Prevalence studies of Alzheimer's disease (AD) have found higher rates of AD among elderly people with fewer years of education.\(^1\)\(^-\)\(^5\) Incidence studies of AD are still rare and inconclusive.\(^6\)\(^-\)\(^9\) Studies on education and incident Alzheimer's disease are generally hampered by two problems. An initial problem in incidence studies is loss to follow-up (including death), which can be substantial. Moreover, loss to follow-up is related to level of education and AD. This study investigated to what extent these selection mechanisms may influence this association.

**Background**

It is still not clear whether a low level of education increases the risk of developing Alzheimer's disease (AD). Two common problems in cohort studies involving an elderly population and a two-step diagnostic procedure are the loss to follow-up without data on the presence of AD, and the fact that, in general, people with higher levels of education perform better on traditional cognitive tests, such as the Mini-Mental State Examination (MMSE). Both phenomena may lead to misclassification, resulting in a biased association between level of education and AD. This study investigated to what extent these selection mechanisms may influence this association.

**Methods**

In the community-based Amsterdam Study of the Elderly (AMSTEL) a cohort at risk for AD was selected of 3778 people aged 65–84 years. Level of education was expressed in two categories: low (primary education or less) versus high (partial secondary education to completed university education). At follow-up, a subsample of elderly people was selected for further diagnostic evaluation, using a memory test in addition to the MMSE. Clinical diagnoses of AD were made according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria. To examine the extent to which loss to follow-up may have affected the results, a sensitivity analysis was performed comparing two extreme possibilities. Furthermore, to examine to what extent use of the MMSE only may have affected the results, the observed odds ratio (OR) was compared with the OR based on only those AD patients who were selected for diagnostics with the MMSE alone.

**Results**

After an average of 3.2 years, 77 people had developed AD. Multivariate logistic regression analyses indicated that a low level of education was associated with incident AD (OR adjusted for age and sex 2.09; 95% CI: 1.29–3.38). The results of the sensitivity analysis still indicated that a low level of education was associated with incident AD. Screening with only the MMSE led to a higher OR than the one observed.

**Conclusion**

Selective attrition and use of cognitive screening tests that are associated with educational level may influence the strength of the association between a low level of education and incident AD; however, it appears that these influences cannot completely explain this association.

**Keywords**

Education, incidence, Alzheimer's disease, selective attrition, Mini-Mental State Examination.
estimates if the diagnosis is unknown for those who were lost to follow-up. A second problem is that higher levels of education are associated with better cognitive test performance. This is especially the case for the Mini-Mental State Examination (MMSE), which is, in Europe, still one of the most widely used mental status tests in epidemiological research based on a two-step diagnostic procedure. The association between a low level of education and incident AD may result in an underestimation if, at baseline, low cognitive performance of subjects with fewer years of education is misinterpreted as dementia (since these subjects are excluded from the cohort at risk for dementia). More importantly, at follow-up, elderly people with higher levels of education may be excluded from the diagnostic evaluation, which could result in an overestimation of the association between a low level of education and AD.

Although both problems are widely recognized, we know of no studies that have investigated to what extent they may influence the association between level of education and incident AD. The objective of the present study was to investigate to what extent these selection mechanisms may influence this association. To examine how loss to follow-up may have affected our estimates of the association a sensitivity analysis was performed. Furthermore, in addition to the MMSE, a memory test was used at follow-up to select subjects for further diagnostic evaluation. This test was less associated with educational level than the MMSE. To examine to what extent use of the MMSE only could have affected our estimates, the observed estimates of the association between level of education and incident AD were compared with those based on selection with the MMSE only. The data were obtained from a large cohort of randomly selected elderly people living in the community (Amsterdam Study of the Elderly, AMSTEL).

Subjects and Methods

Baseline sample

The sampling procedure of the baseline population of the AMSTEL study has been described elsewhere. In brief, 5666 non-institutionalized elderly people, aged 65–84 years, were selected from 30 general practices spread across the city of Amsterdam. In the Netherlands, general practitioners are the gatekeepers to the health care system, and almost all non-institutionalized people are registered in a general practice. Within each practice a fixed proportion of people was randomly selected from each of four 5-year age strata (65–69 years to 80–84 years) to obtain equal-sized strata. Age and sex of the general practice population did not differ from the corresponding general population of Amsterdam. Of the 5666 people sampled, 4051 (71.5%) gave their consent and participated in the study; 23.9% refused to participate, and 4.6% could not be contacted because they had either died, become institutionalized or had moved away from Amsterdam.

Cohort at risk

Trained lay people interviewed all 4051 participants at home. The interview consisted of questions on sociodemographic characteristics, current health status and medical history. Furthermore, it incorporated the Dutch version of the Geriatric Mental State Schedule (community version, GMSA3) and four mental status tests: the MMSE, the Abbreviated Mental Test Score (AMTS), the Mental Status Questionnaire (MSQ) and the Short Portable Mental Status Questionnaire (SPMSQ). The present study sample was selected by excluding all subjects who were diagnosed as having dementia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria or according to GMS-AGECAT criteria (n = 273). The procedures of the diagnostic evaluation at baseline have been described in more detail elsewhere. With respect to the definition of dementia according to GMS-AGECAT, GMS organic illness syndrome levels of 3–5 indicate the presence of dementia, while levels of 0–2 indicate the absence of dementia. Thus, the study sample contained 3778 non-demented people.

Follow-up measurement and diagnostic evaluation

At follow-up, all subjects who were available were interviewed again by trained lay people using the same interview procedure as at baseline. All subjects with MMSE scores of 23 or less were selected for further diagnostic evaluation. In addition, subjects with MMSE scores of 24 and above were selected for diagnostics if they showed signs of memory impairment. Memory impairment was assessed on the basis of the items from the four mental status tests that measured learning, recent memory and orientation. This involved a total of 13 questions, with a maximum score of 23 (Table 1). Reliability indexed by Cronbach’s alpha (i.e. internal consistency) of the memory scale was 0.71 in the baseline sample. Spearman rank correlations between educational level and the memory test and between educational level and the MMSE were 0.26 and 0.37, respectively. The cutoff score of the memory test was set at 18. This was the cutoff that selected all prevalent AD patients at the baseline diagnostic evaluation. Thus, all subjects with MMSE scores of 23 or less or with memory scores of 18 or less, or both, were selected for further diagnostic evaluation. For this diagnostic evaluation, all subjects who were available were visited by physicians specifically trained for this purpose. Subjects underwent the Cambridge examination for mental disorders in the elderly (CAMDEX). The CAMDEX includes a structured psychiatric interview, the Cambridge Cognitive Examination (CAMCOG) and a physical examination. To assess (instrumental) activities of daily living, additional questions were asked. Clinical diagnoses of AD were made according to DSM-IV criteria. Diagnoses were determined during weekly meetings with the senior neurologist and neuropsychologist.

Statistical analysis

To estimate the association of level of education with incident AD, multiple logistic regression analyses were performed in SPSS for Windows (version 7.5, SPSS Inc. Chicago, IL). Level of education (highest grade completed) was established at the initial home visit and was measured on an eight-point ordinal scale ranging from uncompleted primary school to completed university education. The educational levels were grouped into two categories: primary education or less (low education group approximately ≤6 years of education) versus partial secondary education to completed university education (high education group >6 years of education). To check whether the dichotomization may have influenced the results, all the analyses were also performed using educational level as a continuous variable by converting the ordinal variable into years of education.
Firstly, a univariate logistic regression analysis was performed with incident AD (no/yes) as outcome variable and education (low/high) as the independent variable. Secondly, in a multivariate logistic regression analysis, age stratum and sex were added as potential confounding variables. Thirdly, the interactions between education and sex, and between education and age were added to the multivariate model. Reference groups for incidence AD (no/yes) as outcome variable and education, sex, and age or sex. When these analyses were performed using education as a continuous variable, the conclusions did not change.

To examine how loss to follow-up may have affected our estimates, a sensitivity analysis was performed, comparing two extreme possibilities. The first extreme possibility assumed that none of the subjects who were lost to follow-up had developed AD. For both assumptions, crude odds ratios (OR) and OR adjusted for age and sex, with corresponding 95% confidence intervals (CI), were calculated.

To examine how the addition of the memory test affected the estimates of the odds ratios, a logistic regression analysis was also performed, using as outcome only those AD patients who were identified by means of the MMSE alone as selection criterion for diagnostic evaluation.

**Results**

Baseline characteristics of the cohort at risk, according to level of education, are shown in Table 2. As expected, older subjects and women were more likely to be less well educated. The follow-up duration was 3.2 years, on average. At follow-up, 2169 people were available for interview (57.4% of N = 3778), of whom 433 were selected for further diagnostic evaluation; 267 people actually underwent diagnostic evaluation and 77 were diagnosed with AD; 13 people had developed vascular or secondary dementia, and were therefore excluded from the analyses. Of the 1609 people who were not available for interview (42.6% of N = 3778), 551 had died, 256 were too ill to participate, 607 were unwilling to participate and 195 could not be contacted. Of the 166 people (38.3% of N = 433) who were not available for diagnostic evaluation, 71 had died in the period between the follow-up interview and the diagnostic evaluation, 34 were too ill to undergo diagnostic evaluation, 43 were unwilling to participate and 18 could not be contacted.

The results of the univariate logistic regression analysis showed that a low level of education was associated with an increased risk of AD, compared to a higher level of education (OR 2.79; 95% CI: 1.75–4.46). Adjusted for age and sex, a low level of education still predicted incident AD (adjusted OR 2.09; 95% CI: 1.29–3.38). There were no significant interactions between education and age or sex. When these analyses were performed using education as a continuous variable, the conclusions did not change.

Table 3a presents the number of subjects with and without incident AD and the number of subjects who were available for follow-up and those who were lost to follow-up, according to education group. The results of the sensitivity analysis are presented in Table 3b. Under the first assumption, i.e. that none of the subjects who were lost to follow-up had developed AD,
We observed an increased risk of AD in elderly people with a low level of education compared to more highly educated people. Although the observed point estimates may have been somewhat influenced by selective attrition and bias introduced by the two-step diagnostic procedure, the association still remained.

The results of the sensitivity analysis, that compared two extreme possibilities of selective attrition showed that both the crude and the adjusted point estimates observed in this study appeared to be somewhat higher than those calculated from the sensitivity analysis. Nonetheless, this sensitivity analysis also suggests that elderly people with a low level of education are at increased risk of developing AD, compared to more highly educated elderly people. Moreover, when we performed additional analyses (data not shown) that took into account the possibility of selective attrition showed that both the crude and adjusted OR of incident AD associated with level of education were higher than the respective OR observed in this study. A similar result was obtained when education was used as a continuous variable in the analyses.

**Discussion**

Of the 433 people who were selected for diagnostic evaluation at follow-up, 197 were selected by both the MMSE and the memory test (of whom 54.8% had a low level of education), whereas 64 were selected by the MMSE (of whom 76.6% had low education) but were missed by the memory test, and 172 were selected by the memory test (of whom 49.4% had low education) but were missed by the MMSE. As can be seen, a greater proportion of subjects with a low level of education was selected by the MMSE than by the memory test (χ² = 14.08, 2 d.f., P = 0.001). When the logistic regression analyses were performed using the AD patients who were identified based on selection with the MMSE alone, the results showed that both the crude and adjusted OR of incident AD associated with level of education were higher than the respective OR observed in this study. A similar result was obtained when education was used as a continuous variable in the analyses.

Another selection mechanism that may affect the association between education and incident AD is the use of cognitive screening tests that are associated with educational level. At follow-up, a test that focused on memory impairment was used, in addition to the MMSE, to reduce misclassification due to educational level. Memory impairment is a strong predictor of AD.29,30 In general, more highly educated people perform better on the MMSE and, therefore, a smaller percentage of more

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**Table 3a** Number of subjects with and without incident AD and number of subjects who were available for follow-up and those who were lost to follow-up, according to education group

<table>
<thead>
<tr>
<th>Educational level</th>
<th>AD+</th>
<th>AD-</th>
<th>Total available for follow-up</th>
<th>Total loss to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>47</td>
<td>745</td>
<td>792</td>
<td>722</td>
</tr>
<tr>
<td>High</td>
<td>30</td>
<td>1330</td>
<td>1360</td>
<td>879</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>2075</td>
<td>2152</td>
<td>1601</td>
</tr>
</tbody>
</table>

NB The numbers in the two right columns do not add up to 3778 because of 12 missing observations at baseline on educational level and because 13 patients with other types of dementia were excluded from the analyses.

**Table 3b** Results of the sensitivity analysis comparing two extreme possibilities

<table>
<thead>
<tr>
<th>Level of education</th>
<th>Observed&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>None&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
<th>All&lt;sup&gt;c&lt;/sup&gt; OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>2.79 (1.75–4.46)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>2.36 (1.49–3.75)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.51 (1.33–1.72)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.09 (1.29–3.38)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.82 (1.13–2.91)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.44 (1.26–1.64)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>High</td>
<td>1 (reference)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Odds ratios (95% CI) as observed in the data.

<sup>b</sup> Odds ratios (95% CI) under the assumption that none of the subjects who were lost to follow-up had developed AD.

<sup>c</sup> Odds ratios (95% CI) under the assumption that all those subjects who had developed AD.

<sup>d</sup> Crude odds ratios.

<sup>**</sup>Odds ratios adjusted for age and sex.

Low education is primary education or less; high education is partial secondary education to completed university education.

**Table 4** Odds ratios (95% confidence intervals) as observed in the data and odds ratios (95% confidence intervals) using as outcome only those AD patients who would be identified using the MMSE alone as selection criterion for diagnostic evaluation

<table>
<thead>
<tr>
<th>Level of education</th>
<th>Observed&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>MMSE&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>2.79 (1.75–4.46)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>3.37 (1.92–5.91)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.09 (1.29–3.38)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.45 (1.37–4.36)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>High</td>
<td>1 (reference)</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Odds ratios (95% confidence intervals) as observed in the data.

<sup>b</sup> Odds ratios (95% confidence intervals) using as outcome only those AD patients who were identified using the MMSE alone as selection criterion for diagnostic evaluation.

<sup>c</sup> Crude odds ratios.

<sup>**</sup>Odds ratios adjusted for age and sex.

Low education is primary education or less; high education is partial secondary education to completed university education.
highly educated elderly people was expected to be selected for further diagnostic evaluation. Indeed, the MMSE selected a smaller proportion of more highly educated subjects than the memory test and diagnostic evaluation based on selection according to the MMSE only seemed to result in an overestimation of the association.

Researchers have offered several explanations for the increased risk of AD in less well-educated elderly people. Higher levels of education may reflect a ‘reserve’ against the development of AD. This reserve could be conceived as a cognitive reserve, which might delay the clinical expression of AD by means of an acquired set of skills. It is not yet clear whether a cognitive reserve should be interpreted as a true reserve which delays the onset of clinical symptoms in more highly educated elderly people or, alternatively, as an ability to mask the onset of symptoms and to cope with the ongoing decline. Furthermore, the reserve could be conceived as a brain reserve in the sense that more highly educated elderly people have more efficient cerebral processing and/or an increased synaptic density and/or larger brain volumes.

At present, it is not clear whether an aetiologic relationship exists between a low level of education and the development of AD. It may just be that lower levels of education are an indicator of other potential risk factors for AD. For instance, several studies found that an association existed between risk factors for cardiovascular diseases and the prevalence and/or incidence of AD. Since these factors are also more prevalent among those with lower levels of education, an association between a low level of education and AD may be confounded by these factors. Although a recent study could not confirm a confounding effect of smoking or previous history of hypertension, this matter has not been investigated extensively. Moreover, there is a need for testable theoretical models that could explain an aetiologic relationship between a low level of education and AD.

In summary, selective attrition and use of cognitive screening tests that are associated with educational level may influence the strength of the association between a low level of education and incident AD. While the first may underestimate the association, the second may overestimate it. However, it appears that these influences cannot completely explain the association and we conclude that a low level of education is indeed predictive of incident Alzheimer’s disease.

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References


