HHS Public Access

Author manuscript

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2015 September 01.

Published in final edited form as:

Am J Geriatr Psychiatry. 2015 September ; 23(9): 897–905. doi:10.1016/j.jagp.2014.09.002.

Longitudinal Association of Dementia and Depression

Mark B. Snowden, M.D., **David C. Atkins, Ph.D.**, **Lesley E. Steinman, M.S.W., M.P.H.**, **Janice F. Bell, Ph.D., M.P.H.**, **Lucinda L. Bryant, Ph.D., M.S.H.A.**, **Catherine Copeland, M.P.A.**, and **Annette L. Fitzpatrick, Ph.D.**

Department of Psychiatry and Behavioral Sciences (MBS, DCA) and the Health Promotion Research Center (LES, CC) University of Washington School of Medicine, Seattle, WA; the Betty Irene Moore School of Nursing (JFB), University of California, Davis, CA; the Department of Community and Behavioral Health, Colorado School of Public Health (LLB), University of Colorado Anschutz Medical Campus, Aurora, CO; and the Department of Epidemiology, School of Public Health (ALF), University of Washington, Seattle, WA.

Abstract

Objectives—Depression is an important precursor to dementia, but less is known about the role dementia plays in altering the course of depression. We examined whether depression prevalence, incidence, and severity are higher in those with dementia versus those with mild cognitive impairment (MCI), or normal cognition.

Design—Prospective cohort study using the longitudinal Uniform Data Set of the National Alzheimer's Coordinating Center (2005–2013).

Setting—*34 Alzheimer Disease research centers*.

Participants—27,776 subjects with dementia, MCI, or normal cognition.

Measurements—Depression status was determined by a clinical diagnosis of depression within the prior 2 years and by a Geriatric Depression Scale-Short Form score >5.

Results—Rates of depression were significantly higher in subjects with MCI and dementia compared with those with normal cognition at index visit. Controlling for demographics and common chronic conditions, logistic regression analysis revealed elevated depression in those with MCI (OR: 2.40 [95% CI: 2.25, 2.56]) or dementia (OR: 2.64 [95% CI: 2.43, 2.86]) relative to those with normal cognition. In the subjects without depression at the index visit (N = 18,842), those with MCI and dementia had higher probabilities of depression diagnosis 2 years post index visit than those with normal cognition: MCI = 21.7%, dementia 24.7%, normal cognition = 10.5%.

Conclusion—MCI and dementia were associated with significantly higher rates of depression in concurrent as well as prospective analyses. These findings suggest that efforts to effectively engage and treat older adults with dementia will need also to address co-occurring depression.

Send correspondence and reprint requests to Mark B. Snowden, M.D., Health Promotion Research Center, University of Washington, 1107 N.E. 45th St., Ste. 200, Seattle, WA 98105. snowden@uw.edu.

The authors report no conflicts of interest.

Keywords

Dementia; Alzheimer disease; depression

The increasing number of adults over the age of 65 years in the United States is driving a concurrent increase in the number of individuals experiencing significant cognitive impairment. One of every five persons aged 65 years or older will develop Alzheimer disease (AD) in their lifetime, and, by 2050, the number of people with AD and other forms of dementia in the United States is expected to almost triple.[1,2] Similarly, the likelihood of chronic conditions increases with age, and the number of chronic conditions is linked to risks of mortality, poor functional outcomes, and increased health care utilization.[3–5] Persons with multiple chronic conditions use a disproportionate number of resources—for example, 66% of total healthcare spending is directed toward care for the approximately 27% of Americans with multiple chronic conditions.[6]

Depression is a common chronic condition in elderly patients and often accompanies other chronic conditions. Depression carries its own risks for mortality, higher healthcare costs, and disability.[7–10] Though individual studies are not universally consistent, recent reviews demonstrate depression is a risk factor for dementia of both vascular and Alzheimer types.[11–14] The U.S. Department of Health and Human Services' Multiple Chronic Conditions Strategic Framework,[15] the Centers for Disease Control and Prevention's Healthy Brain Initiative Roadmap,[16] and the National Institutes of Health Cognitive and Emotional Health project[17] all call for a better understanding of the impact that cognitive impairment has on chronic conditions. They suggest that analysis of existing data sets is one viable avenue for understanding the public health impact of comorbid cognitive impairment. This project used data from the National Alzheimer Coordinating Center (NACC) to 1) examine the longitudinal association of cognition status with clinician-rated depression and symptom self-report, controlling for demographic, contextual, and medical confounders; and 2) examine the prospective development of depression by cognition status, using the subsample of patients not meeting clinician-rated depression at the index visit (and controlling for the same potential confounders).

METHODS

Setting

Since 2005, the NACC has maintained the Uniform Data Set (UDS) containing standardized clinical, cognition, and diagnostic data on all subjects in the National Institute on Aging Alzheimer Disease Centers. Centers acquire subjects in various ways, including referral from clinicians, self-referral, referrals from concerned family members, active recruitment through community organizations, and volunteers who wish to contribute to dementia research. Most centers also enroll volunteer control subjects through similar mechanisms. Written, informed consent is obtained from subjects or their informants. Data are collected from subjects and self-designated informants by trained personnel using structured, standardized assessment instruments including a battery of neuropsychological tests.

Research using the NACC database has been approved by the University of Washington institutional review board.

At the time of this study, the sample included 27,776 subjects from the 34 past and present Alzheimer Disease Centers. Fifty-seven percent were women, and the mean age at index visit was 73.3 years (SD: 10.5). Eighty percent of the sample identified as White, and 13.9% identified as Black, with 7.8% of participants reporting Hispanic descent. The database spans from September 2005 (start of the UDS) through March 2013 (time of the NACC data freeze).

Measures

Dementia diagnoses are made by a consensus team or the physician conducting the examination using the results of a structured clinical history and clinical dementia rating form.[18–20] Mild cognitive impairment (MCI) classification initially required an amnestic component but was revised to include other cognitive domains and did not require memory impairment.[18] Depression diagnosis within the preceding 2 years was assessed by clinician diagnosis from a structured clinical history based on subject/informant report, medical records, and/or observation. The clinical diagnosis of depression includes depressive disorders for which a clinician was consulted, whether or not treatment (behavioral or drug) was received. Depression includes major depressive disorder, situational depression, bipolar disorders, dysthymic disorders, and other mood disorders. Assessment can include *Diagnostic Statistical Manual diagnoses*, chart reviews, clinicians' opinion, or whether the subject is taking a selective serotonin reuptake inhibitor for a depressive/mood disorder. Current depressive symptoms were assessed using the Geriatric Depression Scale Short Form (GDS-SF)[21] administered at intake and annual follow-up evaluations. Antidepressant medication (ADM) use was obtained using a medication inventory form that recorded all medications taken. Specific dose and duration of use data were not available. Functional independence was determined with the use of a categorical variable in the standardized clinical assessment with response choices of: independent, needing assistance with complex tasks, needing assistance with basic tasks, or dependent.

Statistical Analyses

Subject characteristics were examined via descriptive statistics by cognition status (i.e., normal cognition, mild cognitive impairment, dementia). Differences between cognition groups at the index visit were assessed using one-way analysis of variance for continuous outcomes and χ^2 tests of independence for categorical variables. Primary analyses focused on associations of cognition status with depression outcomes, including clinician-rated depression in the past 2 years and subject-reported depressive symptoms. Logistic regression was used for the binary outcome of clinician-rated depression, whereas negative binomial regression[22] was used for the GDS because it is bounded at zero and strongly skewed in the present sample. An initial model included demographic characteristics only (age, sex, and education), and a second model included a variety of potential confounding variables (current living situation, level of independence, residence, history of heart attack, history of congestive heart failure, history of stroke, current hypertension, and current diabetes).

Both of the regressions examine the cross-time association of cognition status with depression, controlling for potential confounders. To examine the prospective association of cognition status with depression, regressions examined the subsample of individuals who were not classified as depressed (based on clinician report) at the index visit. Although we considered time-to-event regression models, depression status varies over time, and hence similar regression models (i.e., either logit or negative binomial) to those used for previous analyses were used here. The primary interest in this model centered on the interaction between cognition status (MCI, dementia, or normal cognition) and time since index visit to determine whether depression was more likely to develop over time among those with MCI or dementia who were not depressed at the index visit. We also conducted an analysis with people meeting clinical criteria for depression at index to examine whether cognitive status (dementia, MCI, or normal cognition) predicted increased severity of depression as measured by GDS scores, adjusting for the same confounders as outlined above.

All regression models used cluster-adjusted standard errors to control for the within-person correlation due to repeated measures.[23] Use of ADM and participant death were considered in sensitivity analyses. All tests used a two-tailed significance of p less than 0.05, and all analyses were done using R v3.0.1.[24]

RESULTS

Table 1 presents descriptive statistics on study variables at the index visit by cognition status at the index visit. Relative to subjects with normal cognition, those with dementia or MCI were more likely to be women, were somewhat older, had somewhat less educational attainment, and were less likely to live alone. As expected, there were strong differences between groups in their functional independence, with dementia patients much more likely to need some assistance, and virtually all normal cognition patients falling into the fully independent category. Patients with MCI were generally independent. On physical health background characteristics, differences among groups were not as dramatic, with relatively similar prevalence of cardiovascular disease and diabetes. Finally, at the index visit, patients with dementia or MCI were more than twice as likely to have a clinician-rated diagnosis of depression, as well as higher levels of current depressive symptomatology.

Table 2 contains results from logistic and negative binomial regressions for clinician-rated depression and depressive symptoms, respectively. Controlling for basic demographic characteristics, there is a strong association of both dementia and MCI with clinician-rated depression and depressive symptoms as reported by the GDS. Although the association is somewhat attenuated after including additional covariates, results still suggest a strong, contemporaneous relationship between cognition status and depression, with both dementia and MCI patients approximately 2.5 times more likely to have depression. We conducted an additional analysis of persons with a clinical diagnosis of depression at baseline only to examine whether cognition status is associated with increased depression severity as measured by the GDS. We found that, relative to normal controls, both MCI (relative risk [RR]: 1.34, 95% confidence interval [CI]: 1.27, 1.40) and dementia (RR: 1.14, 95% CI: 1.08, 1.21) report significantly more depressive symptoms.

The preceding analyses suggest a strong association between concurrent cognitive impairment and depression over time; however, the descriptive data in Table 1 suggested that dementia and MCI patients were more likely to have depression at the index visit. Thus, a final analysis examined a prospective association, by selecting the subset of individuals who did not have clinician-rated depression at the index visit (normal cognition: N = 8,352; dementia: N = 5,880; MCI: N = 4,610). Analysis of clinician-rated depression included all previous covariates and as well as interaction terms between time since index visit and cognition status. Because there was evidence of nonlinear trends, a quadratic term for time was included.

All time and cognition status × time interaction terms were significant (all $p < 0.001$). Due to the interactions and nonlinear terms for time, predicted regression lines are presented in Figure 1 (with other covariates set to reference values). By definition, all patients in this subsample begin without depression, but there are fairly dramatic differences in proportion of patients with depression by cognition status that begin within the first year or two of follow-up and become more dramatic over time. At 2 years post index visit, 10% of patients with normal cognition are predicted to have developed depression, whereas 22% of MCI patients and 25% of dementia patients have developed depression. By 4 years post index visit, these have increased to 20% (normal cognition patients), 38% (MCI patients), and 43% (dementia patients). A similar set of analyses focused on depression symptoms as measured by the GDS-SF did not reveal a similar pattern; instead, there was a notable main effect of higher depression symptoms in MCI and dementia relative to normal cognition, but depression severity did not increase over time.

Results thus far suggest a strong association over time, as well as a prospective association between cognition status and future depression. Two additional confounds were considered in sensitivity analyses, however. First, there could be differential use of ADM, where underprescribing of ADM to MCI and dementia patients may explain their higher depression rates. This does not appear to be the case, however, as dementia patients are the most likely to report ADM use in subpopulations rated as being depressed ($M_{Dementia} = .69$, $M_{MCI} = .59$, $M_{Normal\ Cognition}$ .59) and among those rated as not being depressed ($M_{Dementia} = .23$, $M_{MCI} = .10$, $M_{Normal\ Cognition}$ .07). Regression analyses controlling for ADM yielded substantively identical conclusions to those presented earlier. Finally, the proportion of dementia patients who died during the study (3,082 of 10,486, 29.4%) was higher than the proportion for MCI (756 of 7,096, 10.7%) or normal cognition patients (740 of 10,194, 7.3%). Regression analyses stratified by death status revealed that the association of depression and cognition status was very similar within patients who died during study follow-up and those who did not. The only notable difference was that patients with normal cognition who died at some point during follow-up were somewhat more likely to have become depressed than those normal cognition patients who did not die during follow-up (see Fig. 2).

DISCUSSION

The results of this large and well-characterized sample, which includes patients with normal cognition, MCI, and dementia, present robust evidence that cognitive impairment is

associated with significantly higher rates of depression. Prior research found no association of cognitive impairment with severe depression in a smaller sample with less–well-characterized dementia status,[25] and some work using only the Mini-Mental State Exam (MMSE) and GDS found increased odds of depression in those with MMSE scores below 24.[26] Although results are strongest using the clinician-rated depression variable, our finding is supported by significantly higher current depression on the GDS-SF. The finding of increased development of depression in subjects without depression at index suggests that the increased risk of depression in cognitively impaired subjects is not entirely due to continued presence of previous depression. The results of analyses of subjects with clinical diagnosis of depression at the index visit also suggest that the severity of depression over time is worse in subjects with MCI or dementia. Antidepressant use does not confound these results.

The results suggest that from a public health standpoint, it is important to consider depression not only as a predictor of dementia as established in prior research, but as a comorbid condition that will develop during the course of dementia—because the results demonstrate significantly higher rates of depression in cognitively impaired subjects who were not depressed at intake. Thus, community-based interventions for treatment of dementia will need to be prepared to address depression[27] and may need to include high levels of collaboration between nurse managers and physicians in order to significantly improve depressive symtpoms.[28] Zlatar and colleagues have made a similar recommendation around the importance of considering depression when evaluating subjects with subjective complaints of cognitive impairment who demonstrate normal cognitive testing.[29] Conversely, evidence-based approaches for treatment of depression in older adults will need to accommodate treatment of subjects with dementia-severity cognitive impairment. Currently, most community- and clinic-based geriatric depression effectiveness trials exclude subjects with significant cognitive impairment. Also, other factors such as race/ethnicity, education, income, language, acculturation, and family and community support need to be considered when examining the recognition and treatment of depression in diverse elders with cognitive impairment.[30]

The continued association of depression and cognitive impairment after the development of MCI or dementia supports a possible common patho-physiological pathway of the conditions. Stress theory models suggest that exposure to significant stress increases corticotropin releasing factor and that impaired hypothalamic-pituitary-adrenal axis inhibitory feedback leads to elevated glucocorticoids, which are associated with smaller hippocampal volumes, depressive features, and dementia.[31,32] Similarly, research on inflammation models of the illnesses find increased inflammatory markers of interleukin and c-reactive proteins in depression and a role for inflammatory disease processes in Alzheimer and vascular dementia pathophysiology.[33] Heterogeneity of types of depression, combined with increased recognition of heterogeneity of types of Alzheimer dementia as well as other dementia, help explain the lack of consistent findings across studies of pathophysiology or treatment trials.[33,34]

This complicates translation of effective treatments to these disease models. Several papers have looked at the prevalence and/or incidence of depression in persons with cognitive

impairment. Lyketsos and colleagues[35] examined the prevalence of depression in persons with dementia and with mild cognitive impairment (N = 682). Depression was defined using the Neuropsychiatric Inventory[36] and 32% and 20% of persons with dementia or MCI, respectively, reported depressive symptoms. These rates are higher than our prevalence of depressive symptoms (as defined by the GDS-SF) of 17% and 14% for persons with dementia or MCI, and lower than our reported depression prevalence using a clinical diagnosis (43% for dementia and 35% for MCI). Our study differs from the Lyketsos paper as it includes a significantly larger sample (N = 27,776) of both persons with and without cognitive¼impairment. We also include information drawn from clinical depression diagnoses in addition to a depression scale instrument and are able to report rates of the development (incidence) of depression in those without depression at intake. Because the GDS scoring is responsive to change over time, we are able to analyze change in depression severity over time as well.

Peters[37] reported prevalence of depressive symptoms data for persons with dementia; with cognitive impairment, no dementia (CIND); and with normal cognition using data from the Cache County Study (N = 5,092). Their reported prevalence of depressive symptoms was comparable to ours for persons with normal cognitive function (4.9% in their study versus 5.0% for our study) and for persons with CIND/MCI (16.9% versus 14.0%), and were higher for persons with dementia (29.9% versus 17%). As with the Lyketsos paper, this study was cross-sectional and used the Neuropsychiatric Inventory and therefore was not able to comment on incident depression in persons with and without cognitive impairment, or on the change in depression severity over time. Lastly, Panza and colleagues[38] conducted a review of studies that compared the prevalence and incidence of depression for persons with MCI only. Most of the reported studies were cross-sectional and/or had a small sample size, and, as defined by their review criteria, none of the papers included persons with normal cognitive function or with dementia. They found a range of prevalence rates for depressive symptoms (4%–69%) largely due to the inconsistencies in how depression is assessed and MCI is defined. Other recent papers such as Reinlieb and colleagues[39] found elevated rates of depressive symptoms for persons with MCI as well compared with those without cognitive impairment. Two papers included in Panza et al.'s review[38] described incident depression, reporting rates of 29.6/100 person-years for the one population-based study and 11.7/100 person years for the one hospital-based study. We conducted a post hoc analysis to estimate our incident rates of depression per 100 person-years and found rates of 4.4/100 person-years for persons with normal cognition, 8.3/100 person-years for persons with MCI, and 11.1/100 person-years for persons with dementia, suggesting lower rates than the two studies described in the Panza review for persons with MCI. It should be noted that our definition of depression/depressive symptoms and our control group are different than those reported in the review by Panza and colleagues.

There are several limitations to this study. Although the GDS-SF is a valid, established, screening instrument, it is not a diagnostic instrument and so the GDSSF findings here should not be interpreted as specific to major depression. We do, however, include information about depression as defined by a clinical diagnosis as well and indicate where the data are consistent and where they differ. The clinical diagnosis was made using a standardized comprehensive history that included other items that may contribute to

depressive symptoms, such as past history of bipolar disorder; medications such as beta-blockers for congestive heart failure or hypertension; and anemia, hypothyroidism, or other medical illnesses. In addition, we adjusted for many of these possible cofounders in our analysis. Dosages and durations of ADM were not available in the UDS and so it is uncertain whether differences in the adequacy of treatment contributed to increased rates of depression in patients with cognitive impairment. Further research is warranted to study the impact of appropriately prescribed and managed ADM in persons with and without cognitive impairment.

Despite these limitations, these results consistently show increased rates of depression in patients with dementia and mild cognitive impairment at cross-sectional intake evaluations and over longitudinal follow-ups, including analysis of incident depression. The results suggest that beyond being a predictor or prodromal condition, depression is an important comorbid chronic condition in patients with dementia and mild cognitive impairment.

Acknowledgments

The NACC database is funded by NIA grant U01 AG016976. This research was funded by the Centers for Disease Control and Prevention's (CDC's) Healthy Aging Program through the CDC Prevention Research Centers Program, Special Interest Project grant (U48-DP000050) to the University of Washington Health Promotion Research Center. The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the CDC.

References

1. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. Lancet Neurol. 2007; 6:1106–1114. [PubMed: 18031707]
2. Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. Arch Neurol. 2009; 66:1210–1215. [PubMed: 19822776]
3. Vogeli C, Shields AE, Lee TA, et al. Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs. J Gen Intern Med. 2007; 22(suppl 3):391–395. [PubMed: 18026807]
4. Wolff JL, Starfield B, Anderson GF. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med. 2002; 162:2269–2276. [PubMed: 12418941]
5. Lee TA, Shields AE, Vogeli C, et al. Mortality rate in veterans with multiple chronic conditions. J Gen Intern Med. 2007; 22(suppl 3):403–407. [PubMed: 18026809]
6. Thorpe KE, Ogden LL, Galactionova K. Chronic conditions account for rise in Medicare spending from 1987 to 2006. Health Aff (Millwood). 2010; 29:718–724. [PubMed: 20167626]
7. Coleman SM, Katon W, Lin E, et al. Depression and death in diabetes; 10-year follow-up of all-cause and cause-specific mortality in a diabetic cohort. Psychosomatics. 2013; 54:428–436. [PubMed: 23756124]
8. Vasiliadis HM, Dionne PA, Préville M, et al. The excess healthcare costs associated with depression and anxiety in elderly living in the community. Am J Geriatr Psychiatry. 2013; 21:536–548. [PubMed: 23567409]
9. Husaini B, Levine R, Sharp L, et al. Depression increases stroke hospitalization cost: an analysis of 17,010 stroke patients in 2008 by race and gender. Stroke Res Treat. 2013; 2013:846732. [PubMed: 23555070]
10. Murray CJ, Abraham J, Ali MK, et al. on behalf of the US Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. JAMA. 2013; 310:591–608. [PubMed: 23842577]
11. Jorm AF. History of depression as a risk factor for dementia: an updated review. Aust NZ J Psychiatry. 2001; 35:776–781.

12. Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. Gerontology. 2000; 46:219–227. [PubMed: 10859462]
13. Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and meta-regression analysis. Arch Gen Psychiatry. 2006; 63:530–538. [PubMed: 16651510]
14. Sullivan MD, Katon WJ, Lovato LC, et al. Association of depression with accelerated cognitive decline among patients with type 2 diabetes in the ACCORD–MIND trial. JAMA Psychiatry. 2013; 70:1041–1047. [PubMed: 23945905]
15. U.S. Department of Health and Human Services. Multiple Chronic Conditions—A Strategic Framework: Optimum Health and Quality of Life for Individuals with Multiple Chronic Conditions. Washington, DC: Dec. 2010 (online). Available at: http://www.hhs.gov/ash/initiatives/mcc/mcc_framework.pdf. [November 1, 2013]
16. Centers for Disease Control and Prevention and the Alzheimer's Association. [November 1, 2013] The Healthy Brain Initiative: A National Public Health Road Map to Maintaining Cognitive Health. 2007. (online). Available at: www.cdc.gov/aging and www.alz.org.
17. Hendrie HC, Albert MS, Butters MA, et al. The NIH Cognitive and Emotional Health Project. Report of the critical evaluation study committee. Alzheimers Dement. 2006; 2:12–32. [PubMed: 19595852]
18. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006; 20:210–216. [PubMed: 17132964]
19. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. Alzheimer Dis Assoc Disord. 2007; 21:249–258. [PubMed: 17804958]
20. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. Alzheimer Dis Assoc Disord. 2009; 23:91–101. [PubMed: 19474567]
21. Sheikh, JI.; Yesavage, JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. In: Brink, TL., editor. Clinical Gerontology: A Guide to Assessment and Intervention. Edited. The Haworth Press; New York, NY: 1986. p. 165-173.
22. Hilbe, JM. Negative Binomial Regression. Cambridge University Press; New York, NY: 2011.
23. Andrews DWK. Heteroskedasticity and autocorrelation consistent covariance matrix estimation. Econometrica. 1991; 59:817–858.
24. R Core Team. [September 19, 2014] R: A language and environment for statistical computing. 2013. (online). Available at: www.R-project.org.
25. Janzing J, Teunisse R, Bouwens P, et al. The course of depression in elderly subjects with and without dementia. J Affect Disord. 2000; 57:49–54. [PubMed: 10708815]
26. Wang JK, Su TP, Chou P. Sex differences in prevalence and risk indicators of geriatric depression: the Shih-Pai community-based survey. J Formos Med Assoc. 2010; 109:345–353. [PubMed: 20497867]
27. Callahan CM, Boustani MA, Unverzagt FW, et al. Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial. JAMA. 2006; 295:2148–2157. [PubMed: 16684985]
28. Samus QM, Johnston D, Black BS, et al. A multidimensional home-based care coordination intervention for elders with memory disorders: the Maximizing Independence at Home (MIND) pilot randomized trial. Am J Geriatr Psychiatry. 2014; 22:398–414. [PubMed: 24502822]
29. Zlatar ZZ, Moore RC, Palmer BW, et al. Cognitive complaints correlate with depression rather than concurrent objective cognitive impairment in the Successful Aging evaluation baseline sample. J Geriatr Psychiatry Neurol. 2014; 27:181–187. [PubMed: 24614203]
30. Chao SZ, Matthews BR, Yokoyama JS, et al. Depressive symptoms in Chinese-American subjects with cognitive impairment. Am J Geriatr Psychiatry. 2014; 22:642–652. [PubMed: 24021225]
31. Raadsheer FC, Hoogendijk WJ, Stam FC, et al. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology. 1994; 60:436–444. [PubMed: 7824085]

32. Palazidou E. The neurobiology of depression. Br Med Bull. 2012; 101:127–145. [PubMed: 22334281]
33. Hermida AP, McDonald WM, Steenland K, et al. The association between late-life depression, mild cognitive impairment and dementia: is inflammation the missing link? Expert Rev Neurother. 2012; 12:1339–1350. [PubMed: 23234395]
34. Craft S, Cholerton B, Baker LD. Insulin and Alzheimer's disease: untangling the web. J Alzheimers Dis. 2013; 33(suppl 1):S263eS275. [PubMed: 22936011]
35. Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA. 2002; 288:1475–1483. [PubMed: 12243634]
36. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44:2308–2314. [PubMed: 7991117]
37. Peters ME, Rosenberg P, Steinberg M, et al. Prevalence of neuropsychiatric symptoms in CIND and its subtypes: the Cache County Study. Am J Geriatr Psychiatry. 2012; 20:416–424. [PubMed: 22522960]
38. 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]
39. Reinlieb M, Ercoli LM, Siddarth P, et al. The patterns of cognitive and functional impairment in amnestic and non-amnestic mild cognitive impairment in geriatric depression. [Epub ahead of print Nov 5, 2013]. Am J Geriatr Psychiatry.

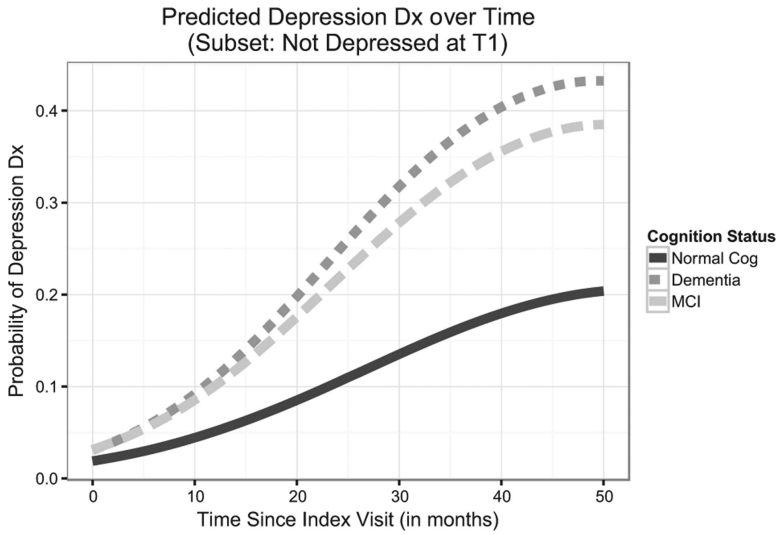

FIGURE 1.

Predicted depression diagnosis over time.

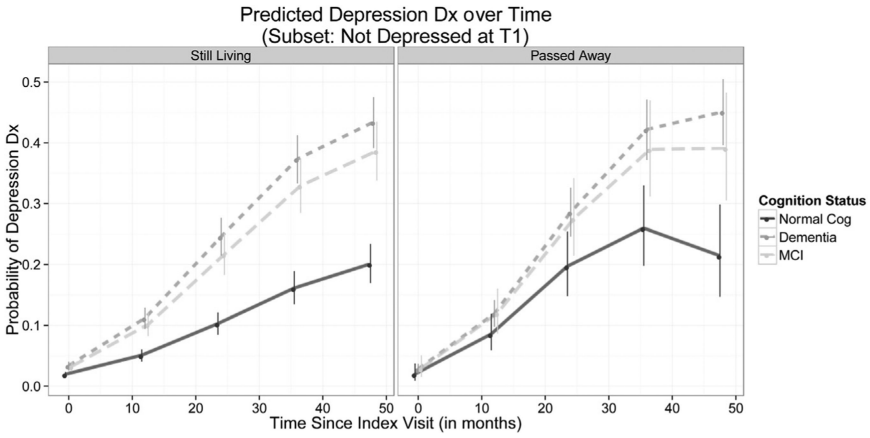

FIGURE 2.

Predicted depression diagnosis over time, by mortality.

TABLE 1

Baseline Characteristics of the NACC Sample (N = 27,776)

	N (%) of Participants			
	Normal Cognition N = 10,194	**Dementia N = 10,486**	**MCI N = 7,096**	**χ^2; df; p Value**
Age, y	72.4	75.7	74.3	433.46; 2; p <0.001
Women	6,654 (65)	5,533 (53)	3,691 (52)	F = 136.74; 2,2773; p <0.001
Race				131.6; 4; p < 0.001
White	8,292 (81)	8,622 (82)	5,526 (78)	
Black	1,511 (15)	1,237 (12)	1,110 (16)	
Other	386 (4)	619 (6)	449 (6)	
Hispanic	613 (6)	919 (9)	625 (9)	69.3; 2; p <0.001
Education				825.5; 8; p <0.001
Less than HS	504 (5)	1,449 (14)	702 (10)	
HS graduate	3,582 (35)	4,384 (42)	2,715 (38)	
Bachelors	2,655 (26)	2,307 (22)	1,693 (24)	
Masters	2,394 (24)	1,429 (14)	1,285 (18)	
Doctorate	1,002 (10)	807 (8)	671 (9)	
Not live alone	6,766 (66)	9,039 (86)	5,162 (73)	1,136.92; 2; p <0.001
Function				1,4847.09; 8; p <0.001
Independent	9,848 (97)	1,929 (18)	5,460 (77)	
Help w/complex activities	241 (2)	4,706 (45)	1,391 (20)	
Help w/basic activities	83 (1)	2,566 (24)	192 (3)	
Dependent	10 (0)	1,213 (12)	25 (0)	
Depression				
GDS-SF > 5	524 (5)	1,455 (17)	981 (14)	628.38; 2; p <0.001
Clinician-rated diagnosis	1,801 (18)	4,474 (43)	2,430 (35)	1,575.98; 2; p <0.001
Heart attack/cardiac arrest				34.68; 4; p <0.001
None	9,650 (95)	9,748 (93)	6,593 (93)	
Recent	95 (1)	119 (1)	72 (1)	
Remote	415 (4)	572 (5)	411 (6)	
CHF				16.37; 4; p = 0.003
None	9934 (98)	10,125 (97)	6,880 (97)	
Recent	179 (2)	229 (2)	150 (2)	
Remote	56 (1)	99 (1)	54 (1)	
Stroke				171.62; 4; p <0.001
None	9,878 (97)	9,701 (93)	6,658 (94)	
Recent	78 (1)	185 (2)	96 (1)	
Remote	218 (2)	527 (5)	305 (4)	
Hypertension				115.46; 4; p <0.001
None	5,075 (50)	4,998 (48)	3,062 (43)	
Recent	4,825 (48)	5,013 (48)	3,768 (53)	
Remote	257 (3)	439 (4)	235 (3)	

	N (%) of Participants			
	Normal Cognition N = 10,194	**Dementia N = 10,486**	**MCI N = 7,096**	**χ^2; df; p Value**
Diabetes				75.32; 4; p <0.001
None	8,984 (88)	9,108 (87)	5,952 (84)	
Recent	1,135 (11)	1,255 (12)	1,054 (15)	
Remote	40 (0)	80 (1)	61 (1)	

Notes: MCI: mild cognitive impairment; df: degrees of freedom; HS: high school; w/: with; GDS-SF: Geriatric Depression Scale-Short Form; CHF: congestive heart failure.

TABLE 2

Regressions for Clinician-Rated Depression and Depressive Symptoms

	Model with Demographics		Model with All Covariates	
	Dementia	**MCI**	**Dementia**	**MCI**
Depression diagnosis[a] OR (95% CI)	4.10 (3.85-4.37)	2.69 (2.52-2.87)	2.64 (2.43-2.86)	2.40 (2.25-2.56)
Depressive symptoms[b] RR (95% CI)	1.95 (1.88-2.01)	1.81 (1.76-1.88)	1.60 (1.53-1.68)	1.71 (1.65-1.77)

Notes: MCI: mild cognitive impairment; OR: Odds Ratio; CI: confidence interval; RR: Relative Risk.

[a] Clinician-rated depression was defined by a standardized assessment of a clinical diagnosis of depression within the prior 2 years.

[b] Depressive symptoms were defined by a Geriatric Depression Scale-Short Form score greater than 5.