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Education and the Risk for Alzheimer's Disease: Sex Makes a Difference. EURODEM Pooled Analyses

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The hypothesis that a low educational level increases the risk for Alzheimer's disease remains controversial. The authors studied the association of years of schooling with the risk for incident dementia and Alzheimer's disease by using pooled data from four European population-based follow-up studies. Dementia cases were identified in a two-stage procedure that included a detailed diagnostic assessment of screen-positive subjects. Dementia and Alzheimer's disease were diagnosed by using international research criteria. Educational level was categorized by years of schooling as low (≤7), middle (8–11), or high (≥12). Relative risks (95% confidence intervals) were estimated by using Poisson regression, adjusting for age, sex, study center, smoking status, and self-reported myocardial infarction and stroke. There were 493 (328) incident cases of dementia (Alzheimer's disease) and 28,061 (27,839) person-years of follow-up. Compared with women with a high level of education, those with low and middle levels of education had 4.3 (95% confidence interval: 1.5, 11.9) and 2.6 (95% confidence interval: 1.0, 7.1) times increased risks, respectively, for Alzheimer's disease. The risk estimates for men were close to 1.0. Finding an association of education with Alzheimer's disease for women only raises the possibility that unmeasured confounding explains the previously reported increased risk for Alzheimer's disease for persons with low levels of education. *Am J Epidemiol* 2000;151:1064–71.

Alzheimer disease; dementia; education; sex

Alzheimer's disease is the most common form of dementia in old age, affecting more than 5 percent of the population older than age 65 years (1). Identification of risk factors for Alzheimer's disease has advanced in the last decade, although many questions still remain. One hypothesis that has engaged the attention of researchers is the link between educational attainment and the risk for Alzheimer's disease (2). Animal studies suggest that exposure to an enriched environment is accompanied by an increase in cortical thickness and number of synapses (3). Such data have led to the theory that persons with higher levels of education may have a greater brain reserve than persons with lower levels of education (4, 5). This greater capacity may enable a more highly educated person to better manage the impairment caused by progressive neurodegeneration. As a result, the threshold for clinical dementia is raised, resulting in later detection of Alzheimer's disease in more highly educated persons. The brain reserve hypothesis is supported by studies showing an association of a high level of education (6) or premorbid intelligence (7) with greater cerebral metabolic deficits in prevalent Alzheimer's disease cases.

Several cross-sectional studies have investigated the association of educational level with the risk for Alzheimer's disease; some have shown a positive association (8–10), but others have not (11, 12). Interpretation of cross-sectional studies is hampered by possible bias introduced through differential survival of subjects associated with educational level. For instance, more highly educated persons with Alzheimer's disease also had a shorter survival in the same sample in which greater cerebral deficits were found (13). This bias would lead to an oversampling of lower-educated demented subjects in prevalent studies.

Prospective studies based on incident cases of dementia are less subject to survival bias. However,

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Abbreviations: CI, confidence interval; EURODEM, European Studies of Dementia; SD, standard deviation.

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the relatively few studies of incident cases also have yielded inconsistent results. A higher incidence of Alzheimer's disease was found among subjects in the North Manhattan (New York) Study who had less than 8 years of education (14). In the East Boston (Massachusetts) Study, fewer years of formal schooling predicted the risk for incident Alzheimer's disease 3 years later (15). Alzheimer's disease, however, was not associated with educational level in studies based on the Mayo Clinic cohort (Rochester, Minnesota) (16) and the Framingham (Massachusetts) cohort (17). These inconsistent results may in part reflect sampling fluctuations due to the small sample size of the individual studies.

In this paper, we report on the association of educational level with incident dementia, specifically Alzheimer's disease, by using pooled data from population-based studies conducted in Europe. These studies were part of the European Studies of Dementia (EURODEM) network formed in 1988 by investigators working on European prospective, population-based studies of dementia. The goal of the network was to harmonize study protocols so the data could eventually be pooled to study geographic differences in, and risk factors for, the incidence of dementia.

MATERIALS AND METHODS

Study design

The individual studies included a population-based sample of persons aged 65 years or older living in the community and in institutions. Samples were drawn from defined geographic areas and included either all eligible persons or subjects selected randomly from predefined strata. Data on risk factors were collected from subjects at baseline, when they were dementia free. Case finding for dementia was conducted in two stages; the total sample was screened by using brief cognitive tests, and screen-positive subjects then underwent follow-up diagnostic assessment. The studies are described more fully elsewhere (18), but a brief description of each follows.

Denmark. The Odense study (1993–1996) was conducted in the municipality of Odense (19). Persons aged 65–85 years who were living in the municipality were randomly selected from the population registry. The original baseline sample included 3,346 persons (64 percent participation rate), and 2,512 initially nondemented subjects were followed. One follow-up was performed 3 years after the baseline visit; the mean follow-up time was 2.1 (standard deviation (SD), 0.2) years, for a total of 4,944 person-years.

France. The Paquid study (1988–1993) was conducted in 75 parishes in the provinces of Gironde and Dordogne (20). The sample was randomly selected from electoral rolls by using a multistage procedure based on strata of age, sex, and size of geographic unit. To be eligible for the study, participants had to have been living at home at baseline. The original sample included 3,777 persons (68 percent participation rate), and 2,712 initially nondemented subjects were followed. Two follow-ups were conducted 1 and 3 years after the baseline visit; the mean follow-up time was 2.8 (SD, 0.9) years, leading to a total of 7,611 person-years.

The Netherlands. The Rotterdam Study (1990–1995) was conducted in Ommoord, a district of the municipality of Rotterdam (21). Although all persons aged 55 years or older and living in the district were eligible to participate, we limited our analysis to those aged 65 years or older. In this group, 5,265 persons participated in the baseline examination (75 percent participation rate), and 4,401 initially nondemented subjects were followed. One follow-up was conducted 3 years after the baseline visit; the mean follow-up time was 2.1 (SD, 0.8) years, for a total of 9,478 person-years.

United Kingdom. The MRC-ALPHA study (1988–1993) was conducted in the municipality of Liverpool (22). Samples were randomly selected from the general practitioner registry in equal-sized strata of age (5-year bands) and sex. The baseline sample included 5,222 subjects (87 percent participation rate), and 3,320 initially nondemented subjects were followed. One follow-up was conducted 3 years after the baseline visit; the mean follow-up time was 2.0 (SD, 0.2) years, leading to a total of 6,734 person-years.

Variables of interest

Case finding. Screen-positive subjects selected for further diagnostic workup had to either score below a given cutoff point on one or two of the screening tests or be clinically suspect, as judged by a clinician. The cutoff points were selected for high sensitivity. The cognitive tests used for screening included the Mini-Mental State Examination (23), the organic section of the Geriatric Mental State Schedule (24), and the Cambridge Examination of Mental Disorders Cognitive Test (25). The diagnostic phase consisted of detailed neuropsychological testing, an informant interview, and a clinical examination. Diagnoses were made in conference or on the basis of medical records when respondents refused to participate fully in the workup (12.8 percent of cases).

For these analyses, we included dementia cases whose illnesses ranged in severity from mild to severe. Dementia and severity were diagnosed according to DSM-IIIR criteria (26). NINCDS-ADRDA criteria (27) were used to diagnose possible and probable Alzheimer's disease; thus, cases with contributing car-

diovascular disease were classified as having possible Alzheimer's disease. A total of 528 cases were detected, of whom 352 had Alzheimer's disease, 92 had vascular dementia, and 84 had other dementias including Parkinson's disease dementia, normal-pressure hydrocephalus, and an undetermined subtype.

To obtain an estimate of study differences in the application of diagnostic guidelines, a EURODEM consensus panel reviewed the computerized diagnostic data (which excluded clinical notes made by the interviewing physician) from a sample of screen-positive subjects (n = 266). This panel included neurologists, psychiatrists, and neuroepidemiologists, each of whom had worked as a clinician on one of the participating studies. We oversampled cases that the study indicated were difficult to diagnose (22 percent of the sample). When the difficult cases were included, the kappa statistic was 0.66 for agreement on dementia (yes/no) between the study and the EURODEM panel diagnosis; for Alzheimer's disease (yes vs. all other diagnoses), it was 0.70. When the difficult cases were excluded, the kappa statistics were 0.75 for dementia and 0.81 for Alzheimer's disease.

Ascertainment of risk factors. Risk factors were ascertained by questionnaire from respondents at baseline, when they were dementia free. Two studies (Odense and MRC-ALPHA) recorded the number of years of schooling, and the other two (Paquid and Rotterdam) recorded education as the maximum level attained as defined by type of school (i.e., primary level, vocational and academic middle and secondary level, and university). These levels were converted into number of years of schooling in accordance with the respective systems in each country. Educational level was then categorized as low (up to and including 7 years of schooling), middle (8–11 years of schooling), or high (12 or more years of schooling). In the analyses, we included as confounders smoking history (never, former, current), self-reported history of myocardial infarction, and self-reported history of stroke. These factors were also ascertained by questionnaire at baseline.

Statistical analyses

Incident cohorts excluded prevalent cases and those for whom data were missing on follow-up time and dementia status after baseline (nonresponders to the follow-up examination and those who died in the incidence interval and whose case status at death was unknown). A total of 16,334 persons were initially included in the baseline incident cohort, and 12,945 were successfully followed up. Very few people (less than 1 percent) were lost to follow-up. Most refused to be seen or died during the incidence interval between baseline and the follow-up visits. We used logistic regression analysis to investigate whether nonresponse was associated with age, sex, or educational level.

The association of education with dementia and Alzheimer's disease was expressed as a relative risk (95 percent confidence interval). In these analyses, we used the midpoint of the interval to estimate the time of disease onset. Parameters of risk were estimated by using Poisson regression (28). Given the relatively short follow-up time (2.24 (SD, 0.73) years), this model produced results equivalent to those based on Cox proportional hazards regression. All relative risks were adjusted for age (in years), the quadratic of age (in years), study, sex, and history of myocardial infarction, stroke, and smoking, as described above. Of the 12,945 subjects followed up successfully, data were complete for 12,647, which yielded 493 cases of dementia and 28,061 person-years of follow-up. Analyses of Alzheimer's disease were based on 328 cases and 27,839 person-years of follow-up. We assumed that incident cases of Alzheimer's disease were not at risk for another dementia at any time during the interval.

Data were pooled after we assessed homogeneity across the studies. Homogeneity was assessed by visually inspecting study-specific risk ratios, testing for significant differences in study estimates by using interaction terms (product of the study and risk factors), and deleting individual studies from the overall analysis to determine how the risk estimates were affected. Effect modification by age (65 to less than 80 years, 80 years or older), sex, and family history was examined systematically by entering into the model a term for the product of educational level and the risk factor of interest. To better visualize significant interactions, we calculated age-specific incidence rates.

RESULTS

We found that as age increased, the likelihood that subjects were included in the follow-up decreased significantly. Compared with subjects aged 65–69 years, those aged 70–74 years and 90 years or older had relative risks of 1.04 (95 percent confidence interval (CI): 0.94, 1.19) and 2.7 (95 percent CI: 2.3, 3.4), respectively, for nonresponse. A lower level of education also was associated with nonresponse; compared with subjects with a high level of education, those with low and middle levels of education had relative risks of 2.01 (95 percent CI: 1.6, 2.5) and 1.4 (95 percent CI: 1.1, 1.7), respectively, for nonresponse. Follow-up did not differ significantly between men and women (relative risk = 0.95, 95 percent CI: 0.87, 1.03). The distribution of responders and nonresponders according to sex and educational level is given in table 1. The interaction

between education and sex was not significant (p = 0.2), suggesting no differential nonresponse between men and women according to educational level.

In the sample, 37.6 percent of the subjects were included in the low, 54.7 percent in the middle, and 7.7 percent in the high level of education groups. The distribution of educational level by study, age standardized to the European population, is shown in table 2. In two studies (Odense and Paquid), more than 50 percent of the subjects were part of the low level of education group, whereas more than 50 percent of the subjects in the Rotterdam and the MRC-ALPHA studies were in the middle level of education group. This distribution reflects the historical differences in compulsory education laws.

The association of educational level with the risk for dementia and Alzheimer's disease was similar across studies (table 3). Compared with the high level of education group, the relative risk for dementia and for Alzheimer's disease was significantly increased for the subjects in the low level of education group and was marginally increased for those in the middle level of education group. However, there was a significant interaction between sex and educational level for the risk of dementia (p = 0.02) and Alzheimer's disease (p = 0.05).

In the sex-specific pooled analyses, we found that the association of education with dementia and Alzheimer's disease was nonsignificant for men; the relative risks were close to 1.0 (table 4). In contrast, the risk for dementia was increased by 3.8 (95 percent CI: 1.6, 8.7) and 2.5 (95 percent CI: 1.1, 5.6), respectively, for women in the low and the middle level of education groups compared with those in the high level of education group. Compared with women in the high level of education group, the risk for Alzheimer's disease was increased by 4.3 (95 percent CI: 1.5, 11.9) for women in the low level of education group and 2.6 (95 percent CI: 1.0, 7.1) for those in the middle level of education group. The age-specific incidence of Alzheimer's disease, by educational level, is

TABLE 1. Distribution of responders and nonresponders, by educational level and sex, EURODEM* pooled studies, 1988–1997

Educational level†	Responders		Nonresponders		Total	
	No.	%	No.	%	No.	%
			Men			
Low	1,790	32.7	525	37.5	2,315	33.7
Middle	3,085	56.3	811	57.9	3,896	56.6
High	605	11.0	64	4.6	669	9.7
Total	5,480	100.0	1,400	100.0	6,880	100.0
			Women			
Low	2,988	41.6	747	44.8	3,735	42.2
Middle	3,836	53.3	854	51.2	4,690	53.0
High	364	5.1	66	4.0	430	4.8
Total	7,188	100.0	1,667	100.0	8,855	100.0

* EURODEM, European Studies of Dementia.
† Low, ≤7 years of education; middle, 8–11 years of education; high, ≥12 years of education.

TABLE 2. Age-standardized* distribution of educational level (%),† by study and sex, of participants in the EURODEM‡ studies, 1988–1997

Educational level§	Study							
	Odense		Paquid		Rotterdam		MRC‡-ALPHA	
	Men (n = 1,140)	Women (n = 1,555)	Men (n = 1,095)	Women (n = 1,378)	Men (n = 1,647)	Women (n = 2,551)	Men (n = 1,591)	Women (n = 1,690)
Low	58.7	68.8	67.1	66.0	21.1	37.6	1.3	1.6
Medium	31.2	28.6	26.6	31.2	61.0	56.3	91.1	91.0
High	9.8	2.9	6.0	2.6	17.9	6.4	7.6	6.8

* Age standardized to the European population (37).
† Some percentages do not total 100 because of rounding.
‡ EURODEM, European Studies of Dementia; MRC, Medical Research Council.
§ Low, ≤7 years of education; middle, 8–11 years of education; high, ≥12 years of education.

TABLE 3. Study-specific estimates of the association of educational level with the risk for incident dementia and Alzheimer's disease, EURODEM* Studies, 1988–1997

Educational level†	Study							
	Odense		Paquid		Rotterdam		MRC*-ALPHA	
	RR‡,§	95% CI‡	RR§	95% CI	RR§	95% CI	RR§	95% CI
Dementia								
Low	1.08§	0.33, 3.48	2.08	0.68, 11.47	1.71	0.82, 3.60	2.67	1.05, 6.78
Medium	0.64	0.18, 2.31	1.93	0.45, 8.26	1.41	0.67, 2.97	1.39	0.73, 2.63
High	1.0		1.0		1.0		1.0	
Alzheimer's disease								
Low	2.26	0.31, 16.26	1.67	0.31, 8.97	2.48	0.60, 10.27	3.34	0.75, 14.85
Medium	1.41	0.18, 10.65	1.46	0.27, 7.99	1.92	0.73, 5.06	1.32	0.37, 4.73
High	1.0		1.0		1.0		1.0	

* EURODEM, European Studies of Dementia; MRC, Medical Research Council.
† Low, ≤7 years of education; middle, 8–11 years of education; high, ≥12 years of education.
‡ RR, relative risk; CI, confidence interval.
§ Adjusted for age, age², and sex.

TABLE 4. Sex-specific pooled estimates of the association of incident dementia and Alzheimer's disease with educational level, EURODEM* pooled analyses, 1988–1997

Educational level†	No. of cases	Person-years	RR‡,§	95% CI‡
Men				
Dementia				
Low	64	4,133	1.09	0.61, 1.94
Medium	95	6,654	0.92	0.54, 1.59
High	17	1,271	1.0	
Alzheimer's disease				
Low	37	4,093	0.94	0.44, 1.99
Medium	49	6,595	1.00	0.48, 2.06
High	9	1,261	1.0	
Women				
Dementia				
Low	158	6,920	3.78	1.64, 8.72
Medium	153	8,291	2.48	1.09, 5.60
High	6	792	1.0	
Alzheimer's disease				
Low	122	6,870	4.30	1.55, 11.90
Medium	107	8,232	2.63	0.97, 7.15
High	4	788	1.0	
Total				
Dementia				
Low	222	11,053	1.83	1.16, 2.89
Medium	248	14,945	1.32	0.85, 2.05
High	23	2,063	1.0	
Alzheimer's disease				
Low	159	10,963	1.96	1.09, 3.52
Medium	156	14,827	1.42	0.80, 2.50
High	13	2,049	1.0	

* EURODEM, European Studies of Dementia.
† Low, ≤7 years of education; middle, 8–11 years of education; high, ≥12 years of education.
‡ RR, relative risk; CI, confidence interval.
§ Adjusted for age, age², and study.

shown in figures 1 (women) and 2 (men). For women, the age-specific incidence rates for Alzheimer's disease after age 70 years were consistently higher as educational level decreased.

DISCUSSION

For women but not for men, we found an increasing risk for dementia, specifically Alzheimer's disease, associated with a decreasing number of years of schooling. These analyses were based on pooled data from four population-based studies, with probably the largest numbers of cases and person-years of follow-up to date for which these associations have been examined.

Previous studies (8–10) showing a significantly increased risk for Alzheimer's disease associated with low educational level adjusted for sex but did not examine modification of the association by sex. The advantage of pooled data is increased power to examine effect modification. In this cohort, the risk for Alzheimer's disease was higher for women compared with men (29). One explanation for this finding is that women were on average more poorly educated and therefore had a higher risk for Alzheimer's disease. However, several other explanations should be considered.

First, the sex-specific association between low educational level and dementia could be explained by differential inclusion of subjects in the follow-up by educational level and sex. Increasing age and decreasing educational level were associated with nonresponse. Because the incidence of dementia increases with age and is hypothesized to be higher for subjects with lower levels of education, a higher refusal or mortality rate for older subjects or for those with lower levels of education would lead to a loss of power, but this explanation was unlikely to have biased the estimate. The

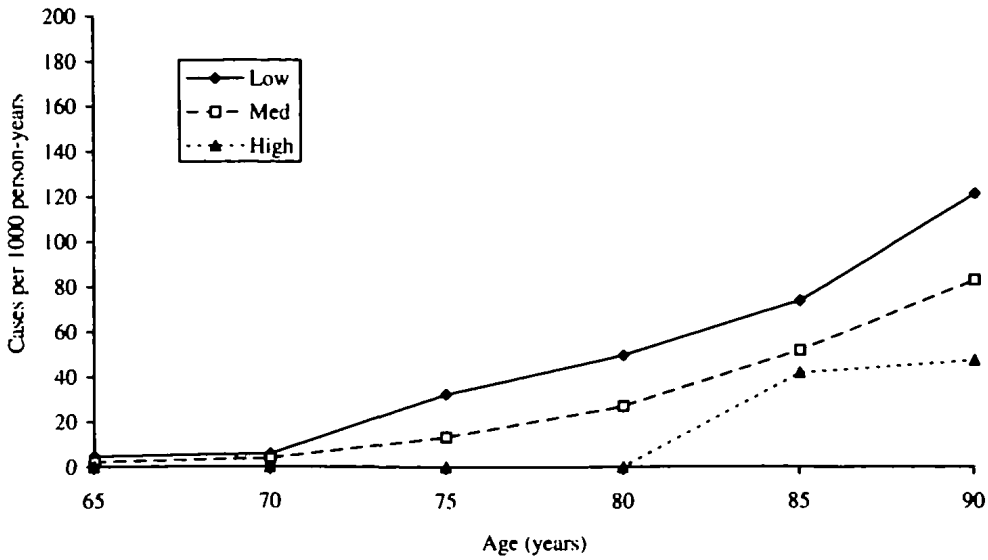

FIGURE 1. Age-specific incidence rates of Alzheimer's disease, by educational level, for women. Pooled analyses from the European Studies of Dementia. Low, ≤7 years of education; middle, 8–11 years of education; high, ≥12 years of education.

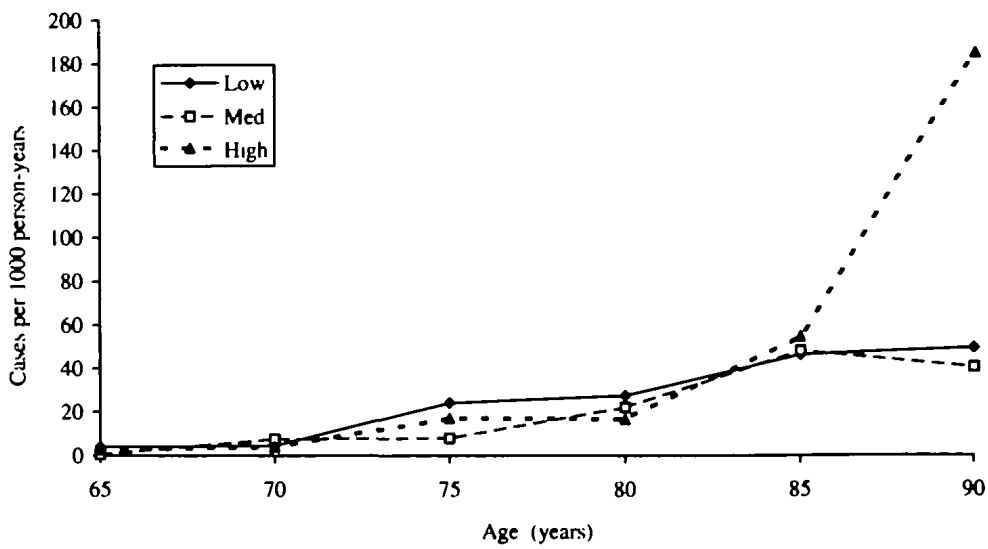

FIGURE 2. Age-specific incidence rates of Alzheimer's disease, by educational level, for men. Pooled analyses from the European Studies of Dementia. Low, ≤7 years of education; middle, 8–11 years of education; high, ≥12 years of education.

nonsignificant differences in follow-up between men and women and the nonsignificant interaction between sex and educational level suggest that the association between education and nonresponse was the same for men and women. Thus, a differential follow-up by education and sex, which have would biased the estimates, is also unlikely to explain the results.

Second, one study could have unduly influenced the results of the pooled analyses. Several different strategies were used to examine this possibility, including estimating homogeneity in study-specific coefficients and removing individual studies from the analyses. The association between education and risk of dementia remained similar, suggesting that none of the studies had a major influence on the results.

Third, the differential association could have been due to screening bias. Different screening instruments were used for the studies, a relatively sensitive cutoff point was used for screening, and more than one mechanism was used to identify cases. To explore further a possible bias at the screening level, we estimated the risk of being screened positive by using logistic regression analysis. Neither sex nor the interaction between sex and education were significantly associated with positivity. Therefore, the probability of being screened positive was equivalent for

men and women and did not depend on educational level.

Subjects with low educational attainment might have been more easily classified as demented than those with a higher level of education. For this possibility to explain the sex differences, either women with lower levels of education were more likely to have been diagnosed as demented compared with men or higher educated women were less likely to have been diagnosed with dementia compared with men. Although we could not totally eliminate the possibility of a diagnostic bias, it seems unlikely that it occurred for women only.

Sex differences in cognitive abilities, which have been described frequently, may explain the differences in the risk for dementia. For instance, Halpern (30) found that compared with men, women scored higher on tasks that required rapid access to and use of phonologic and semantic information in long-term memory, production and comprehension of complex prose, fine-motor skill, and perceptual speed. Men, on the other hand, scored higher on tasks that required transformation in visual-spatial working memory, motor skills involved in aiming, spatiotemporal responding, and fluid reasoning, especially in mathematical and scientific domains. Hedges and Nowell (31) analyzed mental scores collected over 30 years from six studies; they found that women tended to perform slightly better on reading comprehension, perceptual speed, and associated memory tests and that men performed slightly better on mathematics and social studies tests. However, these results cannot explain the difference in the risk for developing dementia among men and women with low levels of education. The psychometric tests used to screen demented subjects explore several cognitive functions and do not favor abilities performed well by men or abilities acquired by men but not by women with low levels of education.

Effect modification by sex also may reflect a differential distribution of unmeasured confounding factors related to educational level and the risk for Alzheimer's disease. One source of this type of confounding may be socioeconomic status and its effect on early-life exposures related to brain development. Different types of studies suggest that estrogens may slow the progression of Alzheimer's disease (32, 33). As Mortimer and Graves pointed out (2), low economic status is associated with reduced body size and delayed function, such as later menarche. Low socioeconomic status in adulthood also may be associated with an earlier age of menopause (34). Together, these occurrences may result in a shorter period of exposure to estrogens for women in lower compared with higher socioeconomic classes. It is also possible that these sex-specific differences reflect differences in stress levels. Stress increases cortisol levels, which in turn has been hypothesized to damage the hippocampus, an area of the brain involved in learning memory (35, 36).

Finally, although we found that the relative risk for Alzheimer's disease increased with a decreasing number of years of education, the number of Alzheimer's disease cases among women with high levels of education was low ($n = 6$). Therefore, we cannot exclude the possibility that this was a chance finding.

In conclusion, our results suggest that a low number of years of schooling is a risk factor for Alzheimer's disease, but only for women. The reasons for this association are still unclear. Confirmation of these findings in other prospective studies is needed. However, finding a significant sex modification argues that unmeasured confounding explains educational differences in the risk for dementia and not a direct effect of educational level itself on the brain. As the factors related to the risk for Alzheimer's disease become better known, this effect modification should be reexamined.

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