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Late-Life Depression as a Risk Factor for Mild Cognitive Impairment or Alzheimer's Disease in 30 US Alzheimer's Disease Centers

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Abstract

Identification of potentially modifiable risk factors for cognitive deterioration is important. We conducted a prospective study of 5,607 subjects with normal cognition and 2,500 subjects with mild cognitive impairment (MCI) at 30 Alzheimer's Disease Centers in the Unites States between 2005 and 2011. Cox regression was used to determine whether depression predicted transition from normal to MCI, or MCI to Alzheimer's disease (AD). Over an average of 3.3 visits, 15% of normal subjects transitioned to MCI (62/1000 per year), while 38% of MCI subjects transitioned to AD (146/1000 per year). At baseline, 22% of participants had recent (within the last two years) depression defined by clinician judgment; 9% and 17% were depressed using the Geriatric Depression Scale (GDS score ≥5) and the Neuropsychiatric Inventory Questionnaire (NPI-Q), respectively. At baseline, depressed subjects performed significantly worse on cognitive tests. Those always depressed throughout follow-up had an increased risk for progression from normal to MCI (RR = 2.35; 95% CI 1.93–3.08) versus never depressed. Normal subjects, identified as depressed at first visit but subsequently improved, were found to have an increased but lower risk of progression (RR = 1.40 (1.01–1.95)). The 'always depressed' had only a modest increased risk of progression from MCI to AD (RR = 1.21 (1.00–1.46). Results were similar using time-dependent variables for depression or when defining depression via the GDS or NPI-Q. We found no effect of earlier depression (>2 years past). The effect of recent depression did not differ by antidepressant treatment, APOE4 allele status, or type of MCI. In conclusion, late-life depression is a strong risk factor for normal subjects progressing to MCI.

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Keywords

Alzheimer's disease; dementia; depression; mild cognitive impairment

INTRODUCTION

There is great interest in identifying modifiable risk factors for Alzheimer's disease (AD) that could reduce the burden of the disease. Some models suggest that 10–25% of AD cases could be prevented with the elimination of specific risk factors, although these models assume that the risk factors are well established and of necessity make broad assumptions about their estimated prevalence [1]. Depression is often cited as a common and treatable condition [2]. Depression prevalence in the United States has been estimated at 11% in the elderly [3], with a lifetime prevalence of major depressive episode of 19% [4]. Barnes and Yaffe [1] calculated that ~10% AD cases are potentially attributable to depression.

Depression has been frequently associated with dementia (most of which is AD) and mild cognitive impairment (MCI), a prodromal condition that frequently leads to AD, yet the role of depression as a risk factor for dementia or AD is controversial. Differentiation between cause and effect is particularly challenging since depression can be a symptom of AD. In light of uncertainty about temporal sequence, it is important to study whether depression is a risk factor for the progression from normal cognitive status to MCI, versus the progression from MCI to dementia.

An earlier 2006 meta-analysis found that a history of depression increased risk 2-fold for subsequent dementia, without discussion of MCI [5]. This meta-analysis included case-control studies, with retrospective ascertainment of depression. There have been a number of studies since 2006, and a more recent review focusing on prospective studies concluded that the existing literature is inconsistent regarding the role of depression in increasing the risk of progression from normal cognition to MCI, or from MCI to dementia [2]. There are nine longitudinal studies of depression and progression from normal to MCI [6–14], of which six show a sig-nificant positive association. There are another eleven longitudinal studies of depression and progression to dementia [15–25], of which six had significant positive findings.

The conflicting results may in part be due to varying definitions of depression, MCI, and dementia. Furthermore, adjustment for baseline cognitive stratus, co-morbidities, the timing of depression (early versus late-life), and the taking of antidepressant medication, all of which could confound or potentially modify the effect of depression, was uncommon. For example, baseline cognitive status might act as a confounder of the association between depression and outcomes, because depressed subjects have worse cognitive function [26–28], which is associated with a greater risk of MCI and/or dementia. Finally, many studies relied on baseline depression only, without consideration as to whether depression or antidepressants medication may have occurred later during follow-up. For these and other reasons, a recent National Institute of Health consensus statement by a panel-of-experts, who reviewed depression and cognitive decline, noted that "the overall scientific quality of the evidence is low" [29].

To address many of these issues we employed the large National Alzheimer's Coordinating Center (NACC) database, called the Uniform Data Set (UDS). The UDS consists of standardized, longitudinal data obtained by annual comprehensive evaluations of thousands of subjects at the 30 National Institute on Aging-funded Alzheimer's Disease Centers (ADCs), as described in detail elsewhere [30].

We analyzed separately the role of depression in the progression from either normal cognition to MCI, or from MCI to AD, while adjusting for baseline cognitive status. We considered depression defined as either clinician-reported, or via the Geriatric Depression Score (GDS-15) or the Neuropsychiatric Inventory Questionnaire (NPI-Q). We analyzed 1) the relative contribution of late-life versus earlier depression; 2) the possible modifying role of antidepressants; and 3) the possible modifying role of APOE status. We hypothesized that late-life depression would increase the risk of transition from normal to MCI, and from MCI to AD, while earlier episodes of depression would have little effect.

METHODS

The NACC database includes data collected annually across 30 US ADCs. There are 174 data items collected for live subjects. Data include 1) subject demographics, 2) informant data, 3) family history, 4) medications, 5) health history, 6) physical exam, 7) Hachinski score and cerebrovascular disease evaluation, 8) United Parkinson's Disease Rating Scale, 9) global Clinical Dementia Rating (CDR), 10) NPI-Q, 11) Functional Assessment Questionnaire, 12) neurologic findings, 13) clinical symptoms, 14) neu-ropsychological battery, 15) clinical diagnosis, and 16) imaging and lab data (not available for everyone). Subject recruitment is done by each ADC, but typically includes the neurology clinic patients and interested volunteers with normal cognition.

Each ADC has its own IRB clearances for data collection. We were provided with de-identified already collected data by NACC, which was exempt from Emory IRB review.

NACC's definition of MCI and AD can be found on Form D1 (Clinician Diagnosis) in the NACC UDS Coding Guidebook (http://www.alz.washington.edu/NONMEMBER/UDS/DOCS/VER2/ivpguide.pdf, last accessed 9 March 2012), which provides a description of the process each Center is required to use to define normal cognition, dementia, MCI, and AD. If the subject does not have normal cognition and does not have dementia, then MCI is defined by the presence of cognitive complaint not normal for age, cognitive decline, and essentially normal functional activities. Amnestic MCI is defined by memory impairment, either as single domain or multiple domain. Non-amnestic MCI single or multiple domain is similarly determined. AD is defined in the NACC UDS using NINCDS/ADRDA criteria, including "dementia established by clinical examination and documented by the Mini-Mental Test or some similar examination and confirmed by neuropsychological tests; deficits in two or more areas of cognition; progressive worsening of memory and other cognitive functions; no disturbance of consciousness; onset between ages 40 and 90, most often after age 65; and absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficit in memory and cognition".

The population studied included all subjects with at least two visits who were considered to have either normal cognition (n = 5,845) or MCI (n = 3010) at baseline. Subjects were seen during the period September 2005 through January 2011.

Initial analyses evaluated cognitive tests for the depressed versus non-depressed at first visit (baseline) using linear regression, separately for subjects normal and MCI at first visit. We considered ten cognitive tests and assessment scales (Trails A and B, Digits Forward and Backward, WAIS digit-symbol, Logical Memory (recall), Boston Naming, Mini-mental status examination (MMSE), CDR sum of boxes, and category fluency (animals + vegetables). We used linear regression (SAS, PROC GLM; SAS v9.2, Cary, NC) to adjust for potential confounders. We log-transformed Trails A and B which gave them a normal distribution; however, results with transformed and untransformed outcomes were similar, and we report results for the untransformed variables only. All models adjusted for the

following variables at first visit: age, gender, race, education (high school or less), self-reported history of hypertension, of diabetes, and of heart disease (defined as any of following forms of cardiovascular disease, including heart attack, atrial fibrillation, angioplasty/endarterectomy/stent, cardiac bypass procedure, pacemaker, congestive heart failure).

Depression in all analyses, unless otherwise spec-ified, was defined for any given visit as either (1) depression within the last two years as determined by clinical judgment, taken from the subject health history (UDS Form A5, question 6), or (2) as clinician-reported depression at time of visit following DSM-IV guidelines, from the clinical diagnosis (Form D1, question 20). The subject health history (Form A5) is completed by a "clinician, based on subject/informant report, medical records, and/or observation" using the clinician's best judgment. Question 6 documents depression as "no", "yes", and "unknown", with instructions to "include 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, and other mood disorders. Assessment can include DSM diagnoses, chart reviews, clinicians' opinion, or whether the subject is taking an SSRI for a depressive/mood disorder". Question 6a was used to determine if depression was active within the past 2 years. In sum, this definition of "clinically defined" recent depression is broadly based on DSM criteria, as that is typical training for the clinicians.

We used 'depression' defined in this manner as our key variable, signifying current or recent depression. We further categorized (current/recent) depression into four mutually exclusive groups based on the pattern of depression across visits, as (1)'always depressed' across all visits; (2) 'initially depressed' but then getting better (non-depressed); (3) 'intermittently depressed' across visits; and (4) 'never depressed' across all visits. The 'never-depressed' were used as the referent group in calculating rate ratios. The number of subjects in these four categories can be found in Table 1.

'Past depression' in our analyses was based on question 6b (Form A5) in the UDS subject health history, in which the presence of 'other episodes (prior to 2 years)' was noted. Past and current/recent depression were not mutually exclusive.

Our principal analyses focused on the risk of the depressed versus non-depressed to progress to a worse diagnosis. These analyses were conducted via survival analysis using Cox regression models, using the SAS procedure PHREG (SAS v9.2, Cary, NC). Missing values for covariates were imputed (see below). For the Cox analysis of transition from normal to MCI, we excluded 238 persons whose status went from normal to MCI and back again, because we could not easily classify their outcome. Analogously, for the analyses of the transition from MCI to AD, we excluded any subjects whose cognitive status improved to normal at any point ($n = 510$), as it was not clear if they how their status at baseline should be classified. In sensitivity analyses, we later included these subjects; results were similar and we only report here the analyses excluding these two subgroups.

Two separate Cox models were run for 1) subjects classified as normal at first visit ($n =$ 5,607) who could progress to a worse state defined as either impaired/not MCI ($n = 211$), MCI ($n = 508$), or dementia ($n = 164$), and 2) for MCI subjects at first visit ($n = 2,500$) who might transition to dementia ($n = 974$). Of those transitioning to dementia, 868 (87%) had either probable or possible AD; non-AD dementias were treated as censored in Cox analyses. Follow-up time in these analyses was time since first visit (in days).

Complete data for the variables included in the model were available for 86.2% of the subjects. The variables with the most missing data were the cognitive tests; 7.4%, 3.6%,

3.2%, 3.0%, and 1.4% were missing data for WAIS, logical memory, FAQ, category fluency, and MMSE, respectively. A multiple imputation procedure (SAS PROC MI, SAS Institute Inc., Raleigh, NC) was used to impute the values for the missing data, with separate imputations for those normal and MCI at first visit. An imputation model was created in which missing data were imputed based on observed values of all model covariates and the final outcome variable (progression to worse cognitive status). Using the imputation model results, Monte Carlo methods were used to create five separate data sets with different imputed values for missing data, and these five data sets were then combined together for our basic analysis of the risk of progression for depressed versus non-depressed (analytic model). Reported analytic model estimates and standard errors are adjusted to account for uncertainty in the imputed data using SAS PROC MIANALYZE (SAS Institute Inc.).

In sensitivity analyses, we also considered depression as a time-dependent variable, where the risk of transition for depressed versus non-depressed was evaluated at each time when any subject transitioned ("failed") to a worse state. We tested for but found no departures for the proportional hazards assumption for all depression variables, via interaction terms between follow-up time and depression.

In addition to determination of recent depression based on clinician judgment, in other analyses, we defined depression via the GDS Depression Scale (GDS ≥5) and NPI-Q. Analyses were conducted using the same variables for depression as described above.

APOE genotype status was available for 68% of subjects. We analyzed the effect of depression among those with or without the APOE4 allele. Because MCI subtypes may have different underlying pathologies [31], we also analyzed the conversion from normal to either amnestic or non-amnestic MCI (in the analyses for each one, subjects progressing to the other were excluded, as were subjects progressing to either impaired-not-MCI, or directly to dementia), as well as the conversion from either amnestic MCI or non-amnestic MCI to dementia (with a dichotomous variable for amnestic/non-amnestic included in the model, and an interaction term with depression).

We also included in all models (time-dependent) variables for antidepressant treatment. We evaluated interaction terms between antidepressant drug-taking and depression, seeking to discover if those treated had less risk of progression than those not treated. Medication data were collected by clinicians at each visit. Antidepressant drugs were classified into selective serotonin reuptake inhibitor (SSRI) antidepressants and other/non-specific mode of action antidepressants [32].

After including variables for depression and antide-pressants in our models, we included a set of covariates which were the same for models analyzing both progression to MCI/dementia and progression to AD. Variables for age, gender, race, and education (high school or less, greater than high school) were included *a priori*. We also controlled for baseline cognitive status because worse cognitive status increases the risk of progression, and because depressed subjects might have worse cognitive status than the non-depressed at baseline. We also considered a variable functional status using the Functional Assessment Questionnaire (FAQ). To determine which of these variables (10 cognitive tests as well as the FAQ) to include, we used backward selection with a $p = 0.05$ criterion for selection. This resulted in inclusion in our models of four cognitive tests (MMSE, logical memory, WAIS (digit symbol), category fluency), and the FAQ. We then added a set of other predictor variables including alcohol, smoking, family history, and co-morbidities, all as defined and collected within the UDS. These were included if significant (at the < 0.05 level) for either type of progression. Co-morbidities included stroke, transient ischemic attack, hypertension, diabetes, and cardiovascular disease (any of eight categories). Of these, cerebrovascular

disease and diabetes were sig-nificant predictors for progression and were included. Alcohol, smoking, and family history were not significant predictors of progression and were not included.

RESULTS

Table 1 displays descriptive statistics for the cohort at baseline. For normal and MCI subjects combined, the mean number of visits was 3.3, and the mean follow-up time was 2.6 years. Recent depression was present for 24% of subjects, while 15% had past depression, as defined in the methods. These two groups overlapped but were not completely concordant; 63% of those reporting past depression reported recent depression, while 40% of those reporting recent depression reported past depression. Individuals with MCI were twice as likely to have a recent history of depression as their normal cognition counterparts (35% versus 18%).

Table 1 also shows the numbers of ‘always depressed’ (depressed throughout follow-up), ‘initially depressed’ (depressed at first but later improving and staying depression-free throughout the remainder of follow-up), ‘intermittently depressed’ (back and forth status of depression during follow-up), and ‘never depressed’ (throughout follow-up). The percentage of those in each of these four groups taking antidepres-sant medication at baseline was 65%, 30%, 30%, and 5%, respectively.

Table 1 also shows the frequency of depression at baseline defined by scales; either via NPIQ or GDS. The GDS and NPIQ defined depression were not more common than ‘clinically-defined recent depression’.

Table 2 shows the cognitive performance at baseline for subjects with or without recent depression. For those with a diagnosis of ‘normal cognition’ at baseline, depressed subjects performed significantly worse on two global measures (MMSE, CDR sum of boxes), and four specific tests (Digits Forward, WAIS-R Digit Symbol, and Trails B). Among those diagnosed as having MCI at baseline, the depressed group performed significantly worse on one global test (CDR sum of boxes), and four tests requiring speeded responses (WAIS-R Digit Symbol, Trails A and B, and Category Fluency). It is notable that the two specific tests with the biggest performance difference between depressed and non-depressed individuals (Digit Symbol and Trails B) relate to executive function, specifically the ability to rapidly shift response sets.

Over the course of follow-up, 15% of individuals with normal cognition progressed to MCI, and 38% of individuals with MCI (42% for amnestic MCI, 26% for non-amnestic) progressed to AD.

The annual incidence rate for normal transitioning to either MCI or impaired-not-MCI was 62/1000; men had higher rates than women (72/1000 versus 57/1000). These figures replicate almost exactly another recent population based study by investigators at the Mayo clinic (64/1000 overall, 72/1000 in men, 57/1000 in women) [33]. However, if the impaired-not-MCI are excluded, our rate drops to 42/1000. The incidence rate for a transition from MCI to AD, for the 3010 individuals with MCI at baseline, was 146/1000 per year. This rate conforms broadly with other reports in the literature, but transition rates from MCI to AD vary widely depending on the definition of MCI [34].

In Cox models adjusting for other variables, depression considered as ‘always depressed’ during follow-up versus ‘never depressed’ during follow-up was associated with progression (RR = 2.35; 95% CI 1.86–2.96) for patients normal at baseline (Table 3). The RR was similar for those with intermittent depression (RR = 2.22, 1.86–2.65), but notably decreased

for those with initial depression only (i.e., depression was judged to be absent during all subsequent follow-up assessments) (RR = 1.41, 1.01–1.95), suggesting that improvement of depression substantially lowers risk of progression. Episodes of past depression did not increase risk of progression. MCI subjects at baseline who were depressed throughout follow-up had an increased rate of progression to AD, of borderline statistical significance (RR = 1.22, 1.00–1.46). No other depression variable (only present at first visit, intermittent, past episodes) showed any increased risk for progression from MCI to AD.

In a sensitivity analysis, we found similar but slightly stronger results with time-dependent recent depression.

We sought to determine whether those treated for depression had less risk of progression than those not treated, via examining interaction terms between medication (with either SSRI or other antidepressants) and a variable for ‘ever depressed during follow-up’, and considered the progression from either normal to MCI or from MCI to AD. No interactions between ‘ever-depressed’ and either class of drugs were close to statistical significance (p-values ranging from 0.18 to 0.81), indicating that drug treatment did not change the effect of depression on the risk of progression. We further subdivided normal subjects who were depressed at first visit but later were not depressed into those treated and not-treated with antidepressants; there was no difference in these two groups regarding their rate of progression to a worse diagnosis ($p = 0.90$). Table 4 shows the numbers of subjects taking different types of antidepressant medications.

Of the 2,127 subjects with clinician-determined recent depression at baseline, 45% were defined as depressed by the NPIQ criteria, while 28% were defined as depressed by the GDS criteria. An additional 667 without clinician-determined depression were defined as depressed by NPIQ or GDS (503 by NPIQ, 164 by GDS, 54 by both). We performed secondary analyses using (current) depression defined as either 1) GDS score ≥5, or 2) endorsed as depression present on the NPI-Q. Again, depression defined in these ways was divided between always depressed, depressed only at baseline, and intermittently depressed. Results for these analyses were similar to the results when defin-ing depression more broadly based on best clinical judgment. For GDS-defined depression, the rate ratios for a progression from normal to MCI for the always depressed, depressed only at baseline, and intermittently depressed were respectively 1.92 (1.36–2.73), 1.45 (0.99–2.11), and 1.73 (1.43–2.10). For depression defined by the NPI-Q, these respective rate ratios were 2.87 (2.10–3.91), 1.30 (0.98–1.74), and 1.75 (1.48–2.07). Analogous analyses were conducted for progression from MCI to AD; no rate ratios for progression were statistically significant using any variation of depression definition or occurrence, with rate ratios ranging from 0.88 to 1.24.

In analyses restricted to subjects with APOE data, the APOE4 variant increased risk of transition from normal to MCI (RR = 1.52, 95% CI 1.26–1.83), and also the risk of transition from MCI to dementia (RR = 1.68, 95% CI 1.44–1.96). We found no significant interactions between a variable for “ever depressed during follow-up” and APOE4 (p values = 0.54 for normal progressing to MCI, $p = 0.67$ for MCI progressing to AD), indicating that APOE4 status did not modify the effect of depression.

We conducted analyses to determine the effect of depression among normal subjects who progressed to amnestic versus non-amnestic MCI (excluding those who progressed to either impaired-not-MCI or directly to dementia). We found a similar strong effect among those always depressed during follow-up versus those never-depressed during follow-up on the progression of normals to both amnestic MCI (RR = 2.62 (1.83–3.80)) and non-amnestic MCI (RR = 2.34 (1.19–4.59)). Again, past depression had no effect.

Analogously, we examined the role of depression in the progression from either amnestic MCI or non-amnestic MCI to dementia. An interaction term between MCI subtype and depression ('ever depressed during follow-up) was not significant ($p = 0.30$), indicating no significant difference for the role of depression between the two MCI types in progression to dementia.

DISCUSSION

The major findings of this large, prospective study are that: 1) at baseline depression was associated with cognitive deficits in normal subjects as well as in individuals with MCI; 2) recent depression (within 2 years), but not past depression, was a strong risk factor for progression from normal to MCI, and a borderline-significant risk factor for progression from MCI to AD; 3) the risk of depression on disease progression from normal to MCI was most marked in those who were continually or intermittently depressed over follow-up, while those who were depressed at baseline but subsequently improved had less risk of progression; and 4) the risk of progression from normal to MCI during follow-up did not differ for those treated or not treated with antidepressants. These effects of depression on risk of progression to MCI or AD were seen using several different designations of depression, including clinician judgment, a depression screening instrument (GDS) and a neuropsychiatric symptom rating scale (NPI-Q).

The fact that the risk of progression for the depressed was greater for those subjects who were normal at baseline than MCI at baseline indicates that once the cognitive impairment is present, depression plays less of a role. This may be a reflection of the fact that some subset of MCI patients will inevitably progress to AD, regardless of other risk factors, or differences in cognitive reserve, co-existing conditions, and other possibilities.

The effect of depression was not different in the progression of normal to either amnestic MCI or non-amnestic MCI. If the relation between depression and subsequent progression is indeed causal, this suggests that depression is not affecting solely the memory domain among normal subjects. Likewise, the effect of depression did not change in the progression from amnestic MCI to AD, versus non-amnestic MCI to AD.

Our study is one of the few large prospective studies of the relationship between depression and the risk of both MCI and AD in the same research population, and has a number of strengths including adjustment for cognitive status at baseline, analysis of different definitions of depression, analysis of both recent and past depression, analyses of the effect of medication and APOE status, and the comparison of amnestic versus non-amnestic MCI.

There are also several limitations of our study. First, there was relatively short follow-up time. Second, results could also be biased by subjects lost to follow-up; in February 2011 (the last time point in our data) NACC reported that 63% of subjects were being actively followed, 11% had died, and 26% were lost to follow-up. We had no data to separate out these categories in analyses. In general, however, our data provide unbiased estimates of the effect of depression during active follow-up. Bias is possible only if subjects who dropped out of active follow-up had a different relationship between depression and progression to worse status, compared to those who were still followed. However, there is no *a priori* reason to think this is true, and little basis to speculate about which direction such a bias would take, were it to exist. Third, this is a cohort of clinic patients and volunteers, rather than a population-based cohort. For example, many control volunteers are motivated to participate in research due to family history or other risk factors for AD. This may limit the generalizability of our findings. Nonetheless, the fact that the incidence of progression from normal to MCI, and from MCI to AD, falls with the range of other studies (including

population-based) provides some reassurance on this point. Fourth, we are limited in determining whether medication for depression lessens the risk of progression by the unavailability of data on dose, duration, compliance with therapy, and treatment response. Recent depression was strongly associated with progression among individuals with normal cognition, with a rate ratio of about 2.2–2.3. Depression was also a very common in our study (10–25% at baseline), whether identified during annual research evaluations by clinician judgment, the GDS screening instrument, or the NPI-Q rating scale. Depression was a stronger risk factor than virtually all AD risk factors that have emerged from large epidemiological studies in well-characterized cohorts [35]. Depression was even a stronger risk factor than APOE4 (rate ratio of 1.5) in the same NACC database. However, the APOE4 risk effects in NACC are almost certainly underestimated because of the higher prevalence of APOE4 carrier control subjects compared to population studies.

While depression is strongly associated with the risk of progression to MCI, these findings do not address cause and effect. This is especially relevant since we found (as we did a recent study by Li et al. [36]) that late-life depression, but not earlier depressive episodes, predicted progression. Symptoms of depression may reflect pathophysiological changes due to AD pathology, as amyloid deposition in brain occurs a decade or more before cognitive symptoms become apparent [37]. Our finding of cognitive differences at baseline in subjects with and without depression, for both normals and MCI, may similarly be due to “subclinical” AD pathology. Additional studies using amyloid biomark-ers would be necessary to address this possibility. AD and depression may also share other underlying pathophysiologies, including inflammation [38], genetic risks (e.g., APOE), and vascular mechanisms [39]. From this perspective, depression and cognitive decline may simply reflect common symptoms of cerebral dysfunction due to AD and other disease processes. Alternatively, depression could contribute to progression through effects on brain physiology. Depression is associated with changes in the activity of frontal and limbic circuits [40] and disrupts sleep [41], both of which may alter amyloid production or clearance [42].

Identification of risk factors for MCI and AD is particularly important for modifiable and treatable conditions. If depression increases risk of progression via effects on AD pathophysiology, treatment of depression could potentially lower risk. Since depression at baseline with subsequent improvement at annual assessments had less risk of MCI and AD progression than depression that was more pervasive (i.e., either consistently identified at all follow ups or recurring), it is possible that successful resolution of depressive symptoms mitigated MCI and AD conversion. However, our data also show that antidepressant use was common in the normal and MCI subjects, but did not alter the effect of depression on progression. As noted earlier, our study was limited in that the information collected by the ADCs in the UDS was not designed to capture details of treatment (e.g., dose, duration), use of cognitive and behavioral therapies, and treatment response. Nonetheless, one potential explanation of our results is that successful treatment of depression in lowers the risk, or slows the progression to MCI or conversion to AD, and that medically refractory patients remain at highest risk. Study of depression as a potentially treatable risk factor for MCI and AD deserves further investigation, including possibly direct mechanistic studies and clinical trials. To date, almost all clinical trials of antidepres-sants have addressed depression, agitation, and other neuropsychiatric symptoms or cognition in AD, but they have not been designed to investigate effects of antidepressants on AD pathogenetic mechanisms, risk reduction, and disease prevention.

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Table 1

Descriptive statistics of study subjects from the National Alzheimer's Coordinating Center Uniform Data Set (Sept 2005-Jan 2011)

	Normal (*n* = 5,845)*	MCI (*n* = 3,010)*	Total (*n* = 8,855)
Mean number visits (SD)	3.3 (1)	3.1 (1)	3.3 (1)
Mean follow-up time in years (SD)	2.7 (1)	2.5 (1)	2.6 (1)
Always depressed (all visits)	709 (12)	828 (28)	1537 (17)
Never clinically depressed (all visits)	4119 (70)	1496 (50)	5615 (63)
Initially depressed (subsequently improved)	275 (5)	166 (6)	441 (5)
Intermittently depressed (during follow-up)	742 (13)	520 (17)	1262 (14)
At baseline visit:			
Age – mean (SD)	72 (10)	74 (9)	73 (10)
Gender = Male – *n* (%)	1998 (34)	1458 (48)	3456 (39)
Race = White – *n* (%)	4853 (83)	2449 (82)	7302 (83)
Post-High School Education – *n* (%)	4580 (79)	2135 (70)	6715 (76)
APOE4**	1172 (30)	848 (43)	2020 (33)
Mean GDS (SD)	1.7 (6)	2.9 (7)	2.1 (7)
GDS ≥5 *n* (%)	366 (6)	479 (16)	845 (10)
Recent depression *n* (%)***	1064 (18)	1063 (35)	2127 (24)
In prior 2 years – n (%)	*964 (17)*	*974 (33)*	1938 (21)
Clinician diagnosis of current depression - n (%)	*485 (8)*	*583 (19)*	1068 (12)
Depression reported over 2 years ago – *n* (%)	806 (14)	449 (17)	1305 (15)
Depression defined via NPI-Q	685 (13)	831 (29)	1516 (18)
Stroke/TIA – *n* (%)	405 (7)	359 (12)	764 (9)
Diabetes – *n* (%)	602 (10)	414 (14)	1016 (12)
Cognitive and functional assessments – mean (SD)			
Logical Memory	13.6 (4)	9.4 (4)	12.2 (5)
MMSE	28.9 (1)	27.2 (2)	28.3 (2)
CDR Sum	0.1 (0)	1.3 (1)	0.5 (.9)
WAIS (digit-symbol)	46.8 (13)	36.9 (12)	43.4 (14)
Category Fluency	34.5 (9)	27.0 (8)	32.0 (9)
FAQ	0.5 (2)	3.7 (5)	0.2 (.4)
Antidepressant Drug Use – *n* (%)			
SSRI	568 (10)	625 (21)	1193 (13)
Recent depression and taking SSRI – n (%)	*372 (6)*	*463 (16)*	835 (9)
Non-selective/Other	438 (7)	348 (12)	786 (9)
Recent depressed and taking other AD – n (%)	*248 (4)*	*238 (8)*	486 (5)

* All subjects had at least 2 visits; 510 MCI-at-baseline subjects who reverted to normal during follow up, and 238 normal subjects who progressed to MCI but then reverted to normal, were excluded from analyses, resulting in analytic cohorts of 5,607 and 2,500 respectively.

** APOE4 was available for 69% of the normal subjects and 66% if the MCI subjects.

*** Recent depression defined as clinician-diagnosed current depression (see methods).

Table 2

Comparison of cognitive measures at baseline visit for subjects with and without recent depression*

Normal at first visit (*n* = 5,845)	**Depressed at baseline (*n* = 10,64)**	**Not depressed at baseline (*n* = 4,781)**	
	Mean (std dev)	**Mean (std dev)**	***p*-value for difference***
Trails A**	34.4 (15.1)	35.4 (16.8)	0.09
Digits backwards	6.9 (2.2)	6.8 (2.2)	0.72
Digits forward	8.5 (2.2)	8.6 (2.1)	**0.04**
MMSE	28.9 (1.4)	28.9 (1.4)	**0.006**
CDR sum of boxes	0.2 (0.5)	0.1 (0.3)	**<0.0001**
Logical memory	13.9 (3.8)	13.6 (3.9)	0.92
WAIS (digit-symbol)	46.6 (12.2)	46.8 (12.9)	**<0.0001**
Trails B	94.0 (50.2)	92.0 (52.1)	**<0.0001**
Boston naming	27.0 (3.5)	27.0 (3.5)	0.42
Category fluency (animals + vegetables)	19.9 (5.8)	19.9 (5.8)	0.06
MCI at baseline visit (*n* = 3,010)	Depressed at baseline (*n* = 1,063)	Not depressed at baseline (*n* = 1,947)	
Trails A	46.7 (24.6)	44.8 (23.0)	**<0.0001**
Digits backwards	5.9 (2.1)	5.8 (2.1)	0.95
Digits forward	7.8 (2.2)	7.8 (2.1)	0.25
MMSE	27.3 (2.4)	27.2 (2.5)	0.47
CDR sum of boxes	1.5 (1.2)	1.2 (1.1)	**<0.0001**
Logical memory	9.4 (4.4)	9.4 (4.2)	0.07
WAIS (digit-symbol)	36.3 (12.4)	37.2 (12.5)	**<0.0001**
Trails B	145.0 (78.7)	138.4 (76.2)	**<0.0001**
Boston Naming	24.7 (4.9)	24.5 (4.8)	0.37
Category fluency (animals + vegetables)	15.8 (5.0)	15.9 (4.9)	**0.01**

* *p*-values for the coefficient for a dichotomous variable for depression at baseline, in a regression model including baseline variables age, history of hypertension, history of heart disease, history of diabetes, history of stroke, gender, race, and education. *p*-values < 0.05 are shown in bold. The raw data on test results for depressed and non-depressed are not adjusted for age or any other variables.

** Lower scores are worse for all tests except Trails A and B, and CDR sum of boxes.

Table 3

Model* results for progression for individuals with normal cognition or MCI at baseline

	Always depressed versus never depressed**			
	Rate Ratio (95% CI)			*p*-value
From Normal at Baseline to MCI***				
Always depressed during follow-up	2.35	1.86	2.96	<0.0001
Depressed at 1st visit but later not depressed	1.41	1.01	1.95	0.04
Intermittent depression over follow-up	2.22	1.86	2.65	<0.0001
Prior history of depression	1.00	0.81	1.23	0.99
Antidepressant****				
SSRI	1.22	0.98	1.51	0.08
Non-selective/Other	1.17	0.93	1.48	0.17
From MCI at baseline to AD***				
Always depressed during follow-up	1.21	1.00	1.46	0.06
Depressed after 1st visit but later not depressed	0.86	0.64	1.16	0.33
Intermittent depression over follow-up	1.15	0.97	1.37	0.11
Prior history of depression	0.96	1.04	0.89	0.66
Antidepressant****				
SSRI	1.38	1.17	1.63	0.0001
Non-selective/other	1.25	1.03	1.52	0.02

* All models adjusted for age, gender, race, education, history of stroke/transient ischemic attack (TIA), history of diabetes, four cognitive tests (MMSE, logical memory, category fluency, WAIS), and functional activity (FAQ). Data for missing values imputed.

** depression defined as either current or in the last 2 years.

*** 5,607 (883 transitioned) individuals in analysis from normal to worse, 2,500 (856 transitioned) individuals in analysis from MCI to AD.

**** Drugs are time-dependent, considered at time of failure of each index case.

Table 4

Antidepressant drug use at baseline visit

Non-selective or other mechanisms*	*n*	Selective serotonin reuptake inhibitors	*n*
Desipramine (Norpramin)	6	Citalopram (Celexa)	238
Maprotiline (Ludiomil)	1	Escitalopram (Lexapro)	289
Nortriptyline (Aventyl, Pamelor)	33	Fluoxetine (Prozac)	175
Amitryptiline (Elavil)	72	Fluvoxamine (Luvox)	5
Clomipramine (Anafranil)	1	Paroxetine (Paxil)	110
Bupropion (Wellbutrin; Zyban)	183	Sertraline (Zoloft)	271
Desvenlafaxine (Pristiq)	1		
Doxepin (Sinequan)	13		
Duloxetine (Cymbalta)	92		
Imipramine (Tofranil)	13		
Mirtazapine (Remeron)	55		
Nefazodone (Serzone)	5		
Trazodone (Desyrel)	169		
Venlafaxine (Effexor)	128		

*Other antidepressants were not reported by any subjects: amoxapine, protriptyline.