mean (SD) of 1.0 (1.5) depressive symptoms. Those who developed AD (n=190) showed no increase in depressive symptoms before the diagnosis was made, and this finding was not modified by age, sex, education, memory complaints, vascular burden, or personality. There was no systematic change in depressive symptoms after the AD diagnosis, although symptoms tended to decrease in women relative to men and in those with a higher premorbid level of openness and a lower premorbid level of agreeableness. Among those without cognitive impairment at baseline, depressive symptoms did not increase in those who subsequently developed mild cognitive impairment.

Conclusion: We found no evidence of an increase in depressive symptoms during the prodromal phase of AD.

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PROSPECTIVE OBSERVATIONAL studies have, with some exceptions,[1-3] found higher levels of depressive symptoms in old age to be associated with loss of cognition in the form of increased incidence of mild cognitive impairment (MCI)[4-6] and Alzheimer disease (AD) or dementia[7-12] and more rapid cognitive decline.[11-16] The basis of this association is uncertain, however. A leading hypothesis is that depressive symptoms do not constitute a true risk factor but rather a consequence of the disease.[7,17] One of the implications of the reverse causality explanation is that depressive symptoms increase at some point early in the disease process as an early symptom of its underlying pathologic changes or as a reaction to its early clinical manifestations. Although an increase in depressive symptoms in old age has been reported,[18-21] other studies have reported mixed results,[22,23] no change,[24] or a decrease,[25,26] and the trajectory of depressive symptoms during the prodromal phase of AD is uncertain.

We used data from the Rush Religious Orders Study to examine these issues. Participants are older Catholic nuns, priests, and brothers without dementia at study onset. They underwent annual clinical evaluations that included assessment of depressive symptoms, cognitive testing, and clinical classification of MCI and AD. Because the reverse causality hypothesis posits that AD causes depressive symptoms, we treated incidence of AD as the exposure variable and constructed generalized estimating equation models to characterize the change in

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Table 1. Information on Follow-up Participation and Mortality

Follow-up, y	No. of Participants With Valid CES-D Scores	No. of Participants With Missing CES-D Scores	
		Death	Other Reasons
Baseline	917	0	0
1	900	0	17
2	842	11	21
3	781	26	39
4	691	26	59
5	630	30	61
6	506	35	117
7	462	29	25
8	378	22	40
9	352	33	27
10	308	25	33
11	234	24	32
12	113	16	37
13	23	5	3

Abbreviation: CES-D, Center for Epidemiologic Studies Depression Scale.

depressive symptoms over time and test the hypothesis that symptoms increase during the prodromal period that precedes the appearance of clinically evident dementia in AD. To provide a more complete view of the natural history of depression in AD, we also modeled the course of depressive symptoms after dementia onset.

METHODS

PARTICIPANTS

Participants were from the Religious Orders Study, a longitudinal clinicopathologic study of aging and AD in older Catholic nuns, priests, and brothers.[27] This continuing study, which began in 1994, involves annual clinical evaluations and brain donation at death. After a complete description of the study, participants gave informed consent. The study was approved by the institutional review board of Rush University Medical Center.

At baseline and annually thereafter, participants had a uniform clinical evaluation that included a complete neurological examination, administration of a battery of 19 cognitive tests, and clinical classification of MCI and AD, as previously described.[27,28] A neuropsychologist rated impairment in 5 cognitive domains according to the results of all cognitive tests and educationally adjusted cutoff scores on a subset of them.[29] On the basis of this evaluation and an in-person examination of the participant, an experienced neurologist, geriatrician, or nurse practitioner diagnosed dementia and AD using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA).[30] These criteria require a history of cognitive decline and impairment in at least 2 cognitive domains, one of which must be memory to meet criteria for AD. We also included persons with AD who had another condition determined to contribute to cognitive impairment, termed *possible AD* in the NINCDS/ADRDA terminology.[30]

The diagnosis of MCI was based on established criteria that have been clinically[29] and pathologically[31] validated in this cohort. The criteria require cognitive impairment, as determined by the neuropsychologist's rating, in the absence of dementia, as determined by the examining clinician.

At the time of these analyses, 1013 participants had completed the baseline evaluation and not met criteria for dementia. Of these, 27 died before the first annual follow-up, and 32 had been in the study less than 1 year; of the remaining 954 participants, follow-up data from the Center for Epidemiologic Studies Depression (CES-D) Scale were available for 934 (97.9%). Because our focus was on AD, we excluded 17 participants who developed other forms of dementia on follow-up, leaving 917 individuals. Analyses are based on this group unless otherwise specified. They had a mean (SD) age of 74.8 (7.0) years and a mean (SD) of 18.1 (3.4) years of schooling; 68.5% were women. **Table 1** shows data on follow-up participation and mortality in each study year. Length of follow-up varied because of rolling admission (which continues) and differential mortality. Overall, participants completed 7137 annual clinical evaluations with a valid CES-D score (mean [SD] of 7.8 [3.5] per individual), which constitutes 93.3% of scheduled evaluations in survivors.

ASSESSMENT OF DEPRESSIVE SYMPTOMS

At each annual clinical evaluation, participants completed a 10-item version[32] of the CES-D Scale.[33] For each item, a brief statement of the symptom (eg, "I felt depressed") was read to participants who indicated whether they had felt that way much of the time during the past week. The score was calculated as the number of symptoms reported. This 10-item version of the CES-D Scale has been shown to correspond closely to the original 20-item scale.[32] In this cohort, it has been associated with the incidence of MCI and AD, rate of cognitive decline, and risk of death.[6,11,34]

ASSESSMENT OF OTHER COVARIATES

At baseline, participants were asked how often they had trouble remembering things. In analyses, we contrasted those who responded "very often" or "often" with those who responded "sometimes," "rarely," or "never," as previously described.[11]

Personality was assessed at baseline with the NEO Five-Factor Inventory.[35] The inventory includes 12 items for each of 5 traits. Participants rated agreement with each item on a 5-point scale (range, 0-4), with higher scores indicating a higher level of the trait. Item scores were added to yield trait scores ranging from 0 to 48 for neuroticism (ie, proneness to experience psychological distress), extraversion (ie, tendency to be sociable and engaged with others), openness (ie, intellectual curiosity), agreeableness (ie, tendency to be altruistic and helpful), and conscientiousness (ie, tendency to regulate impulses), as described elsewhere.[36,37]

Information on vascular burden was obtained from the baseline medical history and clinical evaluation, as previously reported.[37] We defined vascular risk factors as the number of 3 possible factors present (ie, hypertension, diabetes mellitus, and smoking) and vascular conditions as the number of 3 possible conditions present (ie, heart attack, stroke, and claudication).

DATA ANALYSIS

We conducted preliminary analyses to verify the previously reported association of depressive symptoms at baseline with subsequent loss of cognition in this cohort.[11] We examined the relation of baseline symptoms to risk of AD in a proportional hazards model[38] and to rate of global cognitive decline in a mixed-effects model,[39] each adjusted for age, sex, and education.

The main analytic aim was to characterize the temporal course of depressive symptoms before the diagnosis of AD, as

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Table 2. Baseline Characteristics of Participants Who Developed AD and Those Who Did Not[a]

Baseline Characteristic	Participants With Incident AD (n=190)	Unaffected Participants (n=727)	*P* Value
Age, y	80.0 (6.4) [65 to 98]	73.5 (6.5) [56 to 102]	<.001
Education, y	17.8 (3.3) [3 to 25]	18.2 (3.4) [0 to 30]	.15
Female, %	71.6	67.8	.32
CES-D score	1.3 (1.7) [0 to 8]	0.9 (1.4) [0 to 8]	<.001
MMSE score	27.4 (2.1) [19 to 30]	28.8 (1.3) [22 to 30]	<.001
Global cognition[b]	–0.30 (0.51) [–1.93 to 0.82]	0.21 (0.45) [–1.52 to 1.40]	<.001
Memory complaint, %	43.2	26.1	<.001
Vascular risk factors[c]	0.8 (0.7) [0 to 3]	0.8 (0.8) [0 to 3]	.75
Vascular conditions[c]	0.3 (0.5) [0 to 2]	0.2 (0.5) [0 to 3]	.10
Trait scores			
Neuroticism	17.5 (5.3) [1 to 33]	16.3 (5.6) [0 to 36]	.01
Extraversion	27.0 (5.3) [12 to 47]	28.2 (5.7) [11 to 46]	.008
Openness	25.4 (4.8) [15 to 41]	26.7 (5.3) [4 to 42]	.003
Agreeableness	33.7 (3.7) [19 to 45]	34.5 (3.7) [21 to 48]	.01
Conscientiousness	33.0 (5.4) [11 to 45]	34.3 (4.8) [11 to 47]	.002

Abbreviations: AD, Alzheimer disease; CES-D, Center for Epidemiologic Studies Depression Scale; MMSE, Mini-Mental State Examination.
[a] Data are expressed as mean (SD) [range] unless otherwise indicated.
[b] Indicates composite measure of global cognition based on 19 individual tests.
[c] Indicates number present at baseline, of a maximum of 3.

a primary effect and conditional on selected covariates. We used people who never developed dementia as the comparison group, and we also examined change after the AD diagnosis to gain a more comprehensive view of the natural history of depressive symptoms in the disease. We used generalized estimating equation models[40] to analyze change in depressive symptoms during the study period, with a logit-link function and a binomial error, treating the number of reported symptoms as a proportion of the 10 possible symptoms. The initial model included terms for the initial level of depressive symptoms and time (in years since baseline) to estimate the intercept and annual rate of linear change of depressive symptoms in unaffected persons as the reference group and in affected persons before and after the diagnosis of AD. Because preliminary analyses with quadratic terms for time showed no evidence of nonlinear change, all analyses in this article are of linear change in depressive symptoms. This and all subsequent models controlled for the effects of age, sex, and education. We repeated the core model with terms for the interactions of sex with time before the diagnosis and time after the diagnosis, followed by identical analyses of interactions involving age and education. In separate subsequent models, we introduced terms for new variables (ie, memory complaint, vascular risk factors and conditions, and personality traits) and the interaction of the new variable with the starting level and rate of change of depressive symptoms in unaffected persons and in affected persons before and after the diagnosis. We then excluded persons with MCI at baseline and tested for change in depressive symptoms before and after the incidence of MCI. Model assumptions were examined graphically and analytically and judged to be adequately met. Programming was performed using SAS statistical software.[41]

RESULTS

CHANGE IN DEPRESSIVE SYMPTOMS

Among the 917 study participants at baseline, the distribution of depressive symptoms on the CES-D Scale was positively skewed, with an overall mean (SD) of 1.0 (1.5) symptom and 53.6% reporting no symptoms, 23.9% reporting 1, 9.7% reporting 2, 6.1% reporting 3, and 6.8% reporting 4 or more. A higher number of depressive symptoms was associated with older age ($\rho=0.11$; $P<.001$) but not with education ($\rho=0.00$; $P=.87$) or sex (Kruskal-Wallis $\chi^2_1=0.1$; $P=.72$). Consistent with earlier findings in this cohort,[11] having more symptoms at baseline was associated with increased incidence of AD (hazard ratio, 1.15; 95% confidence interval, 1.05-1.25) and the rate of decline on a composite measure of global cognition (parameter estimate [SE], –0.009 [0.003]; $P<.001$) in separate analyses adjusted for age, sex, and education.

During follow-up, 190 participants developed AD. They were diagnosed as having AD after a mean (SD) of 3.9 (3.1) years and subsequently followed up for a mean of 2.8 (2.6) years. As shown in **Table 2**, participants who subsequently developed incident AD were older at baseline than the 727 individuals who remained unaffected; they had more depressive symptoms, lower levels of cognitive function, and more concern about their memory; and they differed in personality.

To test the hypothesis that depressive symptoms increase during the prodromal period of AD, we constructed a generalized estimating equation model that simultaneously estimated trajectories of change in depressive symptoms within the unaffected and incident AD subgroups, with separate estimates before the diagnosis in the AD subgroup (ie, from baseline to 1 year before the diagnosis) and after it (ie, from the time of diagnosis to the most recent clinical evaluation). This and all subsequent models included terms to control for the potentially confounding effects of age, sex, and education. In the initial analysis (**Table 3** and **Figure 1**), the baseline number of depressive symptoms in the unaffected group did not differ from the number of symptoms at baseline or at dementia onset in the AD group, as shown by the terms for the pre-AD and post-AD intercepts. In addition, in a paired *t* test, the level of symptoms at the end of the prodromal period did not differ

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Table 3. Analysis of Change in Depressive Symptoms in Unaffected Participants and Those Who Developed Alzheimer Disease (AD)[a]

Model Term	Parameter Estimate	SE	*P* Value
Intercept, unaffected group	–2.296	0.066	<.001
Pre-AD intercept[b]	0.182	0.181	.31
Post-AD intercept[b]	0.412	0.279	.14
Time, unaffected group	–0.002	0.008	.83
Time, additional effect for pre-AD[b]	0.011	0.023	.64
Time, additional effect for post-AD[b]	0.022	0.043	.62

[a] From a logit-link generalized estimating equation model adjusted for age, sex, and education in 727 unaffected individuals and 190 who developed AD. Results show the effect on the Center for Epidemiologic Studies Depression Scale score of a 1-U increase in a given model term.
[b] Indicates relative to unaffected individuals.

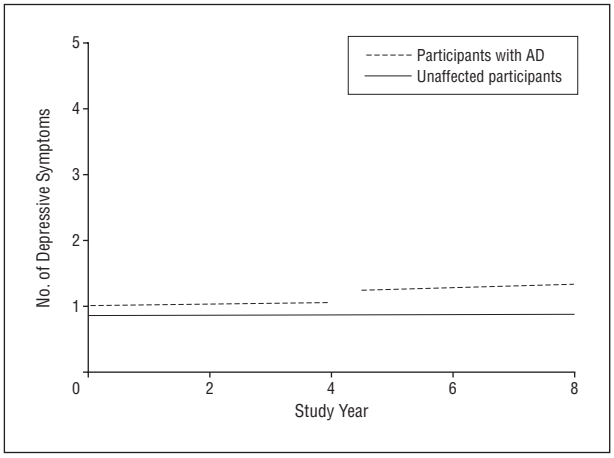

Figure 1. Change in depressive symptoms in incident Alzheimer disease (AD) before (dotted line on the left side) and after (dotted line on the right side) the diagnosis and in unaffected participants, adjusted for age, sex, and education.

from the level at dementia onset (t_{164}=0.9; *P*=.37). There was no evidence of systematic change in depressive symptoms in the unaffected group, as shown by the term for time in Table 3 and the solid line in Figure 1. The rate of change in depressive symptoms in the incident AD subgroup did not differ from the rate in unaffected persons before the AD diagnosis (time, additional effect for pre-AD in Table 3 and dotted line on the left side of Figure 1) or after it (time, additional effect for post-AD in Table 3 and dotted line on the right side of Figure 1). The estimates in Table 3 come directly from the model; to obtain the lines shown in Figure 1, we first created predicted values from the model and back-transformed them so that we could present the lines on the original scale of the CES-D Scale. When we subsequently examined participants with and without incident AD separately, depressive symptoms did not change in either subgroup (data not shown).

We next considered the possibility that a shift in depressive symptoms might be confined to a subgroup of participants who developed AD. Because women are more vulnerable to depressive symptoms than men are,[42] we repeated the analysis with terms for the interactions of sex × time before and after the diagnosis of AD. In this analysis, sex was not related to the level of depressive symptoms within subgroups or to the change in depressive symptoms in unaffected individuals. Among those who developed AD, sex was not related to change before the AD diagnosis (parameter estimate for time, additional effect for pre-AD × sex, 0.021 [SE, 0.057]; *P*=.71), but it was related to change in symptoms after the diagnosis (parameter estimate for time, additional effect for post-AD × sex, 0.185 [SE=0.075]; *P*=.02), with symptoms tending to increase in men but decrease in women. In separate subsequent analyses, age and education were not related to change in depressive symptoms before or after the diagnosis of AD (data not shown).

At baseline, those who later developed AD expressed more concern about their memory than did people who remained unaffected. To see whether such awareness modified the temporal course of depressive symptoms in the prodromal stage of the disease, we repeated the analysis with terms added for memory complaint and its interaction with other model terms. In this analysis, the presence of memory complaint was associated with more depressive symptoms among unaffected persons (parameter estimate [SE], 0.456 [0.113]; *P*<.001) but not in those with AD. Memory complaint did not affect the trajectory of depressive symptoms in the unaffected subgroup (parameter estimate [SE] for memory complaint × time, –0.005 [0.014]; *P*=.72) or in the incident AD subgroup before (parameter estimate [SE] for memory complaint × time, additional effect for pre-AD, –0.037 [0.043]; *P*=.39) or after (parameter estimate [SE] for memory complaint × time, additional effect for post-AD, –0.115 [0.073]; *P*=.11) the diagnosis.

Because vascular conditions have been associated with depressive symptoms[43] and dementia,[44] we considered the possibility that they might modify the course of depressive symptoms. Therefore, we repeated the analysis with composite indexes of vascular risk factors and vascular conditions and the interactions of each index with other model terms. In unaffected persons, higher levels of vascular risk factors (parameter estimate [SE], 0.174 [0.074]; *P*=.02) and vascular conditions (parameter estimate [SE], 0.320 [0.093]; *P*<.001) were each related to a higher baseline level of depressive symptoms but not to change in depressive symptoms. In those with incident AD, neither vascular index was related to the level or change of depressive symptoms before or after dementia onset.

Personality has been associated with depressive symptoms[45] and risk of AD.[46] In separate analyses, therefore, we tested whether any of the big 5 personality traits[35] modified the trajectory of depressive symptoms in AD. Trait scores were missing in less that 1% of the participants (neuroticism in 2; extraversion in 3; openness in 5; agreeableness in 6; and conscientiousness in 2). None of the traits was related to the rate of change in depressive symptoms before the AD diagnosis, but 2 traits were related to the change in symptoms after the diagnosis. A higher level of openness and lower level of agreeableness were associated with decreasing depressive symptoms after the AD diagnosis (parameter estimate [SE] for openness × time, additional effect for post-AD, –0.018 [0.007]; *P*=.01; pa-

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rameter estimate [SE] for agreeableness × time, additional effect for post-AD, 0.018 [0.009]; $P = .045$).

CHANGE IN DEPRESSIVE SYMPTOMS AND INCIDENCE OF MCI

To further investigate the prodromal phase of AD, we examined the change in depressive symptoms in relation to the incidence of MCI, a recognized precursor to dementia in AD. We excluded participants with MCI at baseline (n=230) and constructed a new model to estimate trajectories of depressive symptoms before (during a mean [SD] of 3.2 [3.3] years of observation) and after (during a mean [SD] of 3.9 [3.4] years) the development of incident MCI. In this analysis, (**Table 4** and **Figure 2**), participants who subsequently developed MCI (n=319) had a significantly higher baseline level of depressive symptoms than did the 368 individuals who did not develop MCI, as shown by the term for pre-MCI intercept in Table 4. There was no systematic change in depressive symptoms in the unaffected subgroup (time term in Table 4 and solid line in Figure 2) or in the affected subgroup before (time, additional effect for pre-MCI in Table 4 and dotted line on left side of Figure 2) or after (time, additional effect for post-MCI in Table 4 and dotted line on right side of Figure 2) the initial diagnosis of MCI.

Table 4. Analysis of Change in Depressive Symptoms in 368 Participants Whose Cognition Remained Unimpaired and in 319 Who Developed Mild Cognitive Impairment (MCI)[a]

Model Term	Parameter Estimate	SE	*P* Value
Intercept, unaffected group	−2.505	0.103	<.001
Pre-MCI intercept[b]	0.357	0.152	.02
Post-MCI intercept[b]	0.214	0.168	.20
Time, unaffected group	−0.003	0.012	.78
Time, additional effect for pre-MCI[b]	−0.002	0.020	.92
Time, additional effect for post-MCI[b]	0.028	0.020	.16

[a] From a logit-link generalized estimating equation model adjusted for age, sex, and education in 368 unaffected individuals and 319 who developed MCI. Results show the effect on Center for Epidemiologic Studies Depression Scale score of a 1-U increase in a given model term.
[b] Indicates relative to unaffected persons.

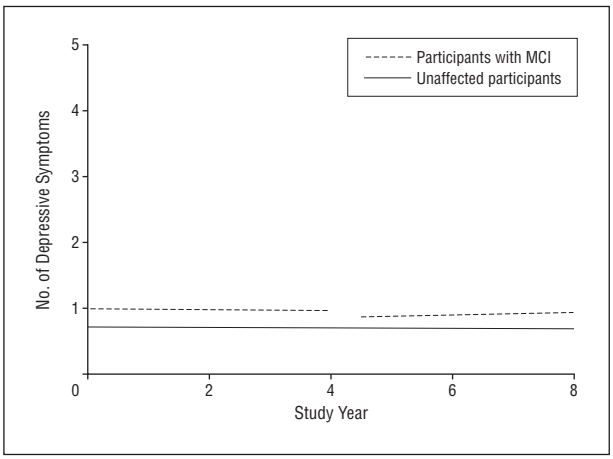

Figure 2. Change in depressive symptoms in incident mild cognitive impairment (MCI) before (dotted line on the left side) and after (dotted line on the right side) the diagnosis and in unaffected participants, adjusted for age, sex, and education.

COMMENT

Numerous prospective studies have found higher levels of depressive symptoms to predict subsequent cognitive loss[4-16] or have found the association to be conditional on some covariate (ie, sex,[47,48] education,[49] or baseline cognitive ability[50]). Among null studies, one[1] subsequently observed the association after further data collection[48]; a second[2] included people with dementia, which may have diminished the validity of self-report about depressive symptoms[51]; and a third[3] excluded cases of incident dementia, thereby truncating the distribution of cognitive decline rates (and their correlation with covariates such as depressive symptoms) without removing the influence of the underlying disease given evidence that the neuropathologic features associated with dementia are commonly found in the brains of old people who died with mild[31,52-54] or no[55,56] cognitive impairment. Overall, this research suggests a robust association between depressive symptoms and dementia, but it raises the critical question of whether depressive symptoms actually contribute to the development of dementia (ie, risk factor hypothesis) or are a manifestation of the dementia syndrome (ie, reverse causality hypothesis).

In this study, we tested an implication of the reverse causality hypothesis. That is, if depressive symptoms predict loss of cognition because they are a consequence of the pathologic processes causing dementia or a reaction to declining function, depressive symptoms are likely to increase at some point before dementia is clinically evident, as has been shown for other early signs of dementia such as parkinsonian gait[57] or decreased body mass index.[58] In a cohort of more than 900 older persons observed for up to 13 years, however, we found no evidence of an increase in depressive symptoms during a mean of approximately 4 years of observation before the onset of dementia in AD. Because the duration of the prodromal phase of AD is uncertain, we cannot rule out the possibility that symptoms increased before our period of observation. However, we saw no increase in symptoms during the 3 to 4 years preceding the onset of MCI, which probably antedates the onset of dementia in AD by several years, making this possibility less likely. Although we are not aware of prior research on change in depressive symptoms before dementia onset in AD, a strong version of the reverse causality hypothesis suggests an overall increase in depressive symptoms in old age. We observed no such increase. This is generally consistent with previous studies that have found little evidence of systematic change in depressive symptoms in old age.[18-26]

We considered the possibility that a prodromal increase in depressive symptoms might be confined to a

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subgroup defined by demographic variables, perceived memory dysfunction, vascular conditions, or personality traits. There was no evidence of such an interaction, however.

Another way to test the reverse causality hypothesis is to examine the relation of depressive symptoms to the pathologic changes underlying AD and other dementias. In previous studies of this cohort, however, we have found no evidence that depressive symptoms proximate to death are related to the neuropathologic features most commonly associated with late life dementia (ie, amyloid plaques, neurofibrillary tangles, Lewy bodies, and cerebral infarction).[59,60]

If, as these data imply, depressive symptoms are a risk factor for AD rather than an early sign of its pathologic processes, how might they be contributing to risk? One possibility is that depressive symptoms might somehow modify the relation of the pathologic changes to cognition as has been reported for education[61] and social network size.[62] However, in previous research on this cohort, we found no evidence of such a modifying effect.[59,60] This implies that depressive symptoms are associated with distinctive changes in the brain that somehow reduce neural reserve. Major depression has been associated with atrophic changes in the hippocampus and anterior cingulate cortex.[63,64] In animals subjected to chronic stress, a spectrum of neurodeteriorative changes in selected limbic regions has been observed, including dendritic atrophy, loss of synapses, down-regulation of glucocorticoid receptors, and reduced expression of brain-derived neurotrophic factor and its tyrosine kinase B receptor, accompanied by impaired learning and memory.[65,66] To the extent that some of these neurobiological changes accompany depressed mood in humans, they might compromise limbic system structure and function in old age such that relatively fewer age-related neuropathologic changes would be needed to cause dementia. Understanding the mechanisms linking depressive symptoms with dementia could suggest novel approaches to delaying dementia onset because animal research suggests diverse means by which the adverse effects of chronic stress may be modified.[67-70]

Once AD became clinically manifest, change in depressive symptoms was associated with sex and personality. These findings were unexpected and their bases are uncertain. The loss of independence in AD may be more distressing to men than women and to those who are less open to new experiences than to those who are more open. A higher level of agreeableness is associated with a lower level of depressive symptoms.[71] Alzheimer disease has been associated with a reduction in agreeableness,[72,73] which may thereby result in an increase in symptoms in those with a high premorbid level of agreeableness. These findings suggest that some people experience a depressive reaction to the dementia of AD. Because this reaction occurs after the appearance of dementia, however, it is unlikely to account for the association of depressive symptoms with the incidence of dementia or MCI. Further research will be needed to confirm these associations and to clarify the mechanisms underlying them.

This study has important strengths. The diagnoses of AD and MCI were based on uniform evaluations and the application of established criteria by experienced clinicians. There was a mean of more than 7 annual assessments of depressive symptoms and a high rate of follow-up participation among survivors, enhancing our ability to characterize change in depressive symptoms during the study period. Study limitations should also be noted. In particular, participants are selected and they differ from older people in general in terms of education and lifestyle. Because these differences might affect the clinical expression of the disease or adaptation to it, replication of these findings in more representative cohorts will be important. In addition, we used a brief measure of depressive symptoms. It is possible that a more comprehensive scale could yield different results. Finally, the validity of self-report about depressive symptoms is reduced in AD.[74,75] This may have affected our estimate of change in symptoms after the diagnosis of AD, but it seems less likely to have affected ascertainment of symptoms before the diagnoses of AD and especially of MCI, the periods of primary interest.

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