

Clinical-pathologic study of depressive symptoms and cognitive decline in old age



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ABSTRACT

Objective: To clarify the relationship between depressive symptoms and the clinical and neuropathologic manifestations of dementia.

Methods: In a clinical-pathologic cohort study, 1,764 older persons without cognitive impairment at enrollment completed annual clinical evaluations for a mean of 7.8 years. The evaluations included assessment of depressive symptoms (10-item Center for Epidemiological Studies Depression Scale) and cognitive function (battery of 17 performance tests). A total of 582 individuals died during follow-up and underwent a uniform neuropathologic examination to quantify β -amyloid plaques and tau tangle density in multiple brain regions and identify neocortical Lewy bodies, hippocampal sclerosis, and gross and microscopic cerebral infarcts.

Results: Level of depressive symptoms slightly increased during follow-up. Incident mild cognitive impairment (52.2%) was associated with higher level of depressive symptoms before the diagnosis but not with change in symptoms after the diagnosis; incident dementia (17.9%) was associated with higher symptom level before dementia onset and with more rapid decline in symptoms after dementia onset. None of the neuropathologic markers was related to level of depressive symptoms or change in symptoms over time. In a mixed-effects model adjusted for the neuropathologic markers, higher level of depressive symptoms averaged over evaluations was associated with more rapid global cognitive decline, accounting for 4.4% of the variability in decline not attributable to the neuropathologic markers. Depressive symptoms did not modify the association of the neuropathologic markers with cognitive decline.

Conclusion: In old age, depressive symptoms have an association with cognitive decline that is independent of the neuropathologic hallmarks of dementia. *Neurology*® 2014;83:702-709

GLOSSARY

MCI = mild cognitive impairment.

Late-life depressive symptoms are associated with an increased rate of cognitive decline^{1,2} and risk of mild cognitive impairment (MCI)^{3,4} and dementia.^{1,5,6} The main hypotheses about the association, which are not mutually exclusive, are that depressive symptoms are a consequence of cognitive decline; depressive symptoms and cognitive decline are manifestations of the same underlying neuropathology; depressive symptoms alter the association of pathology with declining cognition; and depressive symptoms have an independent association with cognitive decline.¹⁻⁷ The first hypothesis has been examined in several studies but only sporadically supported. In contrast, little research has been done on the latter hypotheses because testing them requires longitudinal clinical data on depressive symptoms and cognitive function plus postmortem data on the neurodegenerative and cerebrovascular lesions traditionally associated with cognitive decline and dementia.

In the present study, we used data from 2 clinical-pathologic cohort studies to examine the associations among depressive symptoms, cognitive decline, and neuropathologic lesions. Participants from the Religious Orders Study and Rush Memory and Aging Project completed annual

Supplemental data
at Neurology.org

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assessments of depressive symptoms and cognitive function. Those who died during follow-up underwent a neuropathologic examination to quantify 6 common dementia-related lesions. In analyses, we modeled the relationship of incident MCI and dementia with depressive symptoms during follow-up. We then tested whether depressive symptoms were related to the neuropathologic lesions, modified the association of the neuropathologic lesions with cognitive decline, or had an association with residual cognitive decline not linked to neuropathologic burden.

METHODS Participants. Data are from individuals in 2 ongoing longitudinal clinical-pathologic studies begun in the 1990s, one involving older Catholic clergy recruited from multiple sites in the United States (Religious Orders Study)⁸ and the other involving older lay individuals from the Chicago area (Rush Memory and Aging Project).⁹ Eligibility for each study required baseline age older than 50 years and agreement to yearly clinical assessments and postmortem examination of the brain.

When these analyses were conducted, 2,792 persons had enrolled and finished the initial clinical assessment. As shown in figure 1, those

with MCI or dementia at initial assessment were excluded, and some individuals were not eligible for follow-up because of death in the first year or enrollment in the past year. This left 1,832 people and 1,764 (96.3%) had follow-up data. They began the study at an average age of 76.6 years (SD = 7.5) with an average of 16.2 years of schooling (SD = 3.8); 26.6% were men. After an average of 7.8 years of annual observation (SD = 4.8), 52.2% had developed MCI and 17.9% had developed dementia. Of the 680 individuals who died during follow-up, a brain autopsy was performed on 612 (90.0%) (figure 1). At the time of these analyses, a uniform neuropathologic examination had been completed on the first consecutive 582 participants. They died at an average age of 87.6 years (SD = 6.7) with an average of 16.6 years of schooling (SD = 3.7); 33.7% were men. They completed an average of 8.4 years of follow-up (SD = 4.1). Compared with the 1,182 individuals without neuropathologic data, they were older at baseline ($t_{1,291.7} = 11.0, p < 0.001$), more likely to be men ($\chi^2_1 = 22.4, p < 0.001$), more educated ($t_{1,762} = 2.8, p = 0.005$), and more depressive symptoms at baseline ($\chi^2_1 = 22.5, p < 0.001$), and were more likely to develop MCI ($\chi^2_1 = 62.2, p < 0.001$) and dementia ($\chi^2_1 = 74.0, p < 0.001$).

Standard protocol approvals, registrations, and patient consents. In each study, individuals signed informed consent forms after a detailed conversation with staff. Each project was approved by Rush University Medical Center's institutional review board.

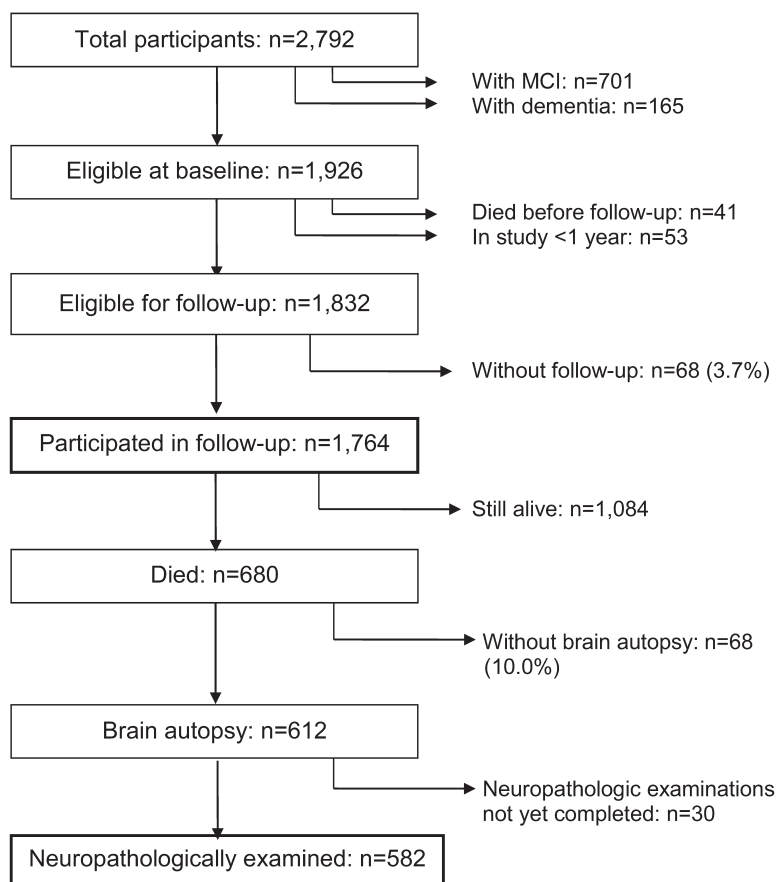
Assessment of depressive symptoms. At each annual visit, a short form¹⁰ of the Center for Epidemiological Studies Depression Scale¹¹ was administered. On each of 10 items, the interviewer read a brief statement (e.g., "I felt lonely") and asked the participant: "Have you felt this way much of the past week?" The score is the number of item responses indicative of depression. This 10-item measure predicts morbidity¹ and mortality.¹² It is psychometrically similar to the original version of the scale, including the ability to capture change in symptoms over time,^{13,14} but differs in 2 important respects: it does not include cognitive symptoms (i.e., "I had trouble keeping my mind on what I was doing," "I talked less than usual") and reduces participant burden (i.e., fewer items, yes/no response format).

Assessment of cognitive function. Each study included annual administration of 18 cognitive tests.¹⁵⁻¹⁷ The Mini-Mental State Examination was included to facilitate comparisons with other cohorts. The other 17 tests consisted of performance measures of multiple cognitive domains, including episodic memory (n = 7), semantic memory (n = 3), working memory (n = 3), perceptual speed (n = 2), and visuospatial ability (n = 2). To construct a global cognitive outcome measure that capitalized on all cognitive data, we transformed the 17 raw test scores to z scores (based on the mean and SD from the initial evaluation of the combined cohorts) and computed the mean of these z scores.

Clinical classification. Clinical diagnoses were rendered as part of each annual assessment. Dementia was based on historical evidence of declining cognition plus evidence on examination of impairment in at least 2 cognitive functions.¹⁸ MCI was diagnosed in individuals who had cognitive impairment but not dementia.¹⁹

Neuropathologic examination. Death occurred a median of 7.3 months after the last clinical evaluation (interquartile range: 3.7-10.9) and the brain was removed a median of 6.3 hours after death (interquartile range: 4.8-9.8). A standard protocol for tissue preservation, tissue sectioning, and quantification of pathologic findings was implemented by examiners kept unaware of all clinical data.^{20,21} The cerebral hemispheres were coronally cut

Figure 1 Composition of the study groups



Flow diagram showing the composition of the full group and the neuropathologically examined subgroup. MCI = mild cognitive impairment.

into 1-cm slabs, the cerebellar hemispheres were sagittally cut into 1-cm slabs, and the brainstem was removed at the level of the mamillary bodies and bisected at the mid-pons level.

We visually inspected slabs for gross infarcts. Slabs from one cerebral hemisphere and one cerebellar hemisphere and all slabs with suspected infarcts were fixed for at least 3 days in 4% paraformaldehyde. In addition, suspected infarcts were processed for histologic confirmation and the age was classified as acute, subacute, or chronic. One hemisphere was examined for microinfarcts in 6 cortical regions, 2 subcortical regions, and the midbrain using 6- μ m paraffin-embedded sections stained with hematoxylin & eosin. Chronic microinfarcts included cavitated lesions with few macrophages and fibrillary gliosis or incomplete infarcts.²² In analyses, gross infarcts and microinfarcts were treated as binary variables.

β -Amyloid-immunoreactive plaques and tau-immunoreactive tangles were assessed in 8 areas: anterior cingulate cortex, dorsal lateral prefrontal cortex, superior frontal cortex, inferior temporal cortex, hippocampus (cornu ammonis subfield 1/subiculum), entorhinal cortex, angular/supramarginal gyrus, and primary visual cortex. In the cortical regions, tissue blocks from adjacent slabs were paraffin-embedded and cut in 20- μ m sections. In the hippocampus, we dissected 0.5-cm blocks from consecutive 1-cm slabs, embedded them in paraffin, and cut them in 20- μ m sections.

An N-terminus-directed monoclonal antibody (1:1,000, 10D5; Elan Pharmaceuticals, Dublin, Ireland) was used to label β -amyloid. Immunohistochemistry was done with diaminobenzidine as the reporter, 2.5% nickel sulfate to sharpen immunoreaction product contrast, and a computer-assisted sampling procedure. We computed the proportion of pixels in each region that was β -amyloid-immunoreactive and used the mean of the regional values as an overall measure of β -amyloid burden.²³

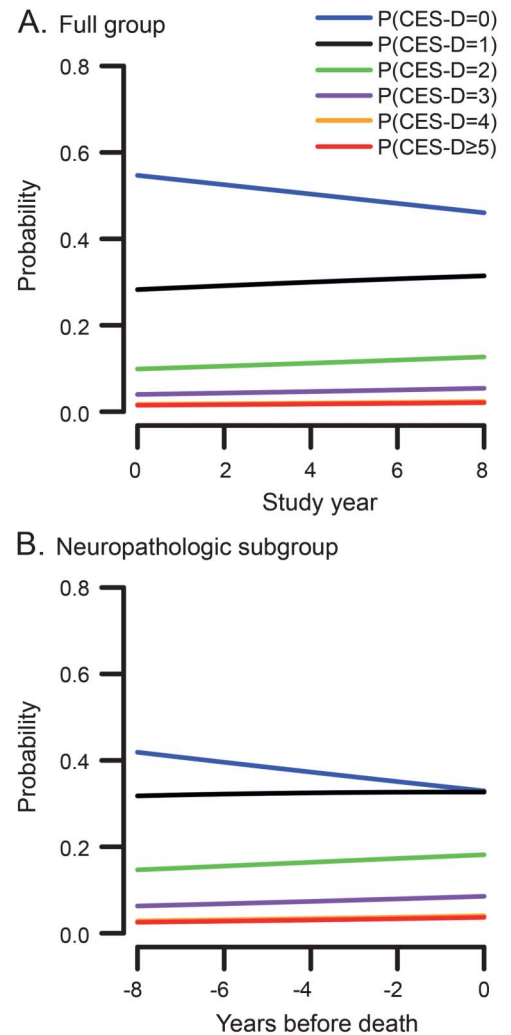
The density of tau-immunoreactive tangles was quantified with an anti-paired helical filament-tau antibody clone AT8 (1:2,000; Thermo-Scientific, Rockford, IL) and computer-assisted sampling. Tangle density/mm² in each region was standardized and the mean of the standard scores was used as a composite measure of tangle density.²³

The substantia nigra, 2 limbic regions (anterior cingulate cortex, entorhinal cortex), and 3 neocortical regions (midfrontal cortex, superior or middle temporal cortex, inferior parietal cortex) were assessed for Lewy bodies using a monoclonal antibody to phosphorylated α -synuclein (1:20,000; Wako Chemical USA Inc., Richmond, VA).^{20,24} Analyses are based on the presence or absence of neocortical disease, and affected individuals usually also had nigral and limbic Lewy bodies.^{24,25}

A hemisection of the mid-hippocampus at the level of the lateral geniculate body was stained with hematoxylin & eosin to assess neuronal loss in the hippocampal subfields CA1–4 and subiculum. Severe diffuse or segmental neuronal loss in the pyramidal cell layer of any of the CA subfields or subiculum was classified as hippocampal sclerosis.

Statistical analysis. Each analysis was adjusted for age, sex, and education. The distributions of depressive symptom scores at each evaluation were skewed. Therefore, to characterize change in symptoms over time and test whether clinical diagnoses were related to prediagnostic symptom level or postdiagnostic rate of change in symptoms, we constructed a series of proportional odds models²⁶ with depressive symptoms treated as an ordinal variable with 6 levels (0, 1, 2, 3, 4, ≥ 5). The proportionality assumption, assessed with the score test for proportional odds and the trend odds model,²⁷ was found to be adequately met. The first model included a term for time (from baseline in years), which indicates the log odds of the outcome shifting 1 level per year. We repeated the model with a time-varying term for MCI onset and its interaction with time and then again with a time-varying indicator for dementia onset and its interaction with time.

Figure 2 Change in depressive symptoms over time



Probability of having different levels of depressive symptoms over time in the full group (A) and the neuropathologically examined subgroup (B), from proportional odds models adjusted for age, sex, and education. CES-D = Center for Epidemiological Studies Depression Scale.

In the neuropathologically examined subgroup, we repeated the first proportional odds model and then added terms for each neuropathologic marker and its interaction with time. We estimated the associations of depressive symptoms (averaged across evaluations) and neuropathologic markers with cognitive decline in mixed-effects models.²⁸ The initial model had terms for time (from death in years), mean depressive symptoms, and their interaction. A second model had terms for time, each neuropathologic marker, and the interaction of each marker with time. We repeated this analysis with terms added for mean depressive symptoms and its interaction with time. We repeated the latter analysis with terms added for the 2-way interactions of mean depressive symptoms with each neuropathologic marker and the 3-way interactions of mean depressive symptoms by each marker by time.

RESULTS Depressive symptoms during development of dementia and MCI. At baseline, the 1,764 participants (figure 1) reported a mean of 1.0 symptom

(SD = 1.6, skewness = 2.0) on the Center for Epidemiological Studies Depression Scale (963 had no symptoms; 371 had 1; 171 had 2; 113 had 3; 64 had 4; and 82 had 5 or more). Over time, the within-person range of scores had a median of 2 (interquartile range: 1–4), suggesting substantial variability. We assessed change in depressive symptoms during a mean of 7.8 years of annual follow-up (SD = 4.8) in a proportional odds model adjusted for baseline age, sex, and education. In this analysis, depressive symptoms increased over time (estimate = 0.043, SE = 0.006, $p < 0.001$). This was mainly attributable to a slight decline in the likelihood of having no symptoms (figure 2A).

During follow-up, 52.2% of the cohort (922/1,764) developed MCI, widely recognized as a precursor to dementia in old age. At baseline, they were older and more educated than those who remained cognitively intact (table e-1 on the *Neurology*[®] Web site at Neurology.org). To determine the relation of MCI to depressive symptoms, we repeated the analysis with the addition of a time-varying indicator of MCI onset and its interaction with time. Incident MCI was associated with a higher level of depressive symptoms before MCI onset but not with rate of change in symptoms after MCI onset (table 1, model A).

A total of 315 individuals (17.9%) developed dementia during follow-up. At baseline, they were older and more depressed than those who did not develop dementia (table e-1). Incident dementia was associated with a higher level of depressive symptoms before dementia onset, but a slight decrease in symptoms thereafter (table 1, model B).

Depressive symptoms and neuropathologic burden. The remaining analyses were conducted on the 582 neuropathologically examined individuals (figure 1). At baseline, they reported a mean of 1.2 depressive symptoms (SD = 1.6, median = 1, skewness = 1.6). In a proportional odds model adjusted for age at death, sex, and education, depressive symptoms

slightly increased during the mean of 8.4 years of observation (estimate = 0.048, SE = 0.013, $p < 0.001$; figure 2B).

On the postmortem neuropathologic examination, the composite measure of β -amyloid plaque burden ranged from 0 to 22.9 (mean = 3.9, SD = 4.3, median = 2.4, skewness = 1.3) and the composite measure of tau tangle density ranged from 0 to 32.2 (mean = 4.4, SD = 5.2, median = 2.8, skewness = 2.2). In addition, 32.1% had one or more chronic gross infarcts, 27.9% had one or more chronic microinfarcts, 12.1% had neocortical Lewy bodies, and 5.9% had hippocampal sclerosis.

We constructed a proportional odds model adjusted for age at death, sex, and education to test whether the neuropathologic markers were related to level of depressive symptoms or to change in depressive symptoms over time. The neuropathologic markers were not related to level of depressive symptoms proximate to death or change in depressive symptoms over time (table 2).

Depressive symptoms, neuropathologic burden, and cognitive decline.

We examined the associations among depressive symptoms, neuropathologic burden, and change in cognitive function in mixed-effects models adjusted for age at death, sex, and education. Because dementia develops by minute degrees,^{13,29} we focused on a continuous outcome (i.e., rate of change in cognitive function) rather than a binary one (e.g., diagnosis of dementia) to better capture this process and maximize statistical power. In the initial model, higher level of depressive symptoms averaged across all clinical evaluations (mean = 1.3, SD = 1.3, median = 0.9, skewness = 1.6) was associated with more rapid cognitive decline (table 3, model A). We then constructed a model with terms for each neuropathologic marker and its interaction with time. Each neuropathologic marker except amyloid and microinfarcts was associated with more rapid cognitive decline (table 3, model B) and together the markers accounted for 31.8% of the variability in rates

Table 1 Relation of incident mild cognitive impairment and dementia to change in depressive symptoms over time^a

Model term	Model A			Model B		
	Estimate	SE	p	Estimate	SE	p
Time	0.021	0.008	0.010	0.039	0.007	<0.001
Mild cognitive impairment	0.200	0.089	0.025			
Time × mild cognitive impairment	0.014	0.011	0.201			
Dementia				0.729	0.220	<0.001
Time × dementia				-0.059	0.024	0.013

Abbreviation: SE = standard error.

^aEstimated from 2 proportional odds models adjusted for age at baseline, sex, and education.

Table 2 Relation of postmortem neuropathologic markers to change in depressive symptoms over time^a

Model term	Estimate	SE	p
Time	0.026	0.019	0.176
Amyloid plaques	0.013	0.022	0.565
Amyloid plaques × time	0.002	0.002	0.354
Tangle density	0.010	0.019	0.618
Tangle density × time	0.001	0.002	0.769
Gross infarcts	0.074	0.201	0.714
Gross infarcts × time	-0.007	0.023	0.754
Microinfarcts	0.315	0.200	0.115
Microinfarcts × time	0.015	0.023	0.495
Lewy bodies	0.428	0.279	0.125
Lewy bodies × time	0.040	0.029	0.167
Hippocampal sclerosis	-0.517	0.375	0.125
Hippocampal sclerosis × time	0.015	0.036	0.680

Abbreviation: SE = standard error.

^a Estimated from a proportional odds model adjusted for age at death, sex, and education.

of cognitive decline. When depressive symptoms and the neuropathologic markers were included in the same analysis, higher level of depressive symptoms continued to be associated with faster rate of cognitive decline (table 3, model C), accounting for 4.4% of the residual variability in cognitive decline not attributable to neuropathologic burden. Figure e-1, which is based on this analysis, shows a dose-response relationship, with

higher levels of depressive symptoms associated with increasingly rapid cognitive decline.

To determine whether depressive symptoms modified the relationship of neuropathologic burden to cognitive decline, we repeated the previous model with terms added for the 2-way interactions of depressive symptoms with each neuropathologic marker, and the 3-way interactions of depressive symptoms, time, and each neuropathologic marker. None of the 12 interactions was significant.

DISCUSSION A group of more than 1,750 older persons without cognitive impairment at study onset completed annual clinical evaluations for a mean of about 8 years during which nearly 600 died and underwent a neuropathologic examination. Depressive symptoms were associated with rate of cognitive decline, and after adjustment for postmortem markers of 6 types of dementia-related pathology, higher level of depressive symptoms during the study period remained associated with faster rate of cognitive decline, accounting for 4.4% of the variability in rates of cognitive decline not attributable to neuropathologic burden.

The observed association of depressive symptoms with cognitive decline is consistent with most prior research,^{1,2} including an earlier analysis of data from the Religious Orders Study.¹ The present results add to that literature by showing that depressive symptoms have an association with cognitive decline that is independent of the neuropathologic conditions

Table 3 Relation of depressive symptoms and neuropathologic markers to global cognitive decline^a

Model term	Model A			Model B			Model C		
	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Time	-0.064	0.007	<0.001	-0.033	0.007	<0.001	-0.015	0.008	0.057
CES-D mean score	-0.113	0.030	<0.001				-0.104	0.026	<0.001
CES-D mean score × time	-0.014	0.003	<0.001				-0.013	0.003	<0.001
Amyloid plaques				-0.005	0.008	0.520	-0.006	0.008	0.438
Amyloid plaques × time				-0.001	0.001	0.369	-0.001	0.001	0.307
Tangle density				-0.058	0.007	<0.001	-0.058	0.007	<0.001
Tangle density × time				-0.006	0.001	<0.001	-0.006	0.001	<0.001
Gross infarcts				-0.423	0.073	<0.001	-0.410	0.072	<0.001
Gross infarcts × time				-0.048	0.008	<0.001	-0.046	0.008	<0.001
Microinfarcts				0.037	0.074	0.620	0.049	0.073	0.507
Microinfarcts × time				0.015	0.008	0.074	0.016	0.008	0.054
Neocortical LB				-0.617	0.103	<0.001	-0.591	0.101	<0.001
Neocortical LB × time				-0.072	0.011	<0.001	-0.069	0.011	<0.001
Hippocampal sclerosis				-0.593	0.137	<0.001	-0.633	0.136	<0.001
Hippocampal sclerosis × time				-0.048	0.014	<0.001	-0.053	0.014	<0.001

Abbreviations: CES-D = Center for Epidemiological Studies Depression Scale; LB = Lewy bodies; SE = standard error.

^a Estimated from 3 mixed-effects models adjusted for age at death, sex, and education. In subsequent analyses, there were no interactions between depressive symptoms and neuropathologic markers.

most strongly linked to late-life cognitive decline and dementia.

How depressive symptoms contribute to cognitive impairment is not known. Prior studies have associated late-life depression, whether defined diagnostically or psychometrically, with abnormalities in frontal-subcortical and limbic networks involved in emotional regulation. These abnormalities include lower brain volume^{30,31} and white matter integrity^{32,33} in antemortem neuroimaging studies and lower density of neurons³⁴ and dendritic spines per neuron³⁵ in postmortem neuropathologic studies. It is not clear, however, whether these or other factors are contributing to the association of depressive symptoms with late-life cognitive decline and dementia.

We found no support for other hypotheses about the association between depression and late-life cognition. First, depressive symptoms did not increase with the onset of MCI and slightly decreased after dementia onset. Although this is not consistent with prior reports of a very slight increase in depressive symptoms before dementia onset,^{13,14} it is consistent with reports of stable¹⁴ or declining³⁶ depressive symptoms after dementia onset and the lack of an association of cognitive level^{37–39} and cognitive change⁴⁰ with change in depressive symptoms. Second, neither level of depressive symptoms nor change in symptoms over time was related to common neuropathologic lesions associated with cognitive decline and dementia. Third, depressive symptoms did not alter the association of neuropathology with cognitive decline. Overall, that depressive symptoms were related to cognitive decline after adjusting for pathology but neither dementia nor pathology was associated with increasing depressive symptoms suggests that depressive symptoms are a risk factor for late-life cognitive decline. Although the neurobiological basis of the association is uncertain, the present results suggest that interventions targeting depressive symptoms and psychological distress have the potential to help maintain cognitive health in old age.

This study has several strengths and limitations. The clinical diagnoses of MCI and dementia were based on a uniform evaluation and widely accepted criteria applied by experienced clinicians, minimizing diagnostic misclassification. Participation in clinical follow-up and brain autopsy was high, reducing the likelihood that selective attrition biased results. The availability of psychometrically sound measures of depressive symptoms and cognitive function administered annually for a mean of about 8 years maximized our ability to characterize change. An important limitation is that the volunteer participants were self-selected and so the generalizability of the results remains to be determined. In addition, our measures of some disease processes were incomplete (e.g., cerebrovascular disease), some disease processes were not measured (e.g., transactive response DNA-binding protein

43), and some markers were infrequently observed (e.g., hippocampal sclerosis). Use of a brief self-report scale may have led us to underestimate depressive symptoms especially as cognition became impaired, although informant report does not suggest that depressive symptoms increase in MCI or dementia.¹⁴

AUTHOR CONTRIBUTIONS

Drafting/revising manuscript for content: Wilson, Capuano, Boyle, Hoganson, Hizek, Shah, Nag, Schneider, Arnold, Bennett. Study concept or design: Wilson, Capuano, Boyle, Hoganson, Hizek, Shah, Nag, Schneider, Arnold, Bennett. Analyses or interpretation of the data: Wilson, Capuano, Boyle, Shah, Nag, Schneider, Arnold, Bennett. Acquisition of data: Bennett, Nag, Schneider. Statistical analysis: Capuano. Study supervision or coordination: Bennett. Obtaining funding: Boyle, Bennett.

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This Week's *Neurology*[®] Podcast



Clinical-pathologic study of depressive symptoms and cognitive decline in old age (See p. 702)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the August 19, 2014, issue of *Neurology*. In the second segment, Dr. Jeff Burns talks with Dr. Robert S. Wilson about his paper on depressive symptoms and cognitive decline in old age. Dr. Adam Numis reads our e-Pearl of the week about ictal syncope. In the next part of the podcast, Dr. Rebecca Wells focuses her interview with Dr. Tieraona Low Dog on complementary alternative medicine therapies using

supplements for the treatment of headaches.

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