

Do Depressive Symptoms Predict Alzheimer's Disease and Dementia?

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Background. Depressive symptoms are common in seniors and may predict dementia. The objective of this study was to evaluate multiple measures of depressive symptoms to determine whether they predict subsequent Alzheimer's disease (AD) or dementia.

Methods. This population-based cohort study with 5-year follow-up included 766 community-dwelling seniors (ages 65+ years) in Manitoba, Canada. Measurements considered were the Center for Epidemiologic Studies Depression (CES-D) scale, participant-reported medical history, and duration of depression.

Results. Total CES-D score was a significant predictor of AD and dementia when categorized as a dichotomous variable according to the cutoff scores of 16 and 17; a CES-D cutoff of 21 was a significant predictor of AD and a marginally significant predictor of dementia. When analyzed as a continuous variable, CES-D score was marginally predictive of AD and dementia. Neither participant-reported history of depression nor participant-reported duration of depression was significant in predicting AD or dementia.

Conclusion. Because depressive symptoms as measured by the CES-D predict the development of AD and dementia over 5 years, clinicians should monitor their older patients with these symptoms for signs of cognitive impairment.

DEMENTIA is a progressive loss of cognitive ability that causes functional impairment (1), and it carries a high risk for institutionalization and death. The most common type of dementia in North America is Alzheimer's disease (AD), which affects an estimated 4 million persons in the United States (2).

Several studies published in the last 15 years have found that depression is associated with AD. However, it is unclear whether depressive symptoms are an early manifestation of AD or dementia, or whether depressive symptoms in seniors increase the risk for developing these conditions. One theory of the interaction between depression and dementia, called the "vascular depression hypothesis," states that cerebrovascular disease can be a root cause of both depression and dementia and therefore may be a link between these two conditions (3).

One systematic review of case-control studies found that depression occurring more than 10 years before AD onset nearly doubled the risk for AD (4). This same study, however, found that depression occurring 10 years or less before AD onset was not a significant risk factor. Because AD was more strongly associated with depression occurring earlier in life than depression occurring during the period immediately preceding the AD onset, these results suggest that depressive symptoms may increase the risk for AD rather than represent an early, preclinical symptom of AD. However, more recent longitudinal studies (5,6) have concluded that depression may be a preclinical symptom of AD. One recent cohort study found that the risk for developing AD rose with increasing depressive symptoms measured 7 years previously on a 10-item Center for Epidemiologic Studies Depression (CES-D) scale (7).

In the current study, we analyzed the association between measures of depression and the development of dementia 5 years later in a population-based cohort study.

Our objective was to evaluate various measures of depressive symptoms (including several cutoff points of the full 20-item CES-D scale, subsets of CES-D items, and participant-reported history and duration of depression) to determine whether depression, as reflected by any of these measures, increases the risk for AD or dementia.

METHODS

Sample

We evaluated the association of incident AD and dementia with multiple measures of depressive symptoms using data from the Manitoba Study of Health and Aging (MSHA). The MSHA is a community-based cohort study of aging and cognition conducted in Manitoba, Canada as a parallel investigation to the Canadian Study of Health and Aging (8). The Faculty of Medicine Committee on the Use of Human Subjects in Research at the University of Manitoba approved the MSHA study, which was in compliance with the Declaration of Helsinki. All participants or appropriate proxy respondents gave informed consent.

In 1991–1992 and again in 1996–1997, participants ages 65 years and older were screened for cognitive impairment with the Modified Mini-Mental State Examination (9). If a participant scored fewer than 78 points (of a possible 100) on the Modified Mini-Mental State Examination at the baseline or follow-up interview, he or she was invited to participate in a clinical examination in which a diagnostic assessment for cognitive impairment was conducted. The CES-D was administered to each participant at both interviews. After the initial interview, participants were given a take-home risk factor questionnaire. The persons described in this report as cognitively intact (scoring 78 or more points on the Modified Mini-Mental State Examina-

Table 1. Characteristics of Study Population

Characteristic	AD Cases (N = 36)	All Dementia (AD + Non-AD) Cases (N = 56)	No Dementia Controls (N = 710)	Total (N = 766)
Age (y)				
Mean \pm SD	79.8 \pm 5.7*	80.1 \pm 5.4*	74.1 \pm 5.9	74.5 \pm 6.0
Min-max	70-93	70-93	65-96	65-96
Sex				
% Female	66.7	66.1	61.4	61.7
Education (y)				
Mean \pm SD	9.1 \pm 3.9 [†]	9.0 \pm 3.7 [‡]	10.5 \pm 3.1	10.4 \pm 3.2
Min-max	0-17	0-17	0-25	0-25
CES-D Score				
Mean \pm SD	8.1 \pm 7.5	8.1 \pm 7.6 [†]	6.0 \pm 6.9	6.1 \pm 7.0
Min-max	0-26	0-36	0-44	0-44

Notes: * $p < .001$.

[†] $p < .05$.

[‡] $p = .005$ compared with controls.

The CES-D ranges from 0 to 60.

AD = Alzheimer's disease; SD = standard deviation; CES-D = Center for Epidemiological Studies Depression scale.

tion) at the 1991-1992 interview answered at least 80% of the questions on the CES-D at baseline, completed the risk factor questionnaire at baseline, and participated in the follow-up assessment in 1996-1997. A total of 766 participants met all four of these criteria. Two hundred seventy-one persons did not participate in the follow-up assessment because of death, refusal to continue, or ineligibility. Persons who died before follow-up were more likely to be men, had higher baseline CES-D scores, were older, and had fewer years of education compared with those who completed the follow-up. Those who refused to participate at follow-up had fewer years of education than did those who completed follow-up, but they did not differ in age, sex, or baseline CES-D score. Those who were ineligible were more likely to be women than were those who completed follow-up, but they did not differ in age, education level, or baseline CES-D score.

Of these 766 participants, 656 (86%) scored 78 or more points on the Modified Mini-Mental State Examination at the second interview in 1996-1997. In addition, 54 participants who had the clinical examination were found not to have dementia. These 710 participants served as the nondementia controls. Cases of AD included 36 participants with probable ($n = 15$) or possible ($n = 21$) AD diagnosed according to standard research criteria (10). Cases of dementia included persons with AD plus 20 participants found to have other types of dementia according to the guidelines published in the *Diagnostic and Statistical Manual of Mental Disorders* (11).

Measures of Depressive Symptoms

Various methods have been used to measure depression in epidemiologic studies. One instrument commonly used to measure depressive symptoms in community samples is the CES-D scale (12). Although the CES-D cannot be used to diagnose clinical depression, this instrument has been used in many large-scale studies and has been found to be applicable as a screening tool across age groups (13). This instrument contains 16 items covering components of depression and four items covering positive affect. Each item is scored from

0 to 3, for a possible total range of 0 to 60. Missing CES-D items were imputed with the mean value of that item for 19 participants who were missing one to three items.

Four factors of the CES-D measure different aspects of depression: depressed affect (range, 0 to 21); positive affect (range, 0 to 12; reverse-scored so that a higher score reflects lack of positive affect); somatic/vegetative, including symptoms related to physical well-being, sleep, and appetite (range, 0 to 21); and interpersonal (range, 0 to 6) (14). We evaluated these four subsets of CES-D items in relation to AD and dementia. Finally, we investigated the association of AD and dementia using participant-reported history and duration of depression.

Data Analysis

We analyzed total CES-D scores as dichotomous values (yes/no) using cutoff points of 13, 16, 17, and 21. The standard cutoff score for indicating depressive symptoms in community populations is 16 or more of a possible 60 points (13); this cutoff has been reported to have a 6% false-positive rate and a 36% false-negative rate (15). Other studies have used the range of scores from 13 to 15 to define "borderline" cases (16), whereas a cutoff of 17 has been used to determine "possible" depression cases in a community sample (17). It has also been suggested that 21 points is the optimum cutoff for screening for major depression, with 92% sensitivity and 87% specificity in a primary care setting (18). We evaluated the effect of CES-D score as a continuous variable when those who scored two or fewer points were excluded from the analysis; persons who report these very low CES-D scores may be unwilling to admit that they experienced any depressive symptoms (16). Because information is lost when cutoff points are used to dichotomize scores, we also analyzed CES-D scores as continuous values of the total score and as continuous values of the four factors.

We analyzed our data using SPSS statistical software, version 10.0 (19). We determined Pearson correlation coefficients between baseline CES-D score and baseline age and education, and between baseline CES-D score and CES-D score at follow-up. We used *T* tests to analyze the relationship between baseline CES-D and sex. To investigate the association of measures of depression with AD and dementia, we conducted multiple logistic regression analyses, adjusting for age, sex, and education.

RESULTS

The participants included those in the "oldest old" category (85+ years) and with both very high and very low levels of formal education (Table 1). Those with AD and dementia were significantly older and had fewer years of formal education compared with the control participants who did not have dementia.

Using the standard cutoff of 16 points, the CES-D score was significant in predicting both AD and dementia (Table 2). Participants with scores of 16 or more points had more than twice the risk for the development of AD or dementia compared with those whose scores were less than 16. A higher cutoff score of 17 points was a slightly stronger predictor of both outcomes than was the standard score of 16. The highest cutoff of 21 was the best predictor of both outcomes, although the finding for all dementia was only marginally significant;

Table 2. Effect of CES-D Cutoff Scores on Alzheimer’s Disease and All Dementia

CES-D Cut-off Score	AD (N = 36)	All Dementia (N = 56)
	OR (95% CI)	OR (95% CI)
CES-D ≥ 13 (n = 107 of 766)	1.83 (0.79–4.26)	1.63 (0.79–3.38)
CES-D ≥ 16 (n = 67 of 766)	2.75 (1.04–7.24)	2.37 (1.02–5.54)
CES-D ≥ 17 (n = 62 of 766)	2.89 (1.09–7.64)	2.50 (1.07–5.85)
CES-D ≥ 21 (n = 35 of 766)	3.49 (1.08–11.28)	2.82 (0.98–8.13)

Notes: Models were adjusted for age, sex, and education. The CES-D ranges from 0 to 60.

AD = Alzheimer’s disease; OR = odds ratio; CI = confidence interval; CES-D = Center for Epidemiological Studies Depression scale.

this was most likely a result of the smaller number of participants (n = 35) who scored at or above this cutoff value. The lowest cutoff score of 13 was not significantly associated with an increased risk for either outcome. Participants who reported a history of depression were not at significantly greater risk for the development of AD (OR = 1.50, 95% confidence interval [CI] = 0.49 to 4.63) or dementia (OR = 1.84, 95% CI = 0.76 to 4.47). Participant-reported duration of depression was also not a significant predictor of either outcome (AD: OR = 1.01, 95% CI = 0.88 to 1.15; dementia: OR = 1.04, 95% CI = 0.97 to 1.11).

The continuous CES-D score at baseline was significantly associated with sex ($p < .001$) and CES-D score at follow-up ($r = .27, p < .001$) and marginally correlated with baseline education ($r = -.07, p = .051$) and age ($r = .06, p = .096$). In a multivariate model adjusted for age, sex, and education, the continuous CES-D score was a marginally significant ($.05 < p < .10$) predictor of AD and dementia (Table 3). Of the four CES-D factors, the somatic/vegetative subset of items was a significant risk factor for dementia and a marginally significant risk factor for AD. Each one-point increase in the score for the somatic/vegetative factor increased the risk for dementia by 10%. Lack of positive affect was a marginally significant risk factor for dementia.

When participants were restricted to those scoring 15 or fewer points on the CES-D (meaning that they did not reach the standard cutoff for depressive symptoms), the somatic/vegetative factor remained marginally significant in predicting dementia (OR = 1.10, 95% CI = 0.98 to 1.22). The pattern of results for the total CES-D score and individual factors was similar when participants who scored two or fewer points on the CES-D were excluded.

DISCUSSION

Total CES-D score, when analyzed as a continuous variable, was a marginally significant predictor of both AD and all dementia 5 years after measurement in a sample of elderly persons; on average, participants exhibited a 4% increase in risk per CES-D point. When the CES-D was categorized as a dichotomous variable, the standard cutoff of 16 points was a significant predictor for both outcomes, with AD or dementia more than twice as likely to develop in participants who scored above this cutoff. Cutoff scores of 17 and 21 points were stronger predictors than 16 points for both outcomes, but a cutoff of 13 points was not significant for AD or dementia. Our results identify seniors who score 16 or more points on the CES-D as a population more likely to be

Table 3. Association of Continuous CES-D Scores and Factors with Alzheimer’s Disease and All Dementia

CES-D Score or Factor	AD (N = 36)	All Dementia (N = 56)
	OR (95% CI)	OR (95% CI)
Total CES-D	1.04 (0.99–1.08)	1.04 (1.00–1.08)
CES-D Factor		
Depressed affect	1.03 (0.91–1.17)	1.03 (0.93–1.14)
Positive affect	1.10 (0.95–1.27)	1.12 (0.99–1.25)
Somatic/vegetative	1.09 (0.99–1.19)	1.10 (1.02–1.18)
Interpersonal	1.05 (0.58–1.91)	1.00 (0.59–1.71)

Notes: Models were adjusted for age, sex, and education. Each OR represents the increase in risk per scale point. The CES-D ranges from 0 to 60; the depressed affect and somatic/vegetative subsets range from 0 to 21; the positive affect subset ranges from 0 to 12; and the interpersonal subset ranges from 0 to 6.

AD = Alzheimer’s disease; OR = odds ratio; CI = confidence interval; CES-D = Center for Epidemiological Studies Depression scale.

diagnosed subsequently with dementia and suggest that clinicians should be alert for signs of cognitive decline in these patients. Although some evidence suggests that depression may be related more closely to specific subtypes of dementia (such as vascular dementia) (3), our results show similar results for AD and all dementia.

It is not yet clear whether depression causes dementia or whether it reflects very early changes in mood as a result of preclinical dementia; the 5-year follow-up period of this study may be too short to distinguish clearly between these two possibilities. However, we believe that our results support the latter hypothesis.

First, participant-reported depression (a lifetime measure) was not a significant predictor of AD or dementia, meaning that depressive symptoms measured at the study baseline in these older persons were more important in predicting AD or dementia than was their history of lifetime depression. Second, the two CES-D factors most closely associated with AD and dementia in our study, somatic/vegetative factor and lack of positive affect, share similarities with apathy. Apathy is characteristic of AD (20,21) and has been suggested as a diagnostic criterion for preclinical AD (22).

The results of this study are consistent with those of the Religious Orders study (7), which found that the risk for AD increased by 19% for every one-point increase in a 10-item version of the CES-D. A review of case-control studies (4) found that medically treated depression occurring more than 10 years before AD onset nearly doubled the risk for AD (relative risk = 1.92, 95% CI = 1.11 to 3.32). In our study, we found that the score of a one-time measure of depressive symptoms (the CES-D) in older adults was associated with a doubling of the risk for AD 5 years later. Despite the fact that our study was a cohort design and our measure was participant-reported rather than medically diagnosed, the magnitude of the association is similar.

One limitation of our study is that the measures of baseline depressive symptoms were collected at a single point in time. Blazer and colleagues (23) reported that, in a multiphase longitudinal study, the participants who were depressed at each stage were not generally the same ones who were depressed at the previous stages. It is possible that the par-

ticipants in our sample with high CES-D scores at baseline had been depressed only for a short time and subsequently improved. However, Beekman and colleagues (24) reported that only 23% of a sample of depressed seniors were no longer depressed by the end of a 6-year follow-up. This finding is consistent with the significant correlation of CES-D scores at baseline and follow-up that we observed in our study.

Another limitation of our study is the short follow-up period compared with the potential duration of preclinical dementia. However, this 5-year follow-up lost nearly 20% of the sample as a result of participant deaths; a longer follow-up period would result in even higher attrition. An additional limitation is that a clinical interview for major depression was not done. However, the CES-D is a well-established, validated measure of depressive symptoms in the general population. Less severe levels of depression, as measured by the CES-D, may be more applicable to general community samples where the prevalence of major depression is low.

A strength of the study was the longitudinal design. In addition, the sample was selected to be representative of the general population 65 years or older and included persons living in urban and rural areas. The complete 20-item CES-D was used and multiple cutoff scores were evaluated. Finally, the association between depressive symptoms and cognitive impairment was studied in overall dementia and in AD, the most common subtype of dementia. Participants were identified as not having dementia at baseline, and both AD and dementia were diagnosed based on a full clinical assessment.

Although it is not clear whether depression is a risk factor for dementia or an early manifestation of dementia, it is clear that depressive symptoms predict the development of dementia in community-dwelling seniors. Clinicians should assess the cognition of seniors with depressive symptoms and should monitor those with depressive symptoms for evidence of cognitive impairment. Somatic and vegetative symptoms may be a more sensitive predictor of cognitive decline even in patients who do not score more than the traditional CES-D cutoff of 16 points; as such, elderly patients with these symptoms warrant particularly close attention and follow-up.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM IV). Washington, DC: American Psychiatric Association, 1994.
2. Alzheimer's Disease Education and Referral Center. Progress report on Alzheimer's disease, 2000: Taking the next step. <http://www.alzheimers.org/pubs/prog00.htm>, accessed June 1, 2002.
3. Alexopoulos GS. Vascular disease, depression, and dementia. *J Am Geriatr Soc*. 2003;51:1178-1180.
4. Jorm AF, van Duijn CM, Chandra V, et al. Psychiatric history and related exposures as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. *Int J Epidemiol*. 1991;20(Suppl 2): S43-S47.
5. Berger AK, Fratiglioni L, Forsell Y, Winblad B, Backman L. The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. *Neurology*. 1999;53:1998-2002.
6. Geerlings MI, Schmand B, Jonker C, et al. Depression and risk of cognitive decline and Alzheimer's disease. Results of two prospective community-based studies in The Netherlands. *Br J Psychiatry*. 2000; 176:568-575.
7. Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*. 2002;59:364-370.
8. Canadian Study of Health and Aging Working Group. Canadian Study of Health and Aging: study methods and prevalence of dementia. *Can Med Assoc J*. 1994;150:899-913.
9. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) Examination. *J Clin Psychiatry*. 1987;48:314-318.
10. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed, revised (DSM IIIR). Washington, DC: American Psychiatric Association, 1987.
12. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measurement*. 1977; 3:385-401.
13. McDowell I, Newell C. *Measuring Health: A Guide to Rating Scales and Questionnaires*. New York: Oxford University Press; 1996:254-259.
14. Rhee SH, Petroski GF, Parker JC, et al. A confirmatory factor analysis of the Center for Epidemiologic Studies Depression Scale in rheumatoid arthritis patients: additional evidence for a four-factor-model. *Arthritis Care Res*. 1999;12:392-400.
15. Myers JK, Weissman MM. Use of a self-report symptom scale to detect depression in a community sample. *Am J Psychiatry*. 1980;137: 1081-1084.
16. Diego MA, Field T, Hernandez-Reif M. CES-D depression scores are correlated with frontal EEG alpha asymmetry. *Depress Anxiety*. 2001;13:32-37.
17. Husaini BA, Neff JA, Stone RH. Psychiatric impairment in rural communities. *J Community Psychol*. 1979;7:137-146.
18. Lyness JM, Noel TK, Cox C, et al. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Arch Intern Med*. 1997;157:449-454.
19. SPSS Inc. *SPSS Base 10.0 for Windows User's Guide*. Chicago, IL: SPSS; 1999.
20. Migneco O, Benoit M, Koulibaly PM, et al. Perfusion brain SPECT and statistical parametric mapping analysis indicate that apathy is a circumscribed syndrome: a study in Alzheimer's disease and nondemented patients. *Neuroimage*. 2001;13:896-902.
21. Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer's disease. *J Am Geriatr Soc*. 2001;49:1700-1707.
22. Derousne C, Lacomblez L. Diagnosis of Alzheimer's disease in the prodromal phase: possibilities and benefits. *Presse Med*. 2000;29: 1663-1669.
23. Blazer DG, Hybels CE, Pieper CF. The association of depression and mortality in elderly persons: a case for multiple, independent pathways. *J Gerontol A Biol Sci Med Sci*. 2001;56:M505-M509.
24. Beekman ATF, Geerlings SW, Deeg DJH, et al. The natural history of late-life depression: a 6-year prospective study in the community. *Arch Gen Psychol*. 2002;59:605-607.

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