The Influence of Education on Clinically Diagnosed Dementia Incidence and Mortality Data From the Kungsholmen Project

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Background: The relationship between education and Alzheimer disease (AD) or dementia has been widely examined and the evidence obtained is mixed. Several hypotheses have been proposed to explain the observed association between them.

Objective: To further understand the relationship between education and incidence of clinically diagnosed AD or dementia.

Subjects and Methods: A community-based, dementia-free cohort of 1296 aged 75 years and older was followed up to detect incident AD or dementia cases using Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria. The vital status of all subjects who underwent the clinical examination at follow-up (n=983) was ascertained for 5 years further. Data were analyzed with Cox proportional hazards model after adjustment for main potential confounders.

Results: Over an average (SD) of 2.8 (1.0) years of follow-up, 147 subjects were diagnosed as having dementia (109 subjects as having AD). Among those who were clinically examined at follow-up, 88 died with dementia (68 died with AD) within 5 years. Subjects with a low level of education (<8 vs ≥8 years) had a relative risk of 2.6 (95% confidence interval, 1.5-4.4) for AD and 1.7 (95% confidence interval, 1.1-2.6) for dementia. A low educational level was significantly related to all-cause mortality (relative risk, 1.3; 95% confidence interval, 1.0-1.7; P<.05), but not to the mortality of subjects with AD (relative risk, 1.1; 95% confidence interval, 0.5-2.2) or dementia (relative risk, 0.9; 95% confidence interval, 0.5-1.5).

Conclusions: A low level of education is related to an increased incidence of clinical AD or dementia, but not to the mortality of subjects with AD or dementia. These findings can be accounted for by the "cognitive reserve" hypothesis. Alternatively, the observed association between educational level and incidence of AD or dementia may partly reflect detection bias, by which subjects with a low level of education tend to be clinically diagnosed at an earlier point in time.

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A complete list of the members of the Kungsholmen Project Steering Group appears in the box on page 2038.
SUBJECTS AND METHODS

STUDY POPULATION

The Kungsholmen Project is a community-based longitudinal study on aging and dementia. The baseline data collection, inception of dementia-free cohort, and follow-up examination have been described in detail elsewhere. Briefly, the initial population included all registered inhabitants who were living in the Kungsholmen district of Stockholm, Sweden, and were aged 75 years and older in October 1987. Of all eligible subjects (N = 2368), 1810 (76.4%) agreed to participate in the baseline survey (1987-1989). By means of a 2-phase design, 1473 baseline participants were diagnosed as being dementia-free. Of these, 172 persons refused the follow-up examination (1991-1993) or had moved out of Stockholm before the examination and educational information was missing for 5 subjects. Thus, the study population used in the incidence analyses consisted of 1296 baseline dementia-free subjects. Of them, 313 subjects died before undergoing the follow-up examination; medical records and death certificate were available for all of these persons. The remaining subjects (n = 983) underwent a comprehensive medical examination. The vital status of these 983 subjects was ascertained for 5 years further through official registers.

BASELINE DATA COLLECTION

Data on demographic variables (age, sex, and educational level) and global cognitive functioning (assessed using the Mini-Mental State Examination) were collected at the baseline interview according to standardized protocols. Education was measured by the maximum years of formal schooling. Subjects were divided into 3 categories according to their highest educational level, including elementary school (<8 years of schooling and/or vocational training), high school (8-10 years of schooling), or university (≥11 years of schooling).

Socioeconomic status was assessed based on the lifetime longest occupation that the subject had held. It was divided into 5 categories (self-employed, intermediate non-manual, assistant non-manual, skilled manual, or semiskilled manual work) according to the occupation-based Swedish Socioeconomic Classification System devised by Statistics Sweden in 1982. Data on socioeconomic status were available for 910 subjects.

Data on vascular disorders and other diseases at baseline were derived from the computerized Stockholm Inpatient Registry System, which encompassed all hospitals in the Stockholm area since 1969. All diseases were diagnosed based on the International Classification of Diseases, Eighth Revision (ICD-8), including heart disease (ICD-8 codes 410-414, 427, and 428), cerebrovascular disease (ICD-8 codes 430-438), diabetes mellitus (ICD-8 code 250), hip fracture (ICD-8 code 820), and malignancy (ICD-8 codes 140-208 and 230-239). Arterial blood pressure was measured with a standardized random-zero sphygmomanometer at the baseline interview.

DIAGNOSIS OF DEMENTIA

The Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (DSM-III-R) criteria were used to define dementia using a 3-step diagnostic procedure as described elsewhere. The diagnosis of dementia was made when a subject completely fulfilled the DSM-III-R criteria, which in this study was labeled clinically diagnosed dementia. The diagnosis of AD requires gradual onset, progressive deterioration, and lack of any other specific causes of dementia. For the deceased subjects, the diagnosis of AD or dementia was made by reviewing medical records, discharge diagnoses, and death certificates. The Clinical Dementia Rating (CDR) score was used to define AD or dementia severity with 3 gradient categories of mild, moderate, and severe.

STATISTICAL ANALYSES

The incidence and mortality rates were calculated as the number of events (AD, dementia, or death) divided by the corresponding follow-up time (person-years at risk). When calculating the incidence, the follow-up time was estimated from the date of the baseline interview to the date of follow-up examination or death for subjects who did not develop dementia. For those who developed AD or dementia, half of this time was assumed due to the insidious nature of dementia onset. We considered the different types of dementia as competing causes of dementia, which means that a subject who developed any type of dementia was no longer at risk of developing other types of dementia. With regard to mortality rates, the follow-up time was defined as the interval between the date of the follow-up examination and the date of death or 3 years.

Cox proportional hazards models were used to estimate the relative risk (RR) and 95% confidence interval (CI) of developing AD or dementia, dying from all causes, or dying with AD or dementia. We assessed interaction effect by including the independent variables and their cross-product term in the same model. Age (in years) at baseline and sex were considered as covariates in all analyses. High blood pressure (systolic pressure ≥160 mm Hg or diastolic pressure ≥95 mm Hg), heart disease, cerebrovascular disease, and diabetes mellitus were combined into one variable called “vascular disease” (yes vs no), which was also used as a covariate in the analysis of education in relation to incidence of clinical AD or dementia. Further, we combined vascular disease, malignancy, and hip fracture into one variable called “comorbidity” (yes vs no), which was also used in the mortality analysis. All types of dementia combined and AD were used as separate outcomes in all regression analyses.

longer (the “cognitive reserve” hypothesis). Others have argued that persons with greater educational attainment and associated higher socioeconomic status may be exposed to fewer toxins and enjoy a generally healthier lifestyle that may spare the brain from lesions contributing to dementing disorders (the “brain battering” hypothesis). In addition, we have suggested that the observed inverse association may reflect an earlier detection of demented subjects with a low level of education irrespective of the underlying pathologic process. The current study aimed to further understand the relationship between education and clinically diagnosed AD or...
dementia by integrating incidence with mortality data from the Kungsholmen Project.

RESULTS

Table 1 gives the baseline characteristics of the study population by follow-up status. Participants were more frequently affected by vascular disease or other disorders than were dropouts, but the 2 groups were comparable for age, sex, educational level, and baseline Mini-Mental State Examination score.

EDUCATION IN RELATION TO INCIDENCE OF AD AND DEMENTIA

Over an average (SD) of 2.8 (1.0) years of follow-up, 147 subjects developed clinical dementia (109 of them were diagnosed as having AD). Table 2 gives the incidence rates of AD and dementia across different educational levels. The dementia incidence for persons with a high school and university education did not differ reliably. Thus, we merged these 2 groups as a reference category (≥8 years of schooling) in the remaining analyses. The association between a low level of education (<8 years) and an increased incidence of AD or dementia was present independently of age, sex, baseline cognitive performance, vascular disease, and socioeconomic status (Table 3).

Table 1. Characteristics of the Dementia-Free Cohort at Baseline by Follow-up Status*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants (n = 1296)</th>
<th>Dropouts (n = 177)</th>
<th>Total (n = 1473)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>81.5 (5.0)</td>
<td>80.4 (3.9)</td>
<td>81.4 (4.9)</td>
</tr>
<tr>
<td>Female subjects</td>
<td>971 (74.9)</td>
<td>141 (79.7)</td>
<td>1112 (75.5)</td>
</tr>
<tr>
<td>Educational level ≥8 y‡</td>
<td>536 (41.4)</td>
<td>64 (37.6)</td>
<td>600 (40.9)</td>
</tr>
<tr>
<td>MMSE, mean (SD), score‡</td>
<td>26.6 (2.7)</td>
<td>26.8 (1.9)</td>
<td>26.6 (2.6)</td>
</tr>
<tr>
<td>Vascular disease§</td>
<td>417 (32.2)</td>
<td>43 (24.3)</td>
<td>460 (31.2)</td>
</tr>
<tr>
<td>Comorbidity¶</td>
<td>596 (46.0)</td>
<td>45 (25.4)</td>
<td>641 (43.5)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of subjects unless otherwise indicated.
†Seven subjects (2 subjects were from the refusals for other reasons) with missing values were excluded.
‡MMSE indicates Mini-Mental State Examination. The score ranges from 0 (the worst) to 30 (the best).
§At least one of the following was present: high blood pressure, heart disease, cerebrovascular disease, or diabetes mellitus.
¶At least one of the following was present: vascular disease, a malignant neoplasm, or hip fracture.

Table 2. Incidence Rate (IR) (per 1000 Person-Years), Relative Risk (RR), and 95% Confidence Interval (CI) of Alzheimer Disease or Dementia by Educational Levels in 1296 Subjects

<table>
<thead>
<tr>
<th>Educational Level</th>
<th>Alzheimer Disease</th>
<th>All Types of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Subjects</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>University (≥11 y)</td>
<td>283</td>
<td>11</td>
</tr>
<tr>
<td>High school (8-10 y)</td>
<td>253</td>
<td>10</td>
</tr>
<tr>
<td>Elementary (&lt;8 y)</td>
<td>760</td>
<td>88</td>
</tr>
</tbody>
</table>

*Value is adjusted for age (in years) and sex.
†Value indicates the reference group; ellipses, not applicable.

The adjusted RRs (95% CIs) of AD and dementia related to a low educational level (<8 vs ≥8 years) were 2.7 (1.5-4.8) and 1.9 (1.2-3.1), respectively, in women, and 2.5 (0.6-10.9) and 1.0 (0.4-2.6), respectively, in men. There was a significant interaction between educational level and sex for the incidence of dementia (adjusted RR for the interaction term, 2.8; 95% CI, 1.1-7.6), but not statistically significant for the incidence of AD (adjusted RR for the interaction term, 1.9; 95% CI, 0.4-8.2). The adjusted RRs (95% CIs) of AD and dementia were 3.0 (1.4-6.3) and 2.0 (1.2-3.4), respectively, in the age group of 75- to 84-year-olds, and 1.5 (0.7-3.4) and 1.0 (0.5-2.0), respectively, in the 85-year-olds and older. No statistically significant interaction between education and age on the incidence of dementia or AD was found.

EDUCATION, AD, AND DEMENTIA IN RELATION TO ALL-CAUSE MORTALITY

Among the 983 subjects who were clinically examined at follow-up, 410 subjects died during an average (SD) of 4.0 (1.5) years of observation, resulting in an overall mortality of 104.3 per 1000 person-years. Low level of education, AD, and dementia were significantly related to all-cause mortality. Moreover, significant interactions of education with AD and dementia (nearly at the borderline) on all-cause mortality were found (Table 4).

Table 3. Relative Risk (RR) and 95% Confidence Interval (CI) of Alzheimer Disease or Dementia Associated With a Low Level of Education (<8 vs ≥8 Years) in 1296 Subjects

<table>
<thead>
<tr>
<th>Model</th>
<th>No.*</th>
<th>RR</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
<th>Covariates†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>1.9-4.8</td>
<td>2.2</td>
<td>1.5-3.1</td>
<td>Age and sex</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>1.4-3.7</td>
<td>1.7</td>
<td>1.1-2.4</td>
<td>Age, sex, and MMSE</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.3</td>
<td>1.4-3.7</td>
<td>1.7</td>
<td>1.1-2.4</td>
<td>Age, sex, MMSE, and VD</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.6</td>
<td>1.5-4.4</td>
<td>1.7</td>
<td>1.1-2.6</td>
<td>Age, sex, MMSE, VD, and SES</td>
<td></td>
</tr>
</tbody>
</table>

*Alzheimer disease and all types of dementia were used as separate outcome variables.
†MMSE indicates Mini-Mental State Examination score (continuous variable); VD, vascular disease (yes vs no); and SES, socioeconomic status (6 categories: self-employed, intermediate nonmanual, assistant nonmanual, skilled manual, unskilled or semiskilled manual work, and missing values). Age was given in years.
These interactions suggested that subjects with AD or dementia with a low educational level had a decreased risk of death compared with those with a high educational level.

**EDUCATION IN RELATION TO MORTALITY OF SUBJECTS WITH AD OR DEMENTIA**

Of the 983 subjects who underwent the follow-up examination, 126 were diagnosed as having dementia (101 as having AD). There was no statistically significant difference in the distribution of CDR scores between subjects with more education and those with less education. Eighty-eight patients with dementia (68 with AD) died within 5 years. The crude mortality of subjects with AD or dementia among persons with less education was about twice as high as that of those with more education in the general population. The relation of less education to the increased mortality of subjects with AD or dementia, however, disappeared after controlling for potential confounding factors, especially dementia severity (Table 5).

In line with several previous follow-up studies, we found that a low level of education was associated with an increased risk for developing clinical AD or dementia, even when several potential confounding factors are controlled for. Furthermore, the increased risk of clinical AD or dementia was mainly confined to persons with less than 8 years of education. The association between a low level of education and an increased risk of AD or dementia was more evident in women than in men and in the younger-old age group (ie, 75-84 years) than in the oldest-old age group (85+ years). These results may partly account for the finding that no association between educational level and the risk of AD or dementia in some previous studies. In the Framingham Study, for example, the study population included only a small proportion (8.0%) of subjects with an elementary school education and few of them were younger-old women.

The main findings from the mortality data can be summarized into 2 main points: (1) A low educational level, AD, and dementia are important risk factors for death even in the very old, which is in agreement with prior findings. The finding of an interaction between educational level and AD or dementia on all-cause mortality suggests that persons with both a low level of education and AD or dementia are at a decreased risk of death compared with those with both a high educational level and AD or dementia, which is in accord with our previous report that patients with AD who were highly educated had poorer survival than those less educated patients. (2) The association between a low level of education and increased mortality of subjects with clinical AD or dementia is influenced by confounders, most prominently dementia severity. These results could be interpreted in view of other findings that the neuropathologic progression in patients with dementia may eventually lead to a mortality-causing condition. First, clinical observations indicate that dementia progression is more rapid in those with a higher education level or with greater premorbid reading activity, following clinical diagnosis. Second, pathophysiological and imaging evidence indicates that AD-related pathologic changes in the brain are more advanced among subjects with dementia who have a high level of educational attainment than in those with a low level of education, given similar clinical dementia severity. Third, autopsy-verified studies have documented that education does not affect the pathologic course of AD. Collectively, these observations suggest that education may influence the clinical expression or the detection of AD or dementia, rather than affect the underlying pathologic process of the disease.

Our results are consistent with the cognitive reserve hypothesis. Alternatively, it is possible that the

### Table 4. Low Educational Level, Alzheimer Disease, and Dementia in Relation to All-Cause Mortality in the 983 Subjects General Population

<table>
<thead>
<tr>
<th>Model</th>
<th>RR†</th>
<th>95% CI†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low educational level (&lt;8 y)</td>
<td>1.3</td>
<td>1.0-1.7</td>
<td>.02</td>
</tr>
<tr>
<td>Alzheimer disease (AD)</td>
<td>3.1</td>
<td>1.8-5.4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Low educational level by AD</td>
<td>0.5</td>
<td>0.3-0.9</td>
<td>.02</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low educational level (&lt;8 y)</td>
<td>1.3</td>
<td>1.0-1.7</td>
<td>.03</td>
</tr>
<tr>
<td>All types of dementia</td>
<td>2.6</td>
<td>1.7-4.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Low educational level by all types of dementia</td>
<td>0.6</td>
<td>0.4-1.0</td>
<td>.07</td>
</tr>
</tbody>
</table>

*Age, sex, baseline Mini-Mental State Examination score, comorbidity, and socioeconomic status were also included in these models.†RR indicates relative risk; CI, confidence interval.

### Table 5. Mortality (per 1000 Person-years), Relative Risk (RR), and 95% Confidence Interval (CI) of Alzheimer Disease or Dementia Across Educational Levels in 983 Subjects

<table>
<thead>
<tr>
<th>Educational Level</th>
<th>No. of Subjects</th>
<th>Subjects With Alzheimer Disease</th>
<th>Subjects With All Types of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>Crude Mortality</td>
<td>RR†</td>
</tr>
<tr>
<td>High (&gt;=8 y)</td>
<td>418</td>
<td>17</td>
<td>10.0</td>
</tr>
<tr>
<td>Low (&lt;8 y)</td>
<td>565</td>
<td>51</td>
<td>23.9</td>
</tr>
</tbody>
</table>

*Value is adjusted for age, sex, baseline Mini-Mental State Examination score, comorbidity, socioeconomic status, and dementia severity (ie, mild, moderate, or severe dementia as assessed with Clinical Dementia Rating).†Value indicates the reference group; ellipses, not applicable.

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These findings may be accounted for by the cognitive regression rather than the pathologic course of AD or dementia. Specifically, subjects with dementia who have a low educational level may be clinically diagnosed at an earlier pathologic stage of the disease compared with those who have a high educational level when current clinical diagnostic criteria and procedures are used. This detection bias may occur in the whole process of clinical evaluation of AD or dementia, and particularly in persons with an educational level of less than elementary school.

Some potential limitations of this study deserve mention. First, we could not directly examine the association between education and the mortality of clinical AD or dementia, as we could not determine whether the deceased subjects who had dementia died of AD, dementia, or some other causes. Rather, we addressed the relation between education and the mortality for subjects with clinical AD or dementia in the general population. However, we attempted to control for the effects of other major death-related disorders by use of a comorbidity variable, which included the most frequent underlying causes of death in persons with dementia. Therefore, it is conceivable that our results largely reflect the relation between education and the mortality of AD or dementia. Second, AD or dementia cases among deceased subjects might have been underdiagnosed. This may not bias our results because additional analysis (data not shown) in the subpopulation that undertook the clinical examination at follow-up yielded very similar results as those found in the entire population. Finally, the newly developed cases of dementia over the 5 years after the follow-up examination were not considered in our mortality data because the relevant information was unavailable. If anything, this might lead to an underestimation of the effect of dementia on death. Thus, it is unlikely that these limitations jeopardize our main conclusions.

**CONCLUSIONS**

This study suggests that a low level of education is associated with an increased risk of developing clinical AD or dementia, particularly in women and in younger-old age. In addition, a low level of education was related to increased mortality of all causes, but not to mortality of subjects with AD or dementia in the general population. These results imply that education may affect the clinical expression rather than the pathologic course of AD or dementia. These findings may be accounted for by the cognitive regression hypothesis, but could also reflect the fact that subjects with dementia who were less educated may be clinically diagnosed at an earlier pathologic stage of the disease (detection bias). This possible interpretation needs to be verified by studies integrating the clinical evaluation of AD or dementia with neuropathologic data.

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