

# Depressive symptoms and cognitive decline in a community population of older persons

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**Background:** An association between depressive symptoms and cognitive decline has been observed in selected cohorts of older people, but studies of defined populations have had conflicting results.

**Objective:** To test whether the level of depressive symptoms predicted the rate of cognitive decline in a biracial community of older persons.

**Methods:** 4392 older people (88% of those eligible) from a defined community in Chicago completed two or three structured interviews at approximately three year intervals for an average of 5.3 years. At the baseline interview, the number of depressive symptoms was assessed with a 10 item version of the Center for Epidemiologic Studies Depression scale. Cognitive function was assessed at each interview with four performance tests, from which a previously established measure of global cognition was derived. Random effects models were used to assess change in cognition and its relation to depressive symptoms, controlling for age, sex, race, education, and baseline cognitive function.

**Results:** Participants reported a median of one depressive symptom at baseline (interquartile range, 0 to 2). For each depressive symptom, the rate of cognitive decline increased by a mean of about 5%. Results were not substantially changed when persons with cognitive impairment at baseline were excluded, or when chronic illness or participation in cognitively stimulating activities was controlled, and the association was not modified by age, sex, race, or education.

**Conclusions:** The results suggest that depressive symptoms predict cognitive decline in old age.

Recent research suggests that depressive symptoms in old age may be associated with the risk of developing Alzheimer's disease,<sup>1–3</sup> but the basis of this association is uncertain. At least some of the risk is probably related to the well established association of depressive symptoms with cognitive impairment.<sup>4</sup> That is, a detrimental effect of depressive symptoms on level of cognitive function in an older person might increase the likelihood of reaching some threshold at which dementia is clinically evident. A more fundamental way in which depressive symptoms might influence the risk of Alzheimer's disease is by an association with decline in cognitive function. Evidence on this issue is inconsistent, however. In several studies of selected groups of older people, the presence of depressive symptoms has predicted more rapid cognitive decline.<sup>3 5 6</sup> One population based study also observed this association,<sup>7</sup> but others have not<sup>8 9</sup> or have found the effect only in those with pre-existing cognitive impairment<sup>10</sup> or with relatively more education.<sup>2</sup>

In this study, we examined the association of depressive symptoms with rate of cognitive decline in older residents of a biracial community on the south side of Chicago. Depressive symptoms were assessed at baseline with a modified version of the Center for Epidemiologic Studies Depression scale (CES-D). During a five to six year period, cognitive function was assessed at approximately three year intervals with four brief performance tests from which a previously established measure of global cognition was constructed. We used a growth curve approach to analyse change in this global cognitive measure and to test whether the level of depressive symptoms predicted the rate of cognitive decline after controlling for baseline level of cognition and for the potentially confounding influence of age, sex, race, and education. In additional analyses, we examined whether selected clinical variables confounded the association and whether education or other demographic variables modified it.

## METHODS

### Participants

From October 1993 to May 1997, a census was carried out on all households in three adjacent neighbourhoods on the south side of Chicago; people aged 65 years or older were invited to participate in an in-home interview, and 6158 of 7826 eligible persons (79%) did so. The interview was repeated twice at approximately three year intervals. The study was approved by the institutional review board of Rush University Medical Center. Further information about the study is contained in previous publications.<sup>11–14</sup>

### Assessment of cognitive function

Each interview included administration of four brief tests of cognitive function. There were two measures of episodic memory: immediate and delayed recall of 12 ideas contained in the East Boston story.<sup>15</sup> There was one measure of perceptual speed: the oral version of the symbol digit modalities test, in which subjects match as many digit–symbol pairs as possible in 90 seconds.<sup>16</sup> The fourth test was the mini-mental state examination (MMSE), which is a widely used 30 item measure of global cognition.<sup>17</sup>

Because we wanted to minimise floor and ceiling artefacts and other sources of measurement error, and because in a previous factor analysis<sup>18</sup> all four tests loaded on a single factor that accounted for about 75% of the variance, we used a composite of all four tests in longitudinal analyses. As previously described,<sup>18</sup> we formed the composite by converting raw scores on each test to *z* scores, using the baseline mean and standard deviation in the population, and then averaging the *z* scores.

**Abbreviations:** CES-D, Center for Epidemiologic Studies Depression scale; MMSE, mini-mental state examination

### Assessment of depressive symptoms

Depressive symptoms were assessed at the baseline interview with a 10 item form<sup>19–21</sup> of the CES-D scale.<sup>22</sup> For each symptom, a brief item stem was read by the examiner, and the participant indicated whether they had experienced the symptom much of the time during the past week. The score was the total number of symptoms experienced. The CES-D is widely used in epidemiological studies of older persons, and the reliability of this version of the CES-D and its correspondence to the original CES-D have been established previously.<sup>19–21</sup> A strong advantage of this format is that it minimises respondent burden by having brief item stems (mean of 4.2 words/item) which are read to the participant and require only a yes or no response.

### Assessment of other variables

Seven medical conditions were reported to have been identified previously by a physician in at least 5% of the population at baseline: heart disease, stroke, hypertension, diabetes, cancer, thyroid disease, and shingles or herpes zoster. We used the number of these conditions reported at the baseline interview as an indicator of chronic illness, as previously described.<sup>13 14</sup>

At the baseline interview, people rated frequency of participation in seven cognitively stimulating activities (for example, reading a magazine) from which a previously established composite measure of cognitive activity participation was derived.<sup>13 14 18 23</sup>

### Data analysis

Because the distribution of CES-D scores was skewed, we estimated its association with age and education using Spearman correlation coefficients and its association with sex and race using the Kruskal–Wallis test.

We used random effects models<sup>24</sup> to characterise change in the global measure of cognitive function during the observation period and to test the association of CES-D score with initial level of cognition and rate of change. In this approach, each individual path of change is assumed to follow the path of the population except for random effects that cause the baseline level of function to be higher or lower and the rate of change to be faster or slower. An important advantage of this approach is that baseline level of cognition is explicitly modelled as a source of random variability and a possible correlate of how rapidly people change. Further information on the application of these models to cognitive function data is published elsewhere.<sup>25 26</sup>

The core model included terms for time since baseline in years, CES-D score, and the interaction of CES-D score with time. The term for time indicates the average annual change in the global cognitive score for a participant with a CES-D score of zero. The term for CES-D score indicates the effect of one depressive symptom on the global cognitive score at baseline. The interaction denotes the effect of one depressive symptom on annual rate of change in global cognition. This and all subsequent models also included terms to account for

the potentially confounding effects of age, sex, race (black/non-black), and education on initial level of cognition and rate of change.

In separate analyses, we repeated the core model with a quadratic term for CES-D score and its interaction with time, excluding persons with evidence of cognitive impairment at baseline, with terms to control for the effects of chronic illness, and terms to control for frequency of cognitive activity.

In subsequent analyses, we repeated the core model with two additional interaction terms: education × CES-D score and education × CES-D score × time. The latter term indicates whether the association of CES-D score with cognitive decline varied by education. We constructed similar models for sex, race, and age.

Programming was done in SAS.<sup>27</sup> All models were validated graphically and analytically, and assumptions were judged to be adequately met.

## RESULTS

### Participation in follow up

Of 6158 persons at baseline, 1175 died before the first follow up interview. Of the remaining 4983 people, 4392 (88%) completed one (n = 1609) or two (n = 2783) follow up interviews during a mean of 5.3 years of observation. Analyses are based on this group. Age at baseline ranged from 65 to 101 years (mean (SD), 73.9 (6.5)). They had a mean of 12.0 (3.7) years of education completed and a mean MMSE score of 26.2 (4.6); 62.1% were women; 38.1% were white, 61.7% were black; 0.1% were American Indians, and 0.1% were Asian or Pacific Islanders.

### Distribution of depressive symptoms

Participants reported a median of one depressive symptom on the CES-D (interquartile range, 0 to 2). The distribution of CES-D scores was positively skewed, with 41% of the cohort reporting no symptoms, 24% reporting one, 12% reporting two, 8% three, and 15% four or more. CES-D score had a small positive correlation with age ( $p = 0.10$ ,  $p < 0.001$ ) and a negative correlation with education ( $p = -0.21$ ,  $p < 0.001$ ). Women reported more symptoms than men ( $\chi^2 = 46.0$ ,  $p < 0.001$ ) and black persons reported more symptoms than those who were not black ( $\chi^2 = 75.3$ ,  $p < 0.001$ ).

### Depressive symptoms and cognitive decline

At baseline, the composite measure of global cognition ranged from 65.0 to 115.4 (mean (SD), 101.2 (7.8)), with higher scores indicating better cognitive function. We examined the relation of CES-D score to baseline level of global cognition and annual rate of global cognitive decline in a random effects model (table 1). This and all subsequent models also included terms to control for the potentially confounding effects of age, sex, race, and education. In this analysis, the global cognitive score declined an average of 0.56 unit per year in those without depressive symptoms, as indicated by the term for time. For each depressive symptom reported on the CES-D scale, the baseline cognitive score was an average of 0.26 unit lower, as shown by the term for CES-D score. There was also a significant interaction between CES-D score and time. For each depressive symptom on the CES-D, the rate of global cognitive decline increased by an average of 0.03 unit, or about 5%. Thus a participant with four symptoms on the CES-D (90th centile) declined an average of 0.68 unit annually, an increase of approximately 21% compared with persons reporting no symptoms on the CES-D.

To see if the association of CES-D score with cognitive decline had a non-linear component, we repeated the analysis with a quadratic term for CES-D score and its

**Table 1** The association of Center for Epidemiological Studies Depression scale (CES-D) score with baseline level of global cognition and annual rate of change estimated from a random effects model adjusted for age, sex, race, and education

Model term	Estimate	SE	p Value
Time	-0.56	0.04	<0.001
CES-D score	-0.26	0.05	<0.001
CES-D score × time	-0.03	0.01	0.002

interaction with time. There was no quadratic effect on baseline cognition or rate of cognitive decline (both  $p > 0.50$ ).

### Influences on the association of depressive symptoms with cognitive decline

Although we controlled for baseline level of global cognition, we considered the possibility that the results depended on a subset of people with substantial cognitive impairment. We repeated the original analysis, therefore, excluding those whose global cognitive score at baseline was at or below the fifth centile. The interaction of CES-D score with time was not substantially changed (estimate  $-0.03$ ,  $SE = 0.01$ ,  $p = 0.007$ ). Results were similar when we excluded those with baseline global cognition at or below the 10th centile (estimate  $-0.03$ ,  $SE = 0.01$ ,  $p = 0.001$ ) or the 15th centile (estimate  $-0.04$ ,  $SE = 0.01$ ,  $p = 0.001$ ).

To determine whether chronic illness contributed to the association of CES-D score with cognitive decline, we repeated the original model with terms for number of chronic medical conditions (mean (SD), 1.1 (1.0), range 0 to 6) and its interaction with time. In this analysis, the association of CES-D score with cognitive decline was not substantially changed (estimate  $-0.03$ ,  $SE = 0.01$ ,  $p = 0.002$ ).

To see whether cognitive activity, by virtue of its association with cognitive decline,<sup>14,23</sup> affected the results, we repeated the original analysis with terms added for cognitive activity frequency and its interaction with time. The interaction of CES-D score with time in this model (estimate  $-0.03$ ,  $SE = 0.01$ ,  $p = 0.011$ ) was comparable to the original analysis.

Because of a previous report that the association of depressive symptoms with cognitive decline depended on level of education,<sup>2</sup> we repeated the original analysis with terms added for the interaction of education with CES-D score and for the triple interaction of education by CES-D score by time. There was no triple interaction ( $p = 0.962$ ), indicating that the association of CES-D with cognitive decline did not vary by education. We conducted a similar set of analyses for sex, race, and age. We found no evidence in these analyses that sex, race, or age modified the association of depressive symptoms with cognitive decline (all  $p > 0.40$ ).

## DISCUSSION

In a biracial community population of more than 4000 older people, we found that level of depressive symptoms was related to rate of global cognitive decline during a five year period. Cognitive decline in those who reported four depressive symptoms (90th centile in this population) was about 20% more rapid than decline in those without depressive symptoms. These results suggest that depressive symptoms predict cognitive decline in old age.

As noted above, some previous studies have observed an association between depressive symptoms and subsequent cognitive decline, consistent with the present findings.<sup>3,5-7</sup> Other studies have not found the association,<sup>8,9</sup> however, or have found it to depend on education<sup>2</sup> or on pre-existing cognitive impairment.<sup>10</sup> We found no evidence education or other demographic variables modified the association in this cohort or that baseline level of cognition affected results.

We suggest two factors that may be contributing to the inconsistency in previous research. First, older people differ widely in level of cognition, and cognitive decline occurs slowly. However, many previous studies are based on only two data points<sup>2,6-9</sup> or less than four years of observation,<sup>2,8,9</sup> and all except one<sup>3</sup> have used individual cognitive tests as outcomes, making it difficult to assess individual paths of cognitive decline reliably. A second factor that is probably contributing to the inconsistent results is the temporal instability of depressive symptoms—that is, although there are enduring individual differences in the tendency to

experience depressive symptoms, the level of symptoms at any given time reflects situational factors (and random error) in addition to this more enduring tendency. The only previous study that assessed depressive symptoms longitudinally found that cognitive decline was most pronounced in those whose symptoms were persistent.<sup>7</sup>

The basis of the association between depressive symptoms and cognitive decline is unknown. Depressive symptoms could be a reaction to cognitive impairment, but we controlled for level of cognitive function at baseline; the results were unchanged when we excluded people with cognitive impairment at baseline, making this explanation unlikely. Alternatively, because depressive symptoms are seen in Alzheimer's disease and other common neurodegenerative conditions like cerebrovascular disease and parkinsonism that contribute to cognitive decline, they could be an early indicator of the presence of one of these conditions. In a recent study,<sup>28</sup> however, depressive symptoms proximate to death were not related to cortical plaques and tangles and did not modify the relation of this pathology to dementia or cognitive impairment proximate to death. Further clinicopathological research is needed to clarify the association of depressive symptoms with different pathological lesions and their clinical consequences.

Another possibility is that depressive symptoms in old age are associated with dysfunction in neural systems that help regulate the hypothalamic–pituitary–adrenal stress axis.<sup>29</sup> In animals, stressful experience has been associated with structural changes in the hippocampal formation<sup>30,31</sup> and impairment in hippocampally mediated forms of learning and memory.<sup>32</sup> In humans, hippocampal atrophy has been reported in persons with major depression.<sup>33,34</sup> Together, those observations suggest that chronic experience of even relatively low levels of depressive symptoms may compromise the hippocampus and perhaps other neural systems that regulate the stress axis, reducing the efficiency of functions mediated by these structures and perhaps making them more vulnerable to neurodegenerative changes. Further research on the relation between chronic psychological distress and cognitive function in old age is needed.

Confidence in these findings is strengthened by two factors. First, they are based on a defined population of older persons, making it likely that there was a broad spectrum of depressive symptoms and cognitive function. In addition, the use of a previously established composite measure of cognition and the availability of an average of more than five years of observation per person with a high rate of follow up participation enhanced our ability to reliably characterise individual paths of change in cognitive function.

Several limitations to these findings should be noted. Because we assessed depressive symptoms at a single point in time with a relatively brief measure, it is possible that these results underestimate the association of depressive symptoms with cognitive decline. In addition, we used a global measure of cognition, but some studies suggest that depressive symptoms may be more strongly related to some forms of cognition than others,<sup>3,35</sup> which may have led us to underestimate the magnitude of the association. Finally, we used the number of symptoms to define the severity of depressive symptomatology. These findings may not generalise, therefore, to syndromic definitions of depression or to other methods of scaling its severity.

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