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# Depressive Symptoms and Risk of Alzheimer's Disease in More Highly Educated Older People

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**BACKGROUND AND OBJECTIVE:** In an earlier study we observed that a depressive syndrome was highly predictive of developing Alzheimer's disease (AD) in older persons with normal baseline cognition and higher levels of education. We interpreted these findings as the depression being an early noncognitive manifestation of AD in persons with more cognitive reserve. The present study examines whether specific symptoms of depression can be identified that predict AD among older subjects with higher levels of education.

**DESIGN AND PARTICIPANTS:** In the community-based Amsterdam Study of the Elderly (AMSTEL), a sample of 3147 nondemented persons with normal cognition, 65 to 84 years old, was selected and divided into subjects with >8 years and ≤8 years of education. At baseline, the presence or absence of 12 specific symptoms of depression was assessed. At follow-up, patients with incident AD were diagnosed according to DSM-IV criteria in a two-step diagnostic procedure.

**RESULTS:** After an average follow-up of 3.2 years, 1911 persons were reevaluated, of whom 22 with >8 years and 31 with ≤8 years of education had developed AD. Multivariate logistic regression analyses showed that among persons with >8 years of education depressed mood and subjective bradyphrenia were strongly associated with incident AD. No association between depressive symptoms and AD was observed among subjects with ≤8 years of education.

**CONCLUSIONS:** Both depressed mood and subjective bradyphrenia seem to indicate subclinical AD in older people with higher levels of education. Clinicians should be alert that in these persons, AD may become apparent within a relatively short period of time. *J Am Geriatr Soc* 48:1092-1097, 2000.

**Key words:** depression; cognitive decline; dementia; depressive symptoms; Alzheimer's disease; education; cohort study

The question of whether depression could be the cause or the consequence of cognitive decline and dementia has received increasing attention.<sup>1</sup> At least three hypotheses can be postulated about the nature of the association between depression and dementia: (1) depression could be an etiological risk factor for the onset of cognitive decline and dementia; (2) depression could be an early symptom or subclinical expression of the dementia process; or (3) depression could be a psychological reaction to perceived cognitive decline. So far, none of these hypotheses have been convincingly confirmed or rejected, because prospective studies have reported divergent results. Devanand et al.<sup>2</sup> found a moderate association between depression and incident Alzheimer's disease (AD), whereas other studies found no association between depressive symptomatology and subsequent cognitive decline,<sup>3,4</sup> or only if cognitive impairment was already present.<sup>5-7</sup>

Earlier, we reported that a depressive syndrome in older people with normal cognition was strongly associated with incident AD in subjects with >8 years of education, but not in those with ≤8 years of education.<sup>8</sup> We hypothesized that, due to greater cognitive reserve, the expression of cognitive symptoms of AD may be delayed in persons with higher levels of education, but not the noncognitive symptoms. Thus, differences in duration of illness and cognitive reserve capacity may have led to differences in risk between the education groups. In a subgroup of more highly educated subjects, depression may be an early noncognitive manifestation of the neuropathological process of AD before cognitive symptoms become apparent.

The finding that depression in later life may be associated with the expression of AD in persons in whom cognitive decline is not yet apparent raises the question of whether this type of depression is characterized by specific symptoms that may distinguish it from other types of depression in later life. This has led us to examine whether specific symptoms of depression predicted developing AD in more highly educated older persons with normal cognition. In addition, because memory complaints are associated with both depression and dementia,<sup>9</sup> we also examined the possible confounding effect of memory complaints.

## METHODS

### Baseline Sample

We used data from a large cohort of community-dwelling older people in the Netherlands (Amsterdam Study of the Elderly (AMSTEL)). The sampling procedure and

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nonresponse of the baseline population of the AMSTEL study have been described in more detail elsewhere.<sup>10,11</sup> In brief, 5666 noninstitutionalized older people, aged 65 to 84 years, were selected from 30 general practices spread across the city of Amsterdam. Within each practice a fixed proportion of persons was randomly selected from each of four 5-year age strata (65–69 years to 80–84 years) to obtain equal-sized strata.<sup>10</sup> Of the 5666 persons sampled, 4051 (71.5%) gave their written consent after the procedures had been fully explained and participated in the study, 23.9% refused to participate, and 4.6% could not be contacted because they had either died, been institutionalized, or moved away from Amsterdam.

### Study Sample

The present study sample was selected in two steps. First, a cohort free of dementia was selected by excluding from the baseline population all subjects ( $n = 273$ ) who were diagnosed as having dementia according to the criteria of either DSM-III-R<sup>12</sup> or GMS-AGECAT (Geriatric Mental State Schedule and its computerized diagnostic system AGECAT).<sup>13–15</sup> The procedures of the diagnostic evaluation at baseline have been described in more detail elsewhere.<sup>9,16</sup> Dementia according to GMS-AGECAT criteria was indicated by organic illness syndrome levels of 3–5. Second, to select subjects with normal cognition only, all subjects with subthreshold levels of dementia were excluded as well (i.e., GMS-AGECAT levels of 1–2 or Mini-Mental State Exam (MMSE)<sup>17</sup> scores of  $\leq 25$  ( $n = 631$ )). In all, 904 subjects were excluded, resulting in a study sample of 3147 nondemented subjects with normal cognition (i.e., MMSE scores of 26–30 and GMS-AGECAT organic illness score of 0).

### Measurements

#### Baseline

From May 1990 to November 1991, trained lay people visited all participants at home. The interview consisted of questions on sociodemographic characteristics, current health status, and medical history. Furthermore, it included the MMSE and the Dutch version of the GMS.<sup>18</sup> The GMS was used to assess the following 12 symptoms of depression: depressed mood, loss of interest, decrease in appetite or loss of weight, insomnia, psychomotor agitation, psychomotor retardation, loss of energy, feelings of guilt, subjective bradyphrenia (feeling of being slowed down in thinking), diminished ability to concentrate, indecisiveness, and suicidal ideation (see Appendix). Level of education (highest grade completed) was measured on an eight-point ordinal scale ranging from uncompleted primary school to completed university education and was converted to years of education. Memory complaints were assessed with the question, "Do you have complaints about your memory?" Answers were coded in two categories ("no/sometimes, but is no problem" vs "yes, is a (serious) problem").

#### Follow-up

At follow-up in 1994, all subjects who were available were interviewed again by trained lay persons using the same interview procedure as in 1990–1991. A subsample of subjects who were suspected of having developed dementia were invited for diagnostic evaluation. The screening procedure and diagnostic evaluation have been described in more detail elsewhere.<sup>9</sup> In brief, all subjects with MMSE scores of 23 or

less or with impairment in orientation in time, recent memory, or learning were invited for diagnostic evaluation. This was done by physicians specifically trained for this purpose who administered the Dutch version of the Cambridge Examination for Mental Disorders (CAMDEX) in the Elderly (CAMDEX).<sup>19</sup> Clinical diagnoses of AD and other types of dementia were made according to the respective DSM-IV criteria.<sup>20</sup> Diagnoses were determined during weekly meetings with the senior neurologist (C.J.) and the neuropsychologist (M.I.G.).

### Statistical Analyses

The statistical analyses were performed for subjects with  $\leq 8$  years of education and subjects with  $>8$  years of education separately (dichotomized at the median of the study sample) using SPSS for Windows (version 7.5, SPSS Inc., Chicago, IL). First, baseline characteristics were compared between subjects of the study sample who were and were not available for follow-up in 1994 and between subjects with low levels and higher levels of education. Second, univariate logistic regression analyses were performed to assess the crude associations between each of the symptoms of depression and incident AD. Third, those symptoms that were significantly associated with incident AD were entered into a multivariate model with adjustments for age (as a continuous variable), sex (women vs men), and memory complaints (yes vs no). Fourth, those depressive symptoms that were not statistically significant in the multivariate model were removed from the model one at a time until the model contained significantly associated variables only.

### RESULTS

Table 1 shows the distribution of baseline characteristics for subjects of the study sample who were and were not available for follow-up in 1994. As can be seen, older people, people without memory complaints, those with psychomotor retardation, loss of energy and a lower level of education were more likely to become lost to follow-up. Table 2 shows the baseline distribution among those subjects of the study sample who were available at follow-up, according to education strata. At baseline, subjects with  $>8$  years of education were somewhat younger on average, were more often male, complained more often about their memory, reported more often feelings of guilt, and had more often subjective bradyphrenia than subjects with  $\leq 8$  years of education. Among subjects with  $\leq 8$  years of education, indecisiveness was more common than among subjects with  $>8$  years of education (Table 2).

The follow-up duration was 3.2 years, on average (SD = 0.36 year, range 2.3–4.3 years). At follow-up, 1911 persons were still available for interview (60.7% of 3147); 414 (13.2%) had died, 202 (6.4%) were too ill to participate, 449 (14.3%) refused to participate, and 171 (5.4%) could not be contacted. Of the 1911 persons who were interviewed, 287 were selected for further diagnostic evaluation, of whom 53 persons received a diagnosis of AD (of whom 22 patients had  $>8$  years of education and 31 had  $\leq 8$  years of education). Seven people had vascular or secondary dementia and were excluded from the analyses.

#### Univariate Analyses

Table 3 shows the univariate associations between age, sex, memory complaints, each of the symptoms of depres-

Table 1. Baseline Distribution Among the Study Sample (n = 3147) of Age, Sex, Memory Complaints, and the Presence of Symptoms of Depression, for Those Who Were and Were Not Lost to Follow-up in 1994

|  | Follow-up<br>Interview<br>n = 1911 | Lost to<br>Follow-up<br>n = 1236 | P-<br>value* |
|--|------------------------------------|----------------------------------|--------------|
| Mean age (SD)                              | 73.1 (5.5)                         | 74.6 (5.7)                       | <.001        |
| Sex (female)                               | 1190 (62%)                         | 739 (60%)                        | .163         |
| Memory complaints (yes)                    | 210 (11%)                          | 108 (9%)                         | .041         |
| Depressed mood (yes)                       | 169 (9%)                           | 111 (9%)                         | .895         |
| Loss of interest (yes)                     | 43 (2%)                            | 29 (2%)                          | .860         |
| Loss of appetite/weight<br>(yes)           | 185 (10%)                          | 139 (11%)                        | .158         |
| Insomnia (yes)                             | 493 (26%)                          | 330 (27%)                        | .574         |
| Psychomotor agitation<br>(yes)             | 111 (6%)                           | 77 (6%)                          | .626         |
| Psychomotor retardation<br>(yes)           | 12 (0.6%)                          | 17 (1.4%)                        | .032         |
| Loss of energy (yes)                       | 223 (12%)                          | 179 (15%)                        | .021         |
| Guilt feelings (yes)                       | 78 (4%)                            | 37 (3%)                          | .112         |
| Subjective bradyphrenia<br>(yes)           | 340 (18%)                          | 234 (19%)                        | .419         |
| Diminished ability to<br>concentrate (yes) | 120 (6%)                           | 69 (6%)                          | .422         |
| Indecisiveness (yes)                       | 244 (13%)                          | 135 (11%)                        | .120         |
| Suicidal ideation (yes)                    | 96 (5%)                            | 61 (5%)                          | .912         |
| Education (>8 years)                       | 1036 (54%)                         | 578 (47%)                        | <.001        |

\*P-values are based on chi-square statistics, except for age, where P-value is based on *t*-test.

sion, and incident AD. Increasing age was associated with incident AD in both education groups, whereas women had a greater risk of AD only in the group with  $\leq 8$  years of education. Memory complaints were associated with incident AD in subjects with  $> 8$  years of education, but not in subjects with  $\leq 8$  years of education. Depressed mood, loss of appetite or weight, psychomotor agitation, subjective bradyphrenia, and suicidal ideation were also univariately associated with incident AD in subjects with  $> 8$  years of education. Among subjects with  $\leq 8$  years of education, subjective bradyphrenia was the only depressive symptom that was significantly associated with incident AD.

#### Multivariate Analyses

When the symptoms of depression that were univariately associated with AD were entered into a multivariate model with adjustments for age, sex, and memory complaints, both depressed mood and subjective bradyphrenia remained strongly associated with incident AD in subjects with  $> 8$  years of education. In these subjects, the predictive effect of memory complaints on AD decreased to a statistically non-significant level (Table 4).

To explore the possibility that more highly educated subjects showed a decline from a previous level of cognitive functioning that could not be detected by the GMS and the MMSE, additional analyses were performed with adjustments for the memory test that was used to select subjects for diagnostic evaluation at follow-up.<sup>9</sup> This memory test measured orientation in time, learning, and recent memory using

Table 2. Baseline Distribution Among Those Subjects of the Study Sample Who Were Available at Follow-up (n = 1911) of Age, Sex, Memory Complaints and the Presence of Symptoms of Depression, According to Level of Education

|  | Education            |                           | P-<br>value* |
|--|----------------------|---------------------------|--------------|
|  | >8 years<br>n = 1036 | $\leq 8$ years<br>n = 871 |              |
| Mean age (SD)                              | 72.5 (5.6)           | 73.7 (5.4)                | <.001        |
| Sex (female)                               | 588 (57%)            | 600 (69%)                 | <.001        |
| Memory complaints<br>(yes)                 | 127 (12%)            | 82 (9%)                   | .046         |
| Depressed mood (yes)                       | 84 (8%)              | 85 (10%)                  | .206         |
| Loss of interest (yes)                     | 19 (2%)              | 24 (3%)                   | .177         |
| Loss of appetite/weight<br>(yes)           | 100 (10%)            | 85 (10%)                  | .938         |
| Insomnia (yes)                             | 271 (26%)            | 222 (26%)                 | .739         |
| Psychomotor agitation<br>(yes)             | 62 (6%)              | 49 (6%)                   | .739         |
| Psychomotor retardation<br>(yes)           | 7 (1%)               | 4 (1%)                    | .534         |
| Loss of energy (yes)                       | 126 (12%)            | 96 (11%)                  | .439         |
| Guilt feelings (yes)                       | 51 (5%)              | 27 (3%)                   | .045         |
| Subjective bradyphrenia<br>(yes)           | 201 (19%)            | 138 (16%)                 | .043         |
| Diminished ability to<br>concentrate (yes) | 63 (6%)              | 57 (7%)                   | .678         |
| Indecisiveness (yes)                       | 114 (11%)            | 128 (15%)                 | .016         |
| Suicidal ideation (yes)                    | 44 (4%)              | 52 (6%)                   | .086         |

The numbers do not add up to 1911 because of some missing values for the variable education.

\*P-values are based on chi-square statistics, except for age, where P-value is based on *t*-test.

the relevant items from four mental status tests that were administered at the baseline interview.<sup>17,21-23</sup> Memory impairment is a strong predictor of AD<sup>24</sup> and probably a more sensitive measure to detect subtle cognitive decline, especially in more highly educated persons.<sup>25</sup> If depressed mood or subjective bradyphrenia could be attributed to a decline in cognitive functioning relative to a premorbid level before study entry, it would be predicted that adding the memory test to the model would result in a less strong association between either or both of these depressive symptoms and AD. The results of this analysis showed that when the memory test was added to the model containing age, sex, memory complaints, depressed mood, and subjective bradyphrenia, the association between subjective bradyphrenia and incident AD changed little (odds ratio (OR) = 4.56; 95% confidence interval (CI) = 1.71-12.18), whereas the association between depressed mood and AD became stronger (OR = 4.37; 95% CI = 1.47-12.97).

#### DISCUSSION

This study examined which specific symptoms of depression were associated with incident Alzheimer's disease in older people with normal baseline cognition and higher levels of education. Both depressed mood and subjective bradyphrenia remained strongly predictive of AD in more highly educated subjects. The independent effects of an affective symptom (depressed mood) and a cognitive symptom (sub-



**Table 3. Univariate Associations (Crude Odds Ratios (OR) with 95% Confidence Intervals (CI)) Between Age, Sex, Memory Complaints, Symptoms of Depression and Incident Alzheimer's Disease for Two Levels of Education**

|   | >8 Years of Education<br>n = 1036 OR (95% CI) | ≤8 Years of Education<br>n = 871 OR (95% CI) |
|---|---|--|
| Age (per year increase)                       | 1.19 (1.10–1.30)                              | 1.18 (1.09–1.27)                             |
| Sex (women vs men)                            | 1.34 (0.56–3.22)                              | 3.13 (1.08–9.03)                             |
| Memory complaints (yes vs no)                 | 4.39 (1.80–10.70)                             | 1.93 (0.72–5.16)                             |
| Depressed mood (yes vs no)                    | 4.48 (1.70–11.78)                             | 0.99 (0.29–3.32)                             |
| Loss of interest (yes vs no)                  | 2.62 (0.33–20.58)                             | 1.18 (0.15–9.03)                             |
| Loss of appetite/weight (yes vs no)           | 2.87 (1.03–7.94)                              | 0.63 (0.15–2.67)                             |
| Insomnia (yes vs no)                          | 0.83 (0.30–2.27)                              | 0.55 (0.21–1.45)                             |
| Psychomotor agitation (yes vs no)             | 3.65 (1.20–11.13)                             | Empty cell*                                  |
| Psychomotor retardation (yes vs no)           | Empty cell*                                   | Empty cell*                                  |
| Loss of energy (yes vs no)                    | 0.71 (0.17–3.09)                              | 1.23 (0.42–3.59)                             |
| Guilt feelings (yes vs no)                    | Empty cell*                                   | Empty cell*                                  |
| Subjective bradyphrenia (yes vs no)           | 6.36 (2.68–15.09)                             | 2.27 (1.02–5.03)                             |
| Diminished ability to concentrate (yes vs no) | 1.58 (0.36–6.93)                              | 0.98 (0.23–4.22)                             |
| Indecisiveness (yes vs no)                    | 0.38 (0.05–2.87)                              | 0.62 (0.18–2.06)                             |
| Suicidal ideation (yes vs no)                 | 3.73 (1.06–13.12)                             | 1.09 (0.25–4.68)                             |

The numbers do not add up to 1911 because of four missing values for the variable education.

\*One cell in the crosstab had no observations and odds ratios could not be calculated.

**Table 4. Odds Ratios (OR) (with Corresponding 95% Confidence Intervals (CI)) Adjusted for Age, Sex, and Memory Complaints of the Association Between Symptoms of Depression and Incident Alzheimer's Disease that Remained Statistically Significant in the Multivariate Analyses**

|                                     | >8 Years of Education<br>n = 1036 OR (95% CI)* | ≤8 Years of Education<br>n = 871 OR (95% CI)* |
|-------------------------------------|--|---|
| Age (per year increase)             | 1.18 (1.08–1.29)                               | 1.17 (1.08–1.27)                              |
| Sex (women vs men)                  | 1.31 (0.51–3.34)                               | 2.42 (0.82–7.11)                              |
| Memory complaints (yes vs no)       | 1.87 (0.67–5.19)                               | 1.64 (0.57–4.73)                              |
| Subjective bradyphrenia (yes vs no) | 4.62 (1.77–12.04)                              | 2.19 (0.92–5.19)                              |
| Depressed mood (yes vs no)          | 3.74 (1.30–10.80)                              | 0.71 (0.20–2.54)                              |

The numbers do not add up to 1911 because of four missing values for the variable education.

\*Adjusted for all other variables mentioned in the table.

jective bradyphrenia) suggest that the depressed mood did not result solely from grief about deteriorating cognitive capacities. It could be argued that the observed association between depressed mood and subjective bradyphrenia and incident AD is explained by the possibility that more highly educated people are more used to articulating their problems or are more critical about subtle changes they might notice. If depressed mood were explained by a pure psychological reaction it would be predicted that the association between depressed mood and AD would decrease or disappear after adjusting for memory complaints and cognitive symptoms of depression. This was not the case, however. Furthermore, depressed mood was more prevalent among people with fewer years of education and, although subjective bradyphrenia tended to be more prevalent among more highly educated subjects, this complaint was fairly frequent among those with fewer years of education (Table 2).

Moreover, we observed that the effect of depressed mood became stronger after adjusting for objective memory performance. At baseline, a study sample was selected with normal scores on mental status tests to minimize the possibility that the depressive symptoms were a consequence of an overt

dementia process. This could not entirely rule out a psychological explanation, however, because more highly educated subjects with subtle cognitive decline may not have been detected by the MMSE and the GMS at baseline. Contrary to our expectation, adding memory performance to the model did not result in a decreased association between depressed mood and AD, which suggests that the association between depressed mood and AD may be independent of cognitive status.

We have to consider the possibility that our findings may be biased due to differential loss to follow-up. In the study sample, the percentage of loss to follow-up was considerable. It has been found that depressed older people are at increased risk of death, compared with nondepressed older people.<sup>26</sup> In our study sample, however, subjects with a depressed mood were not more likely to be lost to follow-up than subjects without a depressed mood (39.6% vs 39.2%; chi-square = 0.017; *df* = 1; *P* = .895), nor were subjects with a diminished ability to think compared with subjects without this complaint (40.8% vs 38.9%; chi-square = 0.654; *df* = 1; *P* = .419). This was irrespective of educational level, and this nondifferential misclassification would have resulted in an underestimation of associations in our analyses.

In summary, a depressed mood and a subjective feeling of being slowed down in thinking were independently associated with incident Alzheimer's disease in more highly educated older persons with normal baseline cognition. These associations were not found among less educated persons. A depressive syndrome, with both an affective and a cognitive component, may appear as an early manifestation of the disease process in a subgroup of patients. Clinicians should be alert that these persons may develop AD in a relatively short period of time and that the subclinical presentation of AD may be different for different levels of education.

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## APPENDIX

### Items from the Geriatric Mental State Schedule That Were Used to Assess 12 Symptoms of Depression

#### (1) Depressed Mood

Have you been sad (depressed, miserable, in low spirits, blue) recently? (yes = often, severe); or observation: looks or sounds sad, gloomy, mournful, or depressed (yes = definite, excessive, and much of the time); or observation: eyes moist, tearful, or crying (yes = definite, excessive, and much of the time).

#### (2) Loss of Interest

How is your interest in things? (Do you keep up your interests?) (Has less interest in things in the last 3 months than he/she used to have.)

#### (3) Decrease in Appetite/Weight Loss

What has your appetite been like? Do you enjoy your food? Have you been eating less than usual? (yes = strong diminution in the desire for food in the absence of known medical condition and without nausea); or, Have you lost any weight during the past 3 months? (yes = lost 4.5 kg in the absence of known medical condition and without nausea.)

#### (4) Insomnia

Have you had any difficulty falling asleep? Do you lie awake for long periods of time? (yes = difficulty falling asleep); or, Have you recently been waking up early in the morning and found it impossible to get back to sleep? What time would that be? Is that your usual time? How often has it happened? (yes = awakens about 2 hours before normal time of awakening, at least two times a week.)

#### (5) Psychomotor Agitation

Do you have difficulty in relaxing (resting)? (yes = severe/frequent/persistent); or observation: restless, keeps fidgeting or squirming in seat (yes = severe); or observation: restless, gets up and moves about restlessly (yes = severe).

#### (6) Psychomotor Retardation

Observation: very slow in all movements.

**(7) Loss of Energy**

Have you had too little energy (to do the things you want to do)? How long have you had that for? Are you like that most days? (yes = loss of energy in the last 3 months.)

**(8) Guilt**

Do you tend to blame yourself or feel guilty about anything? What? Is it reasonable? (yes = obvious excessive guilt or self-blame; do not include justifiable or minor self-blame.)

**(9) Subjective Bradyphrenia**

Do you seem to be slowed down in your thinking recently? Worse than usual? (yes = subjective slowing in thinking.)

**(10) Diminished Ability to Concentrate**

How is your concentration? Can you concentrate on a television (radio, film) program? (Can you watch it (listen to it) all the way through?) (yes = severe difficulty in concen-

trating); or observation: obvious difficulty in concentrating on interview.

**(11) Indecisiveness**

Do you find it difficult to make up your mind (to make decisions)? (yes = feels very indecisive); or observation: appears indecisive.

**(12) Suicidal Ideations**

Have you felt in the last 3 months that life was not worth living? (yes = severe/frequent/persistent); or Have you ever felt you wanted to end it all? (Have you ever thought of doing anything about it yourself?) (Killing yourself?) (yes = has felt suicidal in the last month or for at least 2 weeks in the last month); or Did you actually try anything? When was that? What did you do (or plan to do)? (yes = has done something or planned to do something about killing self.)