Depression as a Risk Factor for Alzheimer Disease

The MIRAGE Study

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Background: Depression symptoms may be associated with the development of Alzheimer disease (AD).

Objectives: To evaluate the association between depression symptoms and risk of AD, and to explore the temporal aspects of this association.

Setting: Academic institutions with specialized memory clinics.

Design: Cross-sectional, family-based, case-control study with standardized self- and proxy questionnaires to collect information on depression symptoms and other risk factors.

Participants: A total of 1953 subjects with AD and 2093 of their unaffected relatives enrolled in the Multi-institutional Research in Alzheimer's Genetic Epidemiology Study.

Main Outcome Measures: Odds ratios (ORs) of AD were estimated with and without depression symptoms, adjusted for age, sex, education, history of head trauma, and apolipoprotein E status.

Results: There was a significant association between depression symptoms and AD (adjusted OR, 2.13; 95% confidence interval [CI], 1.71-2.67). In families where depression symptoms first occurred within 1 year before the onset of AD, the association was higher (OR, 4.57; 95% CI, 2.87-7.31), while in the families where the depression symptoms first occurred more than 1 year before the onset of AD, the association was lower (OR, 1.38; 95% CI, 1.03-1.85). In families where depression symptoms first occurred more than 25 years before the onset of AD, there was still a modest association (OR, 1.71; 95% CI, 1.03-2.82).

Conclusions: Depression symptoms before the onset of AD are associated with the development of AD, even in families where first depression symptoms occurred more than 25 years before the onset of AD. These data suggest that depression symptoms are a risk factor for later development of AD.

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DEPRESSION AND depression symptoms are common in persons with Alzheimer disease (AD).[1-8] When depression symptoms occur just before the development of AD, they may be early symptoms of the dementing process.[9-12] What remains unclear is whether depression occurring many years before the onset of cognitive decline is somehow a risk factor for the future development of AD.

During the past 10 years, we have collected genetic and historical risk information on families with at least 1 person who met research criteria for AD through the Multi-institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) Study. This report provides data on 4046 subjects and examines the association between depression symptoms and AD even where first onset of depression symptoms occurred 25 years before the onset of AD.

METHODS

SUBJECTS AND DATA COLLECTION

The details of MIRAGE Study data collection procedures, protocols for obtaining family histories, and reports demonstrating the validity of proxy reporting in our families have been published elsewhere.[13-16] The starting point for recruitment of MIRAGE Study families is the proband: an individual with probable AD by research criteria,[17] or a deceased patient with definite AD by autopsy. Probands are recruited at each of the sites through research registries and specialized memory clinics. After informed consent is obtained from nondemented persons and a combination of consent or assent, along with informed consent by proxy,

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Table 1. Description of Persons With AD and Family Members Without Dementia

Characteristics	Subjects With AD (n = 1953)	Subjects Without Dementia (n = 2093)	P Value
Respond yes to depression question, No. (%)	277 (14.2)	154 (7.4)	.001
Male, No. (%)	1169 (59.9)	1136 (54.3)	.001
African American (vs white), No. (%)	220 (11.3)	227 (10.9)	.85
Educational level college or higher, No. (%)	595 (30.7)	727 (35.6)	.001
History of head trauma, No. (%)	382 (20.1)	223 (10.9)	.001
Age, mean (SD), y	70.3 (8.5)	70.1 (10.6)	.46

Abbreviation: AD, Alzheimer disease.

is obtained for living demented participants, information is obtained through the standardized MIRAGE questionnaires.

This report examines data on 4046 individuals from 1953 families in which 1778 persons met criteria for probable AD and 175 deceased persons had autopsy-confirmed AD. Information on depression symptoms and other risk factors was available on all of these affected persons from surrogate sources within the family, typically the spouse or adult offspring. Information was also available on 2093 nondemented family members of these patients (856 siblings, 551 spouses, 384 parents, and 302 offspring older than 50 years). Risk factor information about the nondemented relatives was self-reported in 1410 subjects and reported by another family surrogate for 683 subjects. In a subset of 1081 of these family members who were reported to be dementia free, cognitive status was evaluated through the administration of the modified Telephone Interview of Cognitive Status.[18,19] Among the nondemented family members screened with this instrument, less than 0.1% of those who reported themselves to be nondemented had modified Telephone Interview of Cognitive Status scores that suggested otherwise, and these were not included in this analysis. Information on both patients and family members was supplemented where available by multiple informants, medical records including autopsy reports, death certificates, and nursing home records.

The structured and validated MIRAGE questionnaire was used with supplemental information as described above to collect demographic and risk factor information. To elicit depression information, a single question was designed with considerable face validity that avoided formal criteria for depression. The primary question asked was: "Aside from normal reaction to bereavement (death in family) or the impact of physical/medical condition, has there been a period of weeks to several months (or longer) when you were unable to perform social and occupational functions normally because of depression?" For proxy reporting about a relative with AD, the question substituted "your relative was" for "you were." Since this question does not truly identify depression by any recognized clinical criteria, in this report, we will refer to those who answered affirmatively as having had "depression symptoms." For any affirmative answer, a follow-up question asked for the age at the first episode of these symptoms. Apolipoprotein E (APOE) genotyping was available for a subset of 1085 persons with AD and 833 nondemented relatives representing subjects enrolled during the last 4 years of data gathering when APOE genotypes have been collected.

Data on other risk factors for AD were elicited as described elsewhere.[13,14,20] A standard polymerase chain reaction procedure[21] was used for APOE genotyping.

STATISTICAL ANALYSIS

All analyses were performed with SAS version 6.12 (SAS Institute Inc, Cary, NC). Depression was dichotomized into persons who answered yes or no on the question described above. Age represented the age at which AD symptoms began in persons with AD, or the age at which information was obtained on nondemented relatives. History of head trauma was categorized as yes or no to a question in which the respondent or proxy respondent indicated that head trauma had occurred that required medical attention. The APOE genotyping was categorized as having 1 or 2 $\epsilon 4$ alleles vs having no $\epsilon 4$ alleles.

The frequencies of the dichotomized exposure variables were evaluated in persons with AD and nondemented relatives by χ^2 statistics. Stratification was used to detect interaction (with the Breslow-Day test), and to control for confounding (with the Mantel-Haenszel odds ratio [OR] and χ^2 test) with strata defined by dichotomizing each of the variables described above. No interaction was detected.

Since individuals within families were being studied, and since a number of the variables (depression and APOE status) could be correlated within families, the adjusted associations were estimated by means of generalized estimating equations with the presence or absence of AD as the dependent variable. Confounding was evaluated by creating models with different combinations of covariables, and examining the association between depression symptoms and AD for meaningful change. Key variables were retained in the model even though they did not appear to be confounding.

The analysis was systematically repeated after families were excluded on the basis of the reported time between the first evidence of depression symptoms and the onset of AD.

RESULTS

Baseline characteristics of subjects with and without AD are shown in **Table 1**. Subjects with AD were more likely to be male, were less highly educated, and had a higher incidence of reported head trauma. These data include 447 African American subjects (11.3%). The proportion of patients with AD who had a surrogate report of prior depression symptoms was 14.2%, whereas the proportion of nondemented family members who reported prior depression symptoms, or had a family member report them by proxy, was 7.4%.

With the use of generalized estimating equations, the crude OR and 95% confidence interval (CI) describing the association between depression symptoms and AD were estimated as 2.08 (1.70-2.55). This association did not meaningfully change when the model included adjustment for education, head trauma, ethnicity, sex, or age (OR, 2.13; 95% CI, 1.71-2.67) or when these variables and APOE genotype were included in the model for a subset of 1918 subjects for whom APOE genotype information was available (OR, 2.23; 95% CI, 1.59-3.12). The significant associations with educational level (adjusted OR in the entire sample, 0.85; 95% CI, 0.72-1.00), with head trauma (adjusted OR in the entire sample, 2.12; 95% CI, 1.76-2.56), and with the presence of at least one $\epsilon 4$ allele (adjusted OR in the subsample with APOE information, 3.06; 95% CI, 2.50-3.76) are consistent with previously reported data from the MIRAGE Study and other epidemiologic studies of AD.[14,20,22-28]

**Table 2. Examination of Associations Within Data Subsets Based on Time Between Depression Onset and AD Onset in Co-occurring Cases*

| Interval in Years Between Depression Onset and AD Onset (X) | Members of Families (n = 919) Where Co-occurring Depression and AD Were Reported | | | |
| | Interval ≤X | | Interval >X | |
	No. of Subjects	OR (CI)	No. of Subjects	OR (CI)
1	221	4.57 (2.87-7.31)	698	1.38 (1.03-1.85)
2	284	3.41 (2.29-5.08)	635	1.37 (1.03-1.86)
3	305	3.18 (2.18-4.62)	614	1.33 (1.01-1.85)
4	353	2.72 (1.93-3.82)	566	1.39 (1.00-1.91)
5	379	2.60 (1.88-3.61)	540	1.39 (1.00-1.93)
10	428	2.43 (1.80-3.29)	491	1.34 (0.93-1.93)
15	521	2.10 (1.58-2.78)	398	1.58 (1.06-2.37)
20	619	1.99 (1.53-2.59)	300	1.70 (1.06-2.72)
25	685	2.01 (1.56-2.60)	234	1.71 (1.03-2.82)

Abbreviations: AD, Alzheimer disease; CI, confidence interval; OR, odds ratio.

*The ORs look at the association between response on the depression question and presence of AD among data from 2 groups, defined by combining the 3034 family members where there was no co-occurring depression and AD with each of the subsets of family members from families with co-occurring depression and AD. For example, the OR of 4.57 is the association between depression and AD for the population defined by 3034 plus 221 family members where the co-occurring case had 1 year or less between the onset of depression and the onset of AD. The OR of 1.38 is the association between depression and AD for the population defined by 3034 plus 698 family members where the co-occurring case had AD greater than 1 year after the onset of depression.

TEMPORAL ASSOCIATION BETWEEN DEPRESSION SYMPTOMS AND DEMENTIA ONSET

An obvious question in evaluating the association between depression symptoms and AD is the proximity of depression symptoms to the onset of dementia. Apparent depression symptoms such as withdrawal and apathy could actually be the earliest symptoms of the AD. Alternatively, persons with insight into the early deterioration of their memory could become depressed months or even years before the date when AD was recognized or diagnosed. Therefore, it is not surprising that there is an overall association between depression symptoms and the risk of AD. A more interesting question is whether depression starting many years before the onset of AD is a risk factor.

In **Table 2**, we used the age at first depression symptoms and the age at onset of AD to systematically include or exclude families with co-occurring depression symptoms and AD, where the number of years between those 2 ages fell below a specific threshold. For example, when we selected families with co-occurring depression symptoms and AD where the interval between onset of the 2 conditions was less than or equal to 1 year, and included all the family members from families where there were no co-occurring cases, the association between depression symptoms and AD was more robust (OR, 4.57; 95% CI, 2.87-7.31). This association most likely reflects overlap between depression symptoms and early symptoms of AD. When we selected families with co-occurring depression symptoms and AD where the first onset of depression occurred more than 1 year before the reported onset of AD, and again included all the family members from families where there were no co-occurring cases, the association between depression symptoms and AD was more modest, but still significant (OR, 1.38; 95% CI, 1.03-1.85). Since depression symptoms that occur more than a year before the onset of AD are less likely to represent early symp-

toms of AD, this point estimate is probably more accurate in describing the risk of AD associated with "prior" depression symptoms.

Reported age at onset information for persons with AD reflects the family's best estimate of symptom onset; however, we recognized that the degenerative process in AD could have begun more than 1 year before this age. Therefore, we extended the subsetting procedure described above by using a progressively longer interval between the onset of depression symptoms and the onset of AD. No natural cutoff points were seen in the results of this process, and the analysis was repeated yearly up to 25 years, at which point there were sample size limitations. These data are summarized yearly up to the first 5 years, then every 5 years up to 25 years, in Table 2. Of note, when we selected families with co-occurring depression symptoms and AD where the first onset of each was more than 25 years before the onset of AD, the association between depression symptoms and AD remained significant (OR, 1.71; 95% CI, 1.03-2.82).

These data also offered an opportunity to evaluate whether APOE genotype is associated with depression symptoms in these families. When we used the presence or absence of depression symptoms as the outcome, generalized estimating equation modeling of APOE genotype, adjusting for AD (disease status) and for each of the variables described in Table 1, we found an OR of 0.94 (95% CI, 0.69-1.28). Thus, as described elsewhere,[29,30] APOE genotype is not associated with depression and no interaction is observed between APOE and depression.

EVALUATING POTENTIAL BIAS FROM ASYMMETRIC DATA COLLECTION METHODS

Patients with AD are unable to provide accurate personal histories, so medical information about them was, in each case, provided or supplemented by a surrogate,

typically a close family member such as a spouse or adult child. However, when health information was elicited from the nondemented family members, the information was provided by the subject himself or herself in about two thirds of our nondemented subjects, presenting the potential for biases if family members were more or less likely to recall or report certain conditions pertaining to the relative affected with AD, in comparison with self-report. Therefore, we repeated the analysis exclusively using data provided by surrogates for both persons with AD and nondemented family members.

In our study, 683 (32.6%) of the 2093 nondemented participants had information gathered entirely by surrogates, typically by other family members. Restricting the analysis to these 683 nondemented persons along with the 1953 participants with AD yielded an OR of 1.84 (95% CI, 1.23-2.81) for the association between AD and depression symptoms, adjusted for all other variables described already, including APOE genotype. Thus, conducting the analysis in a population in which data is gathered entirely by surrogate family historians did not meaningfully change the point estimate of the association and supports the validity of the findings in the larger sample.

COMMENT

This study examined the association between prior depression symptoms and the development of AD and is the only study to date that has a large enough sample size to examine the temporal association in detail while adjusting for other known risk factors including APOE genotype. This analysis indicates that depression symptoms are associated with the development of AD, and that this association is much stronger among the families where the onset of depression symptoms occurred in the year before the onset of AD symptoms, probably representing very early symptoms of dementia. However, of greater interest, depression symptoms are significantly associated with AD even when the onset of depression symptoms precedes the onset of identified AD symptoms by 25 or more years.

The MIRAGE Study has several strengths. These data include the largest number of subjects in which this question has been examined, including a large number of African American subjects. This is the only large-scale study of depression or depression symptoms and AD to include APOE information. In the MIRAGE Study protocol, subjects with AD are well characterized with research criteria by experienced clinical researchers at academic centers. In more than half of the family members who reported themselves to be nondemented, the reported cognitive status was confirmed by telephone screening. Potential confounders, including the presence of at least one $\epsilon 4$ allele, were measured and adjusted for through multivariate modeling. Moreover, our analysis was enhanced by the use of generalized estimating equations, which allows for correlation of depression symptoms among family members, both because of genetic propensities to depression and because of the potential psychological influence of having a depressed family member.

It is important to acknowledge several sources of potential bias in this study. Cases enrolled into the MIRAGE Study were recruited from research registries and from memory clinics at academic centers, and were therefore not representative of the general population of patients with AD. However, our subjects are likely to be more representative of families under evaluation for memory problems in clinical practice than other population-based studies.

Data indicating the presence or absence of depression symptoms were gathered through a single question that has considerable face validity, but has not been standardized or validated against any conventional measures of depression or depression symptoms. The wording of our question could allow unsophisticated individuals to ascribe their depression symptoms to other causes and inappropriately answer in the negative. However, excellent validity of a single question for depression has been demonstrated in general practice settings among older persons,[31] and applying overly sensitive measures of depression is not a good way to distinguish false-positive cases.[32] We also recognize that the age at onset of depression is difficult to obtain accurately in a retrospective study. However, the well-known phenomenon of "forward telescoping"[33-35] makes it likely that depressed individuals may date the onset of their own depression symptoms closer to the present, which would bias the association with more remote depression symptoms toward the null.

Another methodologic concern is the "asymmetric" reporting of historical information, with self-report among most nondemented family members and surrogate report among the subjects with AD. This potential source of bias could be particularly problematic with a condition such as depression that has social stigma attached. One could imagine a situation in which caregivers readily reported depression symptoms observed before AD onset in the cases, but were hesitant to report such symptoms about themselves, moving estimates of association away from the null. However, if family informants were not aware of depressions earlier in the life of the family member with AD, they might underreport depression symptoms in the affected relative, moving the estimate of association toward the null. Asymmetric data collection is difficult to avoid where cases are cognitively impaired, and may be more accurate than expected in patients with AD where the surrogate historian has a long association with the subject.[15,36,37] Most important, nearly one third of our nondemented family members did not report on themselves but were reported on by a surrogate source within their family. Restricting our analysis entirely to subjects with surrogate reporting did not meaningfully alter the estimate of association. Therefore, we believe that our overall results are not unduly affected by reporting bias.

Our findings extend and clarify earlier observational studies that have demonstrated an association between prior symptoms of depression and AD. One of the earliest publications to address this question compared 40 patients with AD and 80 control subjects and found a nonsignificant OR of 2.38 for a history of "psychiatric disorders."[38] Other small case-control studies found sig-

nificant associations, with an OR for depression of 5.0 (95% CI, 1.04-33.0) in one[39] and an OR of 3.3 (95% CI, 1.1-10.1) in another.[40] A somewhat larger number of subjects were analyzed by Broe et al,[41] who compared 175 patients with 170 control subjects and found an OR of 4.3 (95% CI, 1.37-13.7) for depression within 10 years of the assessment and an OR of 1.5 (95% CI, 0.25-8.87) for depression before the last 10 years of the assessment for dementia. Similarly, Kokmen et al[42] examined the medical records of 415 patients from the Rochester, Minn, community and compared them with 415 age- and sex-matched community control subjects. In this sample, a history of episodic depression was associated with AD with an OR of 1.71 (95% CI, 1.03-2.83). In 1991, a meta-analysis of 6 previous studies pooled data from "medically treated" cases of depression; from a combined total of 743 cases and 818 controls, the OR was estimated to be 1.82 (95% CI, 1.16-1.86). Where data were available, a separate analysis of cases of depression occurring earlier than 10 years before the start of the dementia yielded an OR of 1.92 (95% CI, 1.11-3.32).[43] Similar effect sizes (overall OR of 1.8; 95% CI, 0.9-3.5) were noted in a case-control study of 294 persons with AD and 300 control subjects in whom all data were gathered by proxy report.[44] In a practice-based cohort of older persons in the Netherlands, examined retrospectively for diagnoses of depression preceding diagnoses of dementia, a significant association was observed, with a hazard ratio of 2.5 (95% CI, 1.2-5.5).

There are also several reports from prospective, longitudinal studies that used clinical evaluation of elderly subjects in a circumscribed geographic area and counted incident cases of dementia, AD, or cognitive decline.[45-50] Among 1600 older persons followed up in the Gironde region of southwest France, no association was found between depression symptoms on the Center for Epidemiological Studies Depression Scale and cognitive deterioration 3 years later.[46] In a population-based sample from northern Manhattan (New York, NY), 57 incident cases of AD were found among the 478 subjects for whom at least 1 annual follow-up visit was available. After adjustment for age, sex, education, language, and initial level of cognition, depressed mood at baseline was significantly associated with the development of AD, with an OR of 2.05 (95% CI, 1.16-3.62). Among 121 subjects with APOE, the magnitude of the effect was unchanged, although there was less precision (OR, 2.8; 95% CI, 0.93-8.6).[47] A community-based sample in Australia of 1045 persons older than 70 years was evaluated for depression, then evaluated again 3 to 6 years later, when no association between depression and subsequent dementia was seen.[51] Another study of 2812 elderly residents of New Haven, Conn, showed that an elevated level of depression symptoms when subjects were enrolled in the study was significantly associated with an increased risk of cognitive decline only in those whose cognitive testing at the start of the study placed then in the "medium" rather than the "high" category. In the medium category, a significant association was seen over 3 years (OR, 1.7) and over 6 years (OR, 2.4), but this effect was no longer statistically significant in those who were followed up for 12 years (OR, 1.6).[48] From an original sample of 1366 older subjects in a rural Pennsylvania community, 954 were screened for depression symptoms at the start of the second wave of data collection and 803 completed either wave 3 or 4, in which cognitive screening and subsequent workup detected 78 incident cases of dementia (35 with probable AD). Those subjects with depression at the start of the study were at slightly higher risk for dementia (relative risk, 1.27), but this was not significant.[49] Finally, among 1911 highly educated older persons enrolled in a community-based longitudinal study in Amsterdam, the Netherlands, those with depressed mood on enrollment were more likely to develop AD (OR, 4.3; 95% CI, 1.7-10.7) after an average follow-up of 3.2 years, but this association was not significant among lower-educated persons in the same study.

These longitudinal studies are less subject to recall biases and can provide a much more objective measure of depression or depression symptoms, but they do so only at the points in time when participants were examined. For an intermittent disorder such as depression, this could underestimate the incidence of depression. Moreover, the low numbers of incident cases do not provide as much power to evaluate multiple covariates.

Despite potential biases from cross-sectional ascertainment and retrospective data collection, our study is the only one with sufficient power to simultaneously examine APOE genotype, other known risk factors for AD, and the temporal association between the onset of depression symptoms and the onset of AD symptoms. Our findings on the association between depression symptoms and AD in both of these categories are strengthened by similarities between the effect sizes in our data and those found by other researchers. For example, a prospective study by Alexopoulos and colleagues[52] compared 23 depressed elderly patients who had a "reversible dementia" associated with their depression, with 34 elderly patients with depression in whom depression was not associated with cognitive impairment. Survival analysis after an average follow-up of 33.8 months showed that those with reversible dementia were 4.7 times as likely to develop a subsequent progressive dementing disease. Our finding that depression symptoms occurring for the first time in the year before the development of AD have an OR of 4.6 is consistent with this report. By the same token, when Jorm and coworkers' meta-analysis of studies was restricted to subjects with depression 10 years or more before the start of the dementia,[43] the association of 1.92 (95% CI, 1.11-3.32) was very similar to our findings in similarly defined groups in which depression symptoms occurred 5 to 25 years before the start of AD (see Table 2).

In summary, it seems likely that there are 2 sources of association for persons who become depressed and later develop AD. First, if they develop AD within a year of the depression symptoms, then these probably represent early symptoms of the as yet occult AD. Second, if they develop depression symptoms that are not associated with the early symptoms of AD, even in middle age, our data suggest that there remains a modest but significant association with the eventual development of AD. Like other risk factors for AD that seem to occur well before the first signs of cognitive impairment, such as low

education[26,53,54] or lower lexical density on narrative writing samples,[55] this finding is difficult to interpret. Does AD begin much earlier in life than conventionally thought, perhaps as early as young or midadulthood? Is there something about depression that is potentially "toxic" to the brain and predisposes to a later vulnerability to AD? Or could a propensity for depression be a subtle proxy for lower neurologic "reserve" (even when adjustment has been made for education) that cushions and delays the onset of a dementing syndrome? The answer remains unclear, but through the careful discrimination of risk factors, both genetic and nongenetic, we are moving closer to developing accurate models for who will be at highest risk for AD, and therefore who should receive preventive and disease-modifying treatments as they become available.

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