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Cognitive Decline in Patients With Dementia as a Function of Depression

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Abstract

Objective—There is evidence that major depression increases the risk for dementia, but there is conflicting evidence as to whether depression may accelerate cognitive decline in dementia. The authors tested the hypothesis that decline in cognitive function over time is more pronounced in patients with dementia with comorbid depression, when compared with patients with dementia without depression history.

Design—Prospective, longitudinal cohort study of aging.

Setting—Nursing home.

Participants—Three hundred thirteen elderly nursing home residents (mean age at baseline: 86.99 years, standard deviation = 6.7; 83.1% women). At baseline, 192 residents were diagnosed with dementia, and another 27 developed dementia during follow-up. Thirty residents suffered from major depression at any point during the study, and 48 residents had a history of depression.

Measurements—The authors measured cognitive decline using change in Mini-Mental State Examination (MMSE) scores over up to 36 months. The authors calculated multilevel regression models to estimate the effects of age, gender, education, dementia status, depression, depression history, and an interaction between dementia and depression, on change in MMSE scores over time.

Results—Beyond the effects of age, gender, and education, residents showed steeper cognitive decline in the presence of dementia ($\beta = 13.69$, standard error = 1.38) and depression ($\beta = -4.16$, SE = 1.2), which was further accelerated by the presence of both depression and dementia ($\beta = -2.72$, SE = 0.65).

Conclusions—In dementia, the presence of depression corresponds to accelerated cognitive decline beyond gender and level of education, suggesting a unique influence of depression on the rate of cognitive decline in dementia.

Keywords

Depression; dementia; cognitive decline

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Major depression is a common comorbid disorder in patients suffering from dementia. Most studies report a prevalence of anywhere between 30% and 50% of patients with dementia who suffer from comorbid depression.[1,2] There is evidence to show that depression increases the risk for subsequent onset of dementia. Studies suggest that depression conveys an increased risk for clinically diagnosed dementia in older adults.[3–11] At the same time, geriatric depression in itself has been associated with deficits in episodic memory,[12,13] and there is evidence that a lifetime history of depression may be related to structural changes in the hippocampus.[4,14,15] In late-onset depression, structural imaging studies point to not only changes in deep frontal white matter[16] but also structural changes in the hippocampus[17] and prefrontal cortex.[18] Geriatric depression is often accompanied by cognitive impairments in multiple domains [12,13], which may in itself increase the risk of conversion to dementia and accelerate cognitive decline.[19,20] At the same time, memory dysfunction has been shown to be persistent in older depressed patients even after their mood disorder has responded to anti-depressant medications.[21]

However, there is conflicting evidence as to whether depression in dementia affects cognitive decline over time.[22] Although some studies report no effect of depression on cognitive decline over time,[11,22,23] others report accelerated cognitive decline in patients with dementia and depression.[24,25] On a behavioral level, there is indeed evidence that chronic psychological distress may accelerate cognitive decline in old adults suffering from dementia.[26] Studies reporting contradictory findings differed with respect to the samples under study, in that all the studies that did not find an effect of depression on cognitive decline investigated community-based samples.[22,23] At the same time, two of the studies that did find an effect of depression on cognitive decline in dementia used clinical or nursing home samples and used a clinical diagnosis of depression or depression history,[11,24] whereas other studies used continuous measures of depressive symptoms.[22,23] A recent community-based study using continuous measures of depressivity could not confirm the risk of conveyed by depression to develop subsequent dementia.[27]

Neurobiological mechanisms that may account for the deleterious effects of depression on cognition in patients with dementia include impaired neurotrophy,[28] vascular pathology,[29] and exacerbation of Alzheimer disease (AD).[25,30] Furthermore, there is recent evidence that geriatric patients suffering from depression show increased plasma amyloid levels[31] and increased amyloid pathology in imaging studies,[32] suggesting a possible interaction between depression and the neuropathology and course of AD.

Taken together, these findings raise the possibility that depression may be an important factor in the progression of dementia in very old age. In this study, we examined whether cognitive decline over time differs in patients with dementia with depression, when compared with patients with dementia with no depression.

METHODS

Participants

Participants were 313 elderly nursing home residents from the Jewish Home & Hospital (JHH) in Bronx, NY, and Manhattan, NY. The JHH has been an academic affiliate of the Mount Sinai School of Medicine (MSSM) for the last 25 years. Participants were part of a prospective, longitudinal study of cognition in old age, the Clinical and Biological Studies of Early Alzheimer's Disease project, at the Department of Psychiatry, MSSM. Inclusion criteria in this study were age >54 years, at least two Mini-Mental State Examination (MMSE) assessments, and complete demographic information (age, sex, and education). The study was approved by both the MSSM and JHH institutional review boards.

Clinical Variables

Clinical variables included sex, ethnicity, age at onset of dementia, age at death, depression, and clinical diagnosis of dementia or no dementia. Dementia diagnosis was ascertained through clinical interview, baseline screening using the MMSE,[33] and additional information from the Clinical Dementia Rating (CDR)[34] scales, neuropsychological evaluations, when available, and a short interview assessing diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*)-*III-R* or *DSM-IV*.[35] All diagnoses were confirmed further at a clinical diagnosis consensus conference attended by many of the present authors during which all medical, psychiatric, neuropsychological, and psychosocial information was reviewed.

The MMSE was administered along with a standardized questionnaire assessing psychiatric history and current symptoms. We followed standard administration protocols for the MMSE[33] except for the administration of the Attention item, which was assessed based on spelling *world* backward only—serial seven calculations were not assessed. Trained research assistants administered all tasks.

These research assistants completed a standardized questionnaire assessing the presence or absence of *DSM-III-R* or *DSM-IV* symptoms of major depressive disorder, which was developed as a modified version of the mood disorders module from the Structured Clinical Interview for *DSM-IV* Axis I disorders.[36] The modification essentially entailed a restriction to items specifying depression diagnoses, thus dropping items specifying a diagnosis of bipolar affective disorders. In addition, the presence or absence of both major depression and history of depression was further extracted from medical information, including charts and information obtained from the treating physician, the study subject, and/or knowledgeable informant. The diagnosis of a lifetime depression was reviewed and verified by a physician with specialty training in geriatric psychiatry. Using the information from the psychiatric symptoms and history data, we defined a history of depression as present in patients who had at least one prior episode of major depression before the onset of dementia according to psychiatric history. In an earlier report,[12] the external validity of this variable was assessed in comparison with scores on the Geriatric Depression Scale and shown to be satisfactory (sensitivity = 0.95 and specificity = 0.90).

Statistical Analyses

Raw scores were used for all analyses. Descriptive analyses were performed using SPSS (SPSS Inc, Chicago, IL). Between-group *t*-tests and χ^2 tests were used to assess group differences in descriptive variables and covariates. All tests of significance were two tailed with α set at 0.05. Effect sizes were calculated using Cohen's *d*.[37]

Multilevel regression models were used to examine the relationship between depression and total MMSE scores over time, controlling for age, gender, and level of education. The use of multilevel regression models enabled us to study MMSE scores across time while accounting for within-subject correlations, thus providing an efficient way to use all the information from each participant. Another advantage of using these models is that it permits analysis of the unbalanced data, i.e., different number of follow-up occasions or different follow-up times. All the multilevel models fitted in the present analysis include random intercept and random slope (in follow-up time) to take into account the fact that each participant has different baseline MMSE score and various patterns of decline at follow-up periods. Specifically, we fitted a multilevel regression model that represents scores on the MMSE as a function of age, gender, education, presence of dementia, presence of depression, presence of depression history, and the interaction of depression and dementia:

$$\begin{aligned}\mathrm{MMSE}_{t,i} = {} & \beta_{0t,i}\,\mathrm{age}_{t,1} \\ & + \beta_{1i}\,\mathrm{gender}_{i} \\ & + \beta_{2,i}\,\mathrm{education}_{i} \\ & + \beta_{3t,i}\,\mathrm{dementia}_{t,i} \\ & + \beta_{4t,i}\,\mathrm{depression}_{t,i} \\ & + \beta_{5t,i}\,\mathrm{history\ of\ depression}_{t,i} \\ & + \beta_{6t,i}\,\mathrm{interaction}_{t,i}, \end{aligned} \quad (1)$$

where $\mathrm{MMSE}_{t,i}$ is the MMSE score from time *t* in individual *i*, and age, dementia, depression, and interaction represent the respective predictor variables from time *t* in individual *i*. Note that both gender and education are Level 2 (individual) variables only and were constrained not to vary over time. For the multilevel analysis, we compared several models by subsequently adding all variables as specified in Eq. (1). Furthermore, we ran additional models to control for the effects of type of dementia (AD versus mixed dementia versus vascular dementia versus dementia with Lewy bodies). Model fits were compared using iterative generalized least squares estimators and likelihood ratio tests in MLwiN version 2.02.[38]

RESULTS

Demographic and Clinical Characteristics

The overall study group (N = 313) comprised 260 women (83.1%) and 53 men (16.9%), reflecting the old age and the residence type (nursing home) of the study sample. The mean age at baseline was 86.99 years (standard deviation [SD] = 6.72, range = 55–105), with a mean education level of 12.64 years (SD = 4.8, range = 0–30), and a mean baseline MMSE score of 21.60 (SD = 9.89, range = 0–30); 84.3% of the sample (N = 264) were white, 10.9% (N = 34) were African American, and 3.8%[12] were Hispanic, with all other ethnicities accounting for less than 1% of the sample. Participants were followed up for up to 36 months (range = 3–36 months).

Overall, 15.7% (N = 49) of the final sample had a history of depression, and another 9.6% (N = 30) suffered from major depression at any point during the study. There were no statistically significant differences with respect to age ($t = 0.15$, $df = 311$, $p = 0.88$), gender ($\chi^2 = 0.05$, $df = 1$, $p = 0.82$), education ($t = 1.14$, $df = 311$, $p = 0.26$), and ethnicity ($\chi^2 = 5.55$, $df = 5$, $p = 0.35$) as a function of depression or depression history. Neither baseline MMSE scores ($t = 0.18$, $df = 311$, $p = 0.86$) nor baseline CDR scores differed in patients with or without depression ($t = 0.79$, $df = 311$, $p = 0.43$). Furthermore, the number of comorbid medical diagnoses did not differ as a function of depression ($t = 0.76$, $df = 311$, $p = 0.45$).

At baseline, 192 (61.3%) of the sample suffered from dementia, and subjects with dementia were, on average, older ($t = 2.03$, $df = 311$, $p < 0.05$) and had lower baseline scores on the MMSE ($t = 14.65$, $df = 311$, $p < 0.001$) and CDR at baseline ($t = 29.73$, $df = 311$, $p < 0.001$). There were no statistically significant differences with respect to gender ($\chi^2 = 1.86$, $df = 1$, $p = 0.17$), education ($t = 1.23$, $df = 313$, $p = 0.22$), ethnicity ($\chi^2 = 4.29$, $df = 5$, $p = 0.51$) nor the number of comorbid medical diagnoses ($t = 0.12$, $df = 313$, $p = 0.29$) as a function of dementia. Of the 192 residents with dementia, 77 (40.1%) were diagnosed with AD, 33 (17.2%) suffered from atypical or mixed AD, 46 (24.0%) suffered from vascular dementia, and 12 (6.25%) were diagnosed with dementia with Lewy bodies. Dementia diagnosis was not specified in 24 patients. Characteristics of the sample are listed in Table 1.

Cognitive Decline Over Time as a Function of Depression History

Beyond the effects of age (β = 0.33, SE = 0.01), gender (β = −2.35, SE = 0.39), and education (β = −0.03, SE = 0.01), residents showed steeper cognitive decline in the presence of dementia (β = −13.69, SE = 1.38). History of depression alone did not significantly increase model fit (Δ − 2log likelihood = 46; χ^2 = 2.29, *df* = 4, p = 0.51), but both the presence of major depression at any point during the study (β = −4.16, SE = 1.2) and the interaction of major depression and dementia (β = −2.72, SE = 0.65) did significantly increase model fit beyond the effects of age, gender, education, and the presence of dementia (Δ − 2log likelihood = 732; χ^2 = 13.3, *df* = 5, p < 0.01).

Parameter estimates and changes in model fit are shown in Table 2. The model fit did not change when adding terms for type of dementia (Δ − 2log likelihood = 61; χ^2 = 1.98, *df* = 6, p = 0.64). In addition, we restricted the analyses to cases with either vascular (N = 46) or AD (N = 110) and introduced a dummy variable coding for the type of dementia diagnosis (vascular dementia = 0; AD = 1) and reran the model specified earlier in the text including this variable. Within patients with dementia, and beyond the effects of major depression at any point during the study (β = −3.78, SE = 1.4), the interaction of major depression and type of dementia diagnosis (β = −2.24, SE = 0.71) added significantly to model fit (Δ − 2log likelihood = 598; χ^2 = 9.2, *df* = 6, p < 0.01), indicating that patients suffering from AD exhibited more rapid cognitive decline over time.

Furthermore, to determine the convergent validity of our findings, we reran our models using CDR scores instead of MMSE values. Again, beyond the effects of age (β = 0.11, SE = 0.01), gender (β = −0.25, SE = 0.08), and education (β = −0.02, SE = 0.01), residents showed steeper cognitive decline in the presence of dementia (β = −0.45, SE = 0.17). History of depression alone did not significantly increase model fit (Δ − 2log likelihood = 14; χ^2 = 1.07, *df* = 4, p = 0.71), but both the presence of major depression at any point during the study (β = −0.16, SE = 0.02) and the interaction of major depression and dementia (β = −0.22, SE = 0.05) did significantly increase model fit beyond the effects of age, gender, education, and the presence of dementia (Δ − 2log likelihood = 876; χ^2 = 14.4, *df* = 6, p < 0.01).

DISCUSSION

We found distinct differences in cognitive decline, as measured by the MMSE, over time in residents with depression compared with residents without depression. The effect remained stable beyond the effect of dementia diagnosis alone and was sizable in that it reflected a 4-point decline in MMSE over about 3 years relative to residents without depression. Furthermore, there was a significant depression by dementia interaction, suggesting that the presence of comorbid depression in dementia further accelerates cognitive decline. Although residents suffering from dementia, on average, declined 13.7 points over about 3 years, the presence of depression in dementia led to an additional loss of ~2.7 points on the MMSE during the course of this study, showing that the presence of comorbid depression accelerates cognitive decline associated with dementia in old age. When restricting our analyses to cases with AD and vascular dementia only (N = 156), we found that patients with AD and comorbid depression exhibited an additional decline of ~2.2 points on the MMSE during the course of this study, suggesting that depression may exert specific effects on the course of cognitive decline in AD. Such an interaction could be mediated by effects of depression on AD neuropathology,[23] which may be driven by depression-associated changes in the neurotrophin system,[24] but we cannot characterize such neurobiological changes from the present data.

The assessment of major depression and depression history in dementia, as used in our study, is characterized by intrinsic methodological limitations. The reported point prevalence of depression in older nursing home residents ranges from 6% to 32%[2] and is thus comparable with the prevalence of ~10% in our sample. However, clinical studies suggest that the prevalence of depression in dementia may be even higher, ranging from 30% to >50%,[1] suggesting that the prevalence of depression in our sample may have been underestimated. Prior studies showed that, when informants and structured interviews are used, interrater reliability might not exceed 80%.[39,40] Thus, the accuracy of the depression diagnoses in our sample may be limited. On the one hand, underestimating the incidence of depression is likely to have biased the results toward a reduced estimate of the influence of depression on cognitive function, raising the possibility that depression impacts the rate of progression of dementia more than that observed in this study. On the other hand, the diagnosis of depression in dementia is clinically difficult, and we may have missed depressed patients with dementia with our assessment that could have been detected using specific scales for the assessment of depression in dementia. Therefore, depression severity may have been a factor, with greater depressive symptoms leading to cognitive decline. However, because there was no measure of depression severity, this possibility cannot be tested. In addition, we cannot rule out that the effects of depression on cognitive decline in dementia are in part due to psychotropic medications prescribed, because we lack these data in our sample.

Furthermore, overall sample size made it difficult to examine effects of different types of depression and/or depression duration across the lifespan on cognitive decline in dementia. For example, we explored whether onset of depression (recurrent, early onset versus late onset) had a differential effect on cognitive decline, and model fit did not change when adding that variable (−2log likelihood = 61; $\chi^2 = 1.98$, $df = 2$, $p = 0.64$), but limited power prohibits further interpretation of that finding.

Despite these limitations, the results showed that the presence of depression in older adults suffering from dementia is associated with accelerated cognitive decline. Moreover, we analyzed longitudinal data from elderly with a wide, yet more or less normally distributed, range of educational attainment and a wide range of cognitive functioning. Our study points to an accelerated decline in patients with dementia and specifically patients with AD with comorbid depression. Our study is in line with two other studies showing accelerated cognitive decline in dementia as a function of depression,[24,25] whereas most community-based studies did not find such an effect.[11,22,23] In community-based studies, it has been shown that depression in itself may not be a risk factor for dementia.[27] It may well be that detecting the comparably small additive effects of depression on cognitive decline in dementia is more likely when comparing patients diagnosed with depression to nondepressed patients with dementia, rather than using continuous measures of depression, and associated neurobiological changes may be especially pronounced in major depressive disorder, as has been shown, e.g., changes in the neurotrophin system.[24] A key limitation in that context is that we did not investigate possible underlying neurobiological changes as a function of comorbid depression, and future longitudinal studies are needed to address this issue.

Recent studies suggests accelerated amyloid pathology in subjects with depression.[31,32] Such an increase in amyloid pathology in persons with depression may provide another potential mechanism for the results observed in this study. This hypothesis is consistent with our earlier observation of increased neuritic plaque an neurofibrillary tangle pathology in persons with a lifetime history of depression and AD.[25,30] However, we lack more detailed information on depression that could be of interest, such as disease duration, number of prior episodes, and medication treatment, that could help develop hypotheses on possible

mechanisms of accelerated cognitive decline in depression and dementia. Conceptually, depressive symptoms may be an early manifestation rather than a risk factor for dementia and AD, in that the underlying neuropathological condition that causes dementia may also cause depressive symptoms.[41] It is possible, albeit unproven in this study, that factors such as reduced cognitive[42] or neurobiological reserve in dementia may have contributed to the greater impact of depression on cognitive decline. Comorbid depression in dementia often goes undetected in the clinical context and may result in higher rates of nursing home placement in patients with dementia by increasing their functional disability.[43]

To conclude, we showed that the presence of major depression leads to accelerated cognitive decline in dementia beyond age, gender, and level of education, suggesting a unique influence of depression on cognitive decline in dementia.

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References

1. Olin JT, Katz IR, Meyers BS, et al. Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. Am J Geriatr Psychiatry. 2002; 10:129–141. [PubMed: 11925274]
2. Zubenko GS, Zubenko WN, McPherson S, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. Am J Psychiatry. 2003; 160:857–866. [PubMed: 12727688]
3. Green RC, Cupples LA, Kurz A, et al. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. Arch Neurol. 2003; 60:753–759. [PubMed: 12756140]
4. Steffens DC, Payne ME, Greenberg DL, et al. Hippocampal volume and incident dementia in geriatric depression. Am J Geriatr Psychiatry. 2002; 10:62–71. [PubMed: 11790636]
5. Chen P, Ganguli M, Mulsant BH, et al. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen Psychiatry. 1999; 56:261–266. [PubMed: 10078504]
6. Jorm AF, van Duijn CM, Chandra V, et al. Psychiatric history and related exposures as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. Int J Epidemiol. 1991; 20:S3–S7.
7. Kokmen E, Beard CM, Chandra V, et al. Clinical risk factors for Alzheimer's disease: a population-based case-control study. Neurology. 1991; 41:1393–1397. [PubMed: 1891088]
8. Van Duijn CM, Clayton DG, Chandra V, et al. Interaction between genetic and environmental risk factors for Alzheimer's disease: a reanalysis of case-control studies. EURODEM Risk Factors Research Group. Genet Epidemiol. 1994; 11:539–551. [PubMed: 7713394]
9. Speck CE, Kukull WA, Brenner DE, et al. History of depression as a risk factor for Alzheimer's disease. Epidemiology. 1995; 6:366–369. [PubMed: 7548342]
10. Devanand DP, Sano M, Tang MX, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. Arch Gen Psychiatry. 1996; 53:175–182. [PubMed: 8629893]
11. Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. Neurology. 2002; 59:364–370. [PubMed: 12177369]
12. Rapp MA, Dahlman K, Sano M, et al. Neuropsychological differences between late-onset and recurrent geriatric major depression. Am J Psychiatry. 2005; 162:691–698. [PubMed: 15800140]
13. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry. 2003; 160:1516–1518. [PubMed: 12900317]

14. Bell-McGinty S, Butters MA, Meltzer CC, et al. Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. Am J Psychiatry. 2002; 159:1424–1427. [PubMed: 12153839]
15. Hickie I, Scott E. Late-onset depressive disorders: a preventable variant of cerebrovascular disease? Psychol Med. 1998; 28:1007–1013. [PubMed: 9794008]
16. Krishnan KR, Taylor WD, McQuoid DR, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol Psychiatry. 2004; 55:390–397. [PubMed: 14960292]
17. Ballmaier M, Narr KL, Toga AW, et al. Hippocampal morphology and distinguishing late-onset from early-onset elderly depression. Am J Psychiatry. 2008; 165:229–237. [PubMed: 17986679]
18. Aizenstein HJ, Butters MA, Wu M, et al. Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena. Am J Geriatr Psychiatry. 2009; 17:30–42. [PubMed: 19001356]
19. Holtzer R, Scarmeas N, Wegesin DJ, et al. Depressive symptoms in Alzheimer's disease: natural course and temporal relation to function and cognitive status. J Am Geriatr Soc. 2005; 53:2083–2089. [PubMed: 16398891]
20. Ballard CG, Patel A, Solis M, et al. A one-year follow-up study of depression in dementia sufferers. Br J Psychiatry. 1996; 168:287–291. [PubMed: 8833681]
21. Nebes RD, Pollock BG, Houck PR, et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. J Psychiatr Res. 2003; 37:99–108. [PubMed: 12842163]
22. Ganguli M, Du Y, Dodge HH, et al. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. Arch Gen Psychiatry. 2006; 63:153–160. [PubMed: 16461857]
23. Bassuk SS, Berkman LF, Wypij D. Depressive symptomatology and incident cognitive decline in an elderly community sample. Arch Gen Psychiatry. 1998; 55:1073–1081. [PubMed: 9862549]
24. Milwain EJ, Nagy Z. Depressive symptoms increase the likelihood of cognitive impairment in elderly people with subclinical Alzheimer pathology. Dement Geriatr Cogn Disord. 2005; 19:46–50. [PubMed: 15383746]
25. Rapp MA, Schnaider-Beeri M, Grossman H, et al. Increased hippocampal plaques and tangles in Alzheimer's disease patients with a lifetime history of major depression. Arch Gen Psychiatry. 2006; 63:161–167. [PubMed: 16461859]
26. Wilson RS, Arnold SE, Schneider JA, et al. Chronic distress, age-related neuropathology, and late-life dementia. Psychosom Med. 2007; 69:47–53. [PubMed: 17244848]
27. Becker JT, Chang YF, Lopez OL, et al. Depressed mood is not a risk factor for incident dementia in a community-based cohort. Am J Geriatr Psychiatry. 2009; 17:653–663. [PubMed: 19634208]
28. Dwivedi Y, Rao JS, Rizavi S, et al. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry. 2003; 60:804–815. [PubMed: 12912764]
29. Steffens DC, Taylor WD, Krishnan KR. Progression of subcortical ischemic disease from vascular depression to vascular dementia. Am J Psychiatry. 2003; 160:1751–1756. [PubMed: 14514484]
30. Rapp MA, Schnaider-Beeri M, Purohit DP, et al. Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression. Am J Geriatr Psychiatry. 2008; 16:168–174. [PubMed: 18239198]
31. Sun X, Steffens DC, Au R, et al. Amyloid-associated depression: a prodromal depression of Alzheimer disease? Arch Gen Psychiatry. 2008; 65:542–550. [PubMed: 18458206]
32. Butters MA, Klunk WE, Mathis CA, et al. Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh compound-B. Alzheimer Dis Assoc Disord. 2008; 22:261–268. [PubMed: 18580591]
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Psychiatry Res. 1975; 12:189–198.
34. Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull. 1988; 24:637–639. [PubMed: 3249765]
35. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. DSM-III-R. 3. Washington, DC: American Psychiatric Association; 1987.

36. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry. 1992; 49:624–62926. [PubMed: 1637252]

37. Cohen, J. Statistical Power Analyses for the Behavioral Sciences. 2. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

38. Rasbash, J.; Charlton, C.; Browne, WJ., et al. MLwiN Version 2.02. Centre for Multilevel Modelling. University of Bristol; Bristol, UK: 2005.

39. Wiener P, Alexopoulos GS, Kakuma T, et al. The limits of history-taking in geriatric depression. Am J Geriatr Psychiatry. 1997; 5:116–125. [PubMed: 9106375]

40. Henkel V, Mergl R, Kohnen R, et al. Use of brief depression screening tools in primary care: consideration of heterogeneity in performance in different patient groups. Gen Hosp Psychiatry. 2004; 26:190–198. [PubMed: 15121347]

41. Panza F, Frisardi V, Capurso C, et al. Late-life depression, mild cognitive impairment, and dementia: possible continuum? Am J Geriatr Psychiatry. 2010; 18:98–116. [PubMed: 20104067]

42. Stern Y. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord. 2006; 20:S69–S74. [PubMed: 16917199]

43. Kales HC, Chen P, Blow FC, et al. Rates of clinical depression diagnosis, functional impairment, and nursing home placement in coexisting dementia and depression. Am J Geriatr Psychiatry. 2005; 13:441–449. [PubMed: 15956263]

TABLE 1

Characteristics of Patients With Dementia and Comparison Subjects With and Without Comorbid Depression

	Nondemented Subjects (121)		Patients With Dementia (192)	
	Nondepressed (99)	Depression or Depression History at Baseline (25)	Nondepressed (154)	Depression or Depression History at Baseline (38)
Age at baseline	86.02 (8.24)	85.11 (3.81)	87.24 (6.09)	88.57 (5.88)
N female (%)	76 (76.7)	19 (76.0)	132 (85.7)	29 (76.38)
Education	11.15 (3.21)	12.23 (2.78)	12.57 (2.98)	11.46 (2.28)
CDR score at baseline	0.16 (.24)	0.48 (0.58)	2.12 (0.47)	2.33 (0.65)
Number of comorbid medical diagnoses	2.61 (1.49)	2.75 (1.44)	2.56 (1.50)	2.73 (1.45)
MMSE at baseline	25.58 (3.07), N=99	25.65 (2.57), N=25	19.01 (4.35), N= 154	19.91 (2.67), N=38
MMSE Year 1	25.56 (3.84), N=89	25.14 (3.62), N=23	16.21 (5.58), N= 128	18.7 (5.14), N=23
MMSE Year 2	26.36 (2.69), N=72	24.75 (3.13), N=16	14.74 (5.93), N= 88	13.84 (8.34), N=22
MMSE Year 3	27.25 (1.77), N=56	23.22 (1.66), N=11	12.24 (7.49), N= 56	10.12 (7.07), N=13

Notes: Values in parentheses reflect standard deviations except where otherwise indicated. Longitudinal sample size is given in each column.

TABLE 2

MMSE Slopes From Linear Mixed Models of Change in MMSE Score Over Time

Variables	Estimate (± SEM)	Δ − 2Log Likelihood
Age	0.33 ± 0.01	1,264[a]
Gender	−2.35 ± 0.39	1,456[a]
Education	−0.03 ± 0.01	408[b]
Dementia	−13.69 ± 1.38	2,467[a]
Depression	−4.16 ± 1.2	1,139[a]
Dementia × depression	−2.72 ± 0.65	732[b]

Notes: Estimates represent standardized regression coefficients for the extent of decline over up to 36 months on the MMSE. *δ*-2loglikelihood denotes change in likelihood estimators (*df* = 1,

[a] $p < 0.001$,

[b] $p < 0.01$).