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Original Research Article

The Alzheimer's Disease Cooperative Study Prevention Instrument Project: Longitudinal Outcome of Behavioral Measures as Predictors of Cognitive Decline

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Key Words
Aging · Depression · Anxiety · Mild cognitive impairment · Alzheimer's disease

Abstract
Background/Methods: The Alzheimer's Disease Cooperative Study Prevention Instrument Project is a longitudinal study that recruited 644 cognitively healthy older subjects (aged between 75 and 93 years, 58% women) at baseline and evaluated their cognitive change over 4 years. The study was structured like a clinical trial to anticipate a prevention trial and to determine the performance of novel trial instruments in a longitudinal non-interventional trial framework. Behavioral symptoms were assessed at baseline. ***Results:*** The existence of participant-reported behavioral symptoms at baseline predicted conversion to Clinical Dementia Rating scale score ≥0.5 over the 4-year period. ***Conclusions:*** The results imply that early anxiety and depression may be harbingers of future cognitive decline, and that patients exhibiting such symptoms, even in the absence of co-occurring cognitive symptoms, should be closely followed over time.

Introduction

The discovery of preventative interventions is a major emphasis of Alzheimer's disease (AD) research. In order to effectively investigate novel therapeutics useful in preventing the development of AD and other neurocognitive decline, instruments need to be identified that

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are sensitive to the earliest stages of dementia and the change from normal cognition to mild cognitive impairment (MCI) and prodromal AD. Effective use of such instruments in diverse settings such as the clinic office or via telephone to the patient's home will enhance the ecological diversity and logistic ease of clinical trials. The Alzheimer's Disease Cooperative Study (ADCS) initiated the Prevention Instrument (PI) Project to develop measures sensitive to emergent dementia to be used for prevention studies. One component of that study was the inclusion of behavioral measures; certain behavioral changes are particularly prevalent in the elderly and those with MCI, and may represent markers of impending decline in cognition. These include anxiety, irritability, apathy and depression [1]. Measures of these behaviors were included in the PI study and were administered either at the clinic or via telephone. Here, we present the 4-year longitudinal data showing the utility of assessing these four symptoms in predicting decline.

The baseline data showed the behavioral experimental instruments to be reliable, and there was no difference between groups of participants who were tested in clinic or home settings [2]. Significantly higher prevalence of behavioral changes were identified in the group of participants with baseline Clinical Dementia Rating (CDR) scale scores of 0.5 compared with those labeled as cognitively normal [3]. Those participants who were considered to have more behavioral change also suffered lower scores on measures of activities of daily living and quality of life.

A predictive relationship between occurrence of depression and later onset of dementia has previously been reported [4, 5]. Both the long-term presence of depression or new onset depression have been related to the development of AD [6]. In MCI, patients who express even mild depressive symptoms are more likely to develop AD [7]. Similarly, apathy has been found to be associated with cognitive decline in otherwise healthy elderly [8], and when it occurs in MCI, it has a high association with development of AD [9, 10]. Anxiety is common in patients with MCI [11], and it has been found to predict progression from MCI to AD [12], although not all studies have replicated this finding [13]. In combination with participant memory complaints, anxiety appears to be predictive of cognitive decline in healthy elderly [14]. Even 'mild worry symptoms' have been found to be predictive of later cognitive decline in the healthy elderly [15]. There has been less research analyzing the isolated effects of increased irritability on future cognitive decline in the healthy or MCI populations, but in AD populations increasing levels of irritability are associated with decline in cognition [16]. Various neuropsychiatric symptoms (including those addressed in the current study) were found to be significantly more prevalent in participants with MCI than those who were exhibiting healthy cognitive aging in a very large cross-sectional study (n = 1,969) [17].

The ADCS PI study used both self- and partner-report. This allows for the analysis of discrepancy between these two reporters, which is of interest given research indicating reduced insight in MCI and AD. Awareness for memory deficits, for example, is reduced in MCI to a similar degree as it is in AD [18]. Behavioral symptoms are often associated with reduced insight in various forms of dementia [19]. Especially in terms of depression, some have found that AD patients underreport low mood compared with their caregivers' ratings [20], whereas others find that AD patients report higher levels of depression than reported by their caregivers [21]. Another group noted that AD patients early in their disease report similar degrees of depression, but as their condition progresses they report less depression in comparison with caregiver reports of the patient's mood [22]. In the current sample at baseline, partners reported higher levels of irritability and apathy in the participants compared with the participants' self-report of those symptoms [23].

The central question that is posed here is whether behavioral symptoms at baseline predict progression to MCI or dementia (defined as CDR ≥0.5) over 4 years. We also ask if particular symptoms are more likely than others to occur in those who progress. We were

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Table 1. Demographic and cognitive data for all participants

Participants, n	644
Male gender, %	41.77
Age, years	79.52±3.62
Education, years	14.96±3.08
CDR-SB	0.31±0.49
mMMSE	95.28±3.68

Values are mean ± SD, except where otherwise indicated. CDR-SB = Clinical Dementia Rating Sum of Boxes.

interested in whether participant's own report or that of their caregivers was more predictive of progression. We queried the progression of behavioral symptoms in this sample over the 4-year period.

Methods

The details of the methodology have been previously described in depth ([23]; Karantzoulis et al., in preparation), therefore, they will be briefly summarized here. The study was designed to mimic a prevention trial beginning with cognitively normal or minimally affected individuals; there was no intervention. The purpose of the study was to determine the psychometric properties of instruments being considered for use in ADCS prevention trials. The overall study assessed brief and mostly self-rated instruments over six domains: cognition, behavior, global change, activities of daily living, quality of life, and pharmacoeconomics. Participants were recruited from 29 different ADCS sites. Demographic details are provided in table 1. Approval was obtained from the Institutional Review Boards at each of these sites. Written informed consent was obtained from all study subjects and their partners. Following telephone screen and screening visit, recruited participants underwent baseline and annual clinical evaluation [including a cognitive battery, a short version of the Geriatric Depression Scale (GDS) [24], the Free and Cued Selective Reminding Test [25] and the modified Mini-Mental State Examination (mMMSE) [26]] in administration of experimental instruments. These were implemented annually for 4 years to participants aged 75 years or older who were considered cognitively normal (with a CDR = 0) or mildly impaired (CDR = 0.5, 23% of all participants). There were two groups of participants: those who received experimental instruments at Home (Home) within 2 weeks of their annual Clinic visit (Clinic), and those who did them during the annual Clinic visit. The experimental instruments included a variety of self-assessment measures and also a cognitive screen that the Home group underwent via telephone screen. All participants had a study partner who also completed several questionnaires about the participant. If, during the annual clinical evaluation, there was suggestion of decline on the mMMSE or the Free and Cued Selective Reminding Test, a diagnostic evaluation was triggered. This comprised the CDR, Neuropsychiatric Inventory [27], ADCS Activities of Daily Living Inventory – MCI version, Dementia Questionnaire, and additional diagnostic tests if progression to dementia was confirmed. A total of 644 participants completed the baseline component of this study, and 417 completed the entire study.

Experimental instruments used specifically to assess behavioral symptoms were focused on the most common behavioral symptoms in cognitively normal elderly, and those with MCI. Specifically, there was a list of 15 yes-no questions. This was composed of the five items on the GDS aimed at Depression, and ten questions adapted from the Neuropsychiatric Inventory to screen for Irritability (three questions), Anxiety (four questions) and Apathy (three ques-

tions). Here, we assess experience of any of these behavioral symptoms (i.e. a score of 1 or more on the combined questions) versus report of no behavioral symptoms.

Progression to MCI was defined as gaining a CDR = 0.5 at a diagnostic evaluation visit, and progression to dementia was defined as gaining a CDR ≥1 at a diagnostic evaluation visit.

Statistical Analysis

Fisher's exact tests were used to compare the number of patients who progressed to MCI and/or dementia who had experienced behavioral symptoms at baseline versus those who had not. Multivariable logistic regression analysis, adjusting for possible confounders, was also performed if there were sufficient number of events. There was a trend toward lower mMMSE and older age in the Home group compared with the Clinic group. For this reason, baseline mMMSE score and age were included as covariates in the models assessing progression to dementia. Due to these differences, we describe the results for the Home and Clinic groups separately. In the models assessing progression to MCI or MCI/dementia combined, only baseline mMMSE was used as a covariate since age was not associated with the outcome variables. Other possible confounding factors such as education, gender, ethnicity and ApoE status showed no imbalance across Home and Clinic groups or association with outcome, and were excluded from the models. When assessing the difference in distribution of symptom reporting in those who progressed compared with participants who remained stable, Fisher's exact tests were used. The same technique was used to compare partner-reported with participant-reported symptoms. The Wilcoxon rank-sum test was used to compare levels of behavioral symptoms in those who did not complete the study with those who did. All statistical analyses were conducted using R, version 2.14.0 (www.r-project.org).

Results

Frequency of Progression

Of the total group, 3.15% of the patients progressed from a CDR of zero at baseline to a CDR of 0.5. There was no significant difference in the frequency of progression in the Clinic (2.58%) or Home (3.7%) groups. A total of 1.55% of the participants progressed to dementia (CDR ≥1). The proportions did not differ between groups (1.59% Clinic, 1.52% Home). Of those who progressed, 90% had a CDR score of 1, and 10% a CDR score of 2. A total of 4.19% of the group progressed to CDR ≥0.5. There was no difference in the numbers who progressed in the Clinic (3.49%) or Home (4.86%) groups. The results reported below will combine the results for those who progressed to a CDR of 0.5 or higher. The mean number of days from baseline to progression to CDR of 0.5 or greater was 883.10 (standard deviation 391.49).

Behavioral Symptoms at Baseline

Based on their own reporting, most participants (60.81%) experienced some behavioral symptoms, and again this did not differ between groups (62.86% Clinic, 58.84% Home). The participants' partners reported a similar overall level of symptoms (56.74% overall, 56.05% Clinic, 57.41% Home).

Depression was the most commonly cited symptom by the participants (on the GDS 5 item, 34.68% of participants reported a score of 1 or greater) followed by Apathy (31.10%). Anxiety was also common (29.28%) and only 16.33% of participants reported Irritability. The frequency of participant- and partner-reported symptoms is displayed in figure 1.

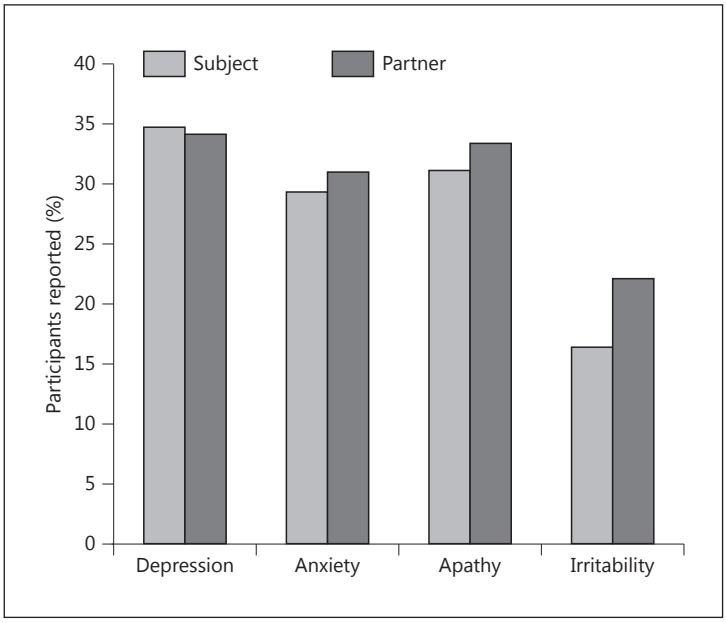

Fig. 1. Percentage of participants reporting each symptom at baseline, separated by subject and partner.

Table 2. Logistic regression model showing predictors of progression to CDR ≥0.5 in the Home group

	Estimate	Standard error	Z value	Pr (>|z|)
Intercept	8.83	5.39	1.64	0.1016
Baseline behavioral symptoms	1.48	0.77	1.92	0.0552
Baseline mMMSE	–0.14	0.06	–2.41	0.0158

Relationship of Baseline Behavioral Symptoms to Progression

Progression to MCI or Dementia (CDR ≥0.5)

In the Home group, participant-reported symptoms at baseline predicted progression (7.25 vs. 1.48%, p = 0.018). mMMSE predicted progression more strongly but participant-reported behavior was also a significant factor (table 2). In this Home group, partner-reported behavioral symptoms did not significantly predict progression.

In the Clinic only analysis, neither participant- nor partner-reported behavioral symptoms significantly predicted progression. mMMSE strongly predicted conversion.

In the combined Clinic and Home group, participant-reported behavioral symptoms significantly predicted progression to MCI or dementia (5.88 vs. 1.59%, p = 0.008). mMMSE was a strong predictor. Partner-reported behavioral symptoms did not significantly predict progression (table 3).

Symptom Frequency at Baseline in Those Who Progressed Compared with Those Who Did Not

The distribution of participant- and partner-reported behavioral symptoms differed in those who progressed compared with those who did not. For participant-reported symptoms, there was no statistical difference in the frequency of Depression, Apathy or Irritability, but those who progressed were more likely to report Anxiety (Fisher's exact p = 0.004) compared with those who did not. For partner-reported symptoms, Depression was more frequent in those who progressed, although the difference did not quite reach the predefined level of

Table 3. Logistic regression model showing predictors of progression to CDR ≥0.5 in the entire group

	Estimate	Standard error	Z value	Pr (>|z|)
Intercept	13.13	4.25	3.09	0.0020
Baseline behavioral symptoms	1.14	0.56	2.05	0.0406
Baseline mMMSE	–0.18	0.05	–4.04	0.00005

significance (Fisher's exact p = 0.061), and the frequency of Anxiety reporting was also higher to an almost significant degree (Fisher's exact p = 0.057). Apathy and Irritability did not differ.

Participant- versus Partner-Reported Symptoms at Baseline

In the small group of participants who went on to progress to CDR ≥0.5, there were no differences between participant- and partner-reporting of behavioral symptoms at baseline. In the larger group of participants who remained at CDR = 0, there was some difference between participant's reporting and that of their partners. Specifically, the partners reported more Irritability (Fisher's exact p = 0.014) and Apathy (Fisher's exact p = 0.021), but there was no difference on Depression or Anxiety.

Change in Behavioral Symptoms between Baseline and 48 Months

The total self-reported behavioral symptoms score did not differ between those who progressed compared with those who did not between baseline and 48 months. The individual symptoms were also assessed: self-reported Depression showed a trend (p = 0.06) toward more increase in progressors compared with non-progressors. Other self-reported symptoms (Irritability, Anxiety and Apathy) showed no difference. There was a larger increase in partner-reported total behavior scores for the progressors compared with non-progressors (p = 0.011). Specifically, they reported higher levels of Anxiety (p = 0.02) and Apathy (p = 0.02) compared with the non-progressor group.

Comparison of Participants Who Completed the Study with Those Who Discontinued Early

A total score was calculated for the behavioral measures taken at baseline. Those who did not complete the study had a higher baseline level of behavioral symptoms compared with those who did (Wilcoxon rank-sum test p < 0.001 when reported by either the participant or their partner).

Discussion

This study assessed the relationship between behavioral symptoms and emergence of MCI or dementia in older adults over a 4-year period. The participants' own complaints of behavioral symptoms at the initial evaluation predicted decline to MCI or dementia. However, the partner's overall report of these same symptoms did not predict decline. Specifically, anxiety (reported by patient or partner) and depression (reported by partner) were more commonly reported at baseline in those who eventually progressed compared with those who remained stable. Participants who progressed showed an increase in partner-reported symptoms over time, specifically anxiety and apathy, and a trend toward increased self-reported depression.

These results suggest that behavioral symptoms might represent precursors to cognitive decline. Depression and apathy were the most commonly reported symptoms at baseline.

However, participants who progressed were more likely to have reported, or have had their partners report, anxiety at baseline. Earlier research has pointed to a relationship between self-reported worry and decline in visual learning and memory function in healthy older adults over a 2-year period. The decline seen was independent of baseline depression, age or baseline cognitive function [15]. In another study employing regression techniques, self-reported anxiety was found to be a more significant predictor of cognitive decline than age, gender, marital status, education, or subjective memory complaints [14]. Partner-reported depression was also more frequent in those who progressed. Earlier research into the predictive values of depression mostly takes into account self-reported symptoms only [4, 6, 28, 29], or involved both partner and self-report but did not analyze these separately [7]. Cross-sectional studies of MCI patients point to prevalent partner-reported neuropsychiatric symptoms including depression [1], the incidence of partner-reported depression is higher in subjects with MCI compared with cognitively intact elderly [17]. In our sample, those who progressed had more partner-reported, but not self-reported, depression at baseline (though not significantly so) compared with those who stayed stable. However, when all baseline behavioral symptoms were combined, self-reported symptoms were more predictive of decline than partner-reported symptoms. Partner-reported irritability and apathy were more common in those who remained stable.

The current study does not address the causal nature of the relationship between behavioral symptoms and cognitive decline, although others have suggested that anxiety and depression are often a reaction to the onset of cognitive decline, rather than a cause of the cognitive decline [30]. The relationships between anxiety, depression and cognitive decline appear to be bidirectional and complex [14], but a patient's early concerns about their memory should be considered as a potential marker for later decline. Biological changes in early AD may also contribute to the occurrence of anxiety.

We found an increase in partner-reported behavioral symptoms, specifically anxiety and apathy, in those who progressed, and a non-significant increase in self-reported depression. These findings are supportive of earlier studies showing an increase in behavioral symptoms in subjects who develop MCI [11, 17]. The difference in self- versus partner report of depression, anxiety and apathy warrants further investigation.

The number of participants who progressed to MCI or dementia in the PI study was unexpectedly small. While good news for the participants involved, this led to small numbers and the potential for underpowered analyses. This is a possible explanation for the lack of findings in the group of participants who was followed in the clinic. An alternative explanation is that the mMMSE scores at baseline were somewhat different, with the clinic group having a slightly higher mMMSE score compared with the home group, thus their cognitive status started out as higher, leaving them perhaps less vulnerable to decline.

As in any longitudinal study, there was some attrition of the group over time. The participants who did not complete the study had more behavioral symptoms at the initial assessment compared with those who did not complete the study. Similarly, the participants who did not complete the study had a lower baseline mMMSE score (Karantzoulis et al., in preparation), thus they may have represented a more vulnerable group in general. The results obtained from those participants who completed may thus not generalize to the population as a whole.

The results of this study suggest that older patients who acknowledge symptoms such as apathy or depression in the context of normal memory may warrant frequent reevaluation, since they appear at risk for cognitive decline. The results also highlight the importance of involving partners in the clinical assessment process even when the patient is cognitively intact, since partner description of change in mood may be a predictor for future decline. The PI study demonstrated the feasibility of assessing behavioral symptoms in prevention trials.

References

1 Hwang TJ, Masterman DL, Ortiz F, Fairbanks LA, Cummings JL: Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. Alzheimer Dis Assoc Disord 2004;18:17–21.
2 Ferris SH, Aisen PS, Cummings J, et al: ADCS Prevention Instrument Project: overview and initial results. Alzheimer Dis Assoc Disord 2006;20(4 suppl 3):S109–S123.
3 Morris JC: The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.
4 Sachs-Ericsson N, Joiner T, Plant EA, Blazer DG: The influence of depression on cognitive decline in community-dwelling elderly persons. Am J Geriatr Psychiatry 2005;13:402–408.
5 van Reekum R, Simard M, Clarke D, Binns MA, Conn D: Late-life depression as a possible predictor of dementia: cross-sectional and short-term follow-up results. Am J Geriatr Psychiatry 1999;7:151–159.
6 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.
7 Copeland MP, Daly E, Hines V, et al: Psychiatric symptomatology and prodromal Alzheimer's disease. Alzheimer Dis Assoc Disord 2003;17:1–8.
8 Onyike CU, Sheppard JM, Tschanz JT, et al: Epidemiology of apathy in older adults: the Cache County Study. Am J Geriatr Psychiatry 2007;15:365–375.
9 Palmer K, Di Iulio F, Varsi AE, et al: Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. J Alzheimers Dis 2010;20:175–183.
10 Robert PH, Berr C, Volteau M, et al: Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: a one-year follow-up study. Clin Neurol Neurosurg 2006;108:733–736.
11 Forsell Y, Palmer K, Fratiglioni L: Psychiatric symptoms/syndromes in elderly persons with mild cognitive impairment. Data from a cross-sectional study. Acta Neurol Scand Suppl 2003;179:25–28.
12 Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L: Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007;68:1596–1602.
13 Devier DJ, Pelton GH, Tabert MH, et al: The impact of anxiety on conversion from mild cognitive impairment to Alzheimer's disease. Int J Geriatr Psychiatry 2009;24:1335–1342.
14 Sinoff G, Werner P: Anxiety disorder and accompanying subjective memory loss in the elderly as a predictor of future cognitive decline. Int J Geriatr Psychiatry 2003;18:951–959.
15 Pietrzak RH, Maruff P, Woodward M, et al: Mild worry symptoms predict decline in learning and memory in healthy older adults: a 2-year prospective cohort study. Am J Geriatr Psychiatry 2012;20:266–275.
16 Mega MS, Cummings JL, Fiorello T, Gornbein J: The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;46:130–135.
17 Geda YE, Roberts RO, Knopman DS, et al: Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. Arch Gen Psychiatry 2008;65:1193–1198.
18 Vogel A, Stokholm J, Gade A, Andersen BB, Hejl AM, Waldemar G: Awareness of deficits in mild cognitive impairment and Alzheimer's disease: do MCI patients have impaired insight? Dement Geriatr Cogn Disord 2004;17:181–187.
19 Banks SJ, Weintraub S: Generalized and symptom-specific insight in behavioral variant frontotemporal dementia and primary progressive aphasia. J Neuropsychiatry Clin Neurosci 2009;21:299–306.
20 Mackenzie TB, Robiner WN, Knopman DS: Differences between patient and family assessments of depression in Alzheimer's disease. Am J Psychiatry 1989;146:1174–1178.
21 Burns A, Jacoby R, Levy R: Psychiatric phenomena in Alzheimer's disease. IV: Disorders of behaviour. Br J Psychiatry 1990;157:86–94.
22 Ott BF, Fogel BS: Measurment of depression in dementia: self versus clinician rating. Int J Geriatr Psychiatry 1992;7:899–904.
23 Cummings JL, Raman R, Ernstrom K, Salmon D, Ferris SH: ADCS Prevention Instrument Project: behavioral measures in primary prevention trials. Alzheimer Dis Assoc Disord 2006;20(4 suppl 3):S147–S151.
24 Yesavage JA, Brink TL, Rose TL, et al: Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37–49.
25 Grober E, Buschke H, Crystal H, Bang S, Dresner R: Screening for dementia by memory testing. Neurology 1988;38:900–903.
26 Teng EL, Chui HC: The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987;48:314–318.
27 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
28 van Reekum R, Simard M, Cohen T: The prediction and prevention of Alzheimer's disease – towards a research agenda. J Psychiatry Neurosci 1999;24:413–430.
29 Chen P, Ganguli M, Mulsant BH, DeKosky ST: The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen Psychiatry 1999;56:261–266.
30 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.