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Education and the Risk of Alzheimer's Disease: Findings From the Study of Dementia in Swedish Twins

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The association between dementia and education was studied in 143 twin pairs discordant for dementia, using a matched-pair design, and in 221 dementia cases and 442 unrelated controls from the same twin registry, using a case-control design. Low education was defined as 6 years or less of schooling. Case-control analyses with prevalent cases showed low education to be a risk for Alzheimer's disease but not dementia in general. Low education did not significantly predict incident cases. In the matched-pairs analysis, which controls for genetic and other familial influences, differences in education between demented twins and twin partners were not statistically significant. However, for Alzheimer's disease, odds ratios resulting from matched pairs and case-control analyses were similar. Twins' comparative reports about intellectual involvement earlier in their lives suggest a long-standing difference on this dimension, with less involvement by the twin who became demented.

THE discovery that Alzheimer's disease occurs more frequently among those with low educational attainment opened new questions about disease mechanisms. Low education is now generally included on lists of established risk factors for Alzheimer's disease (e.g., Cummings, Vinters, Cole, & Khachaturian, 1998). The first indications that rates of dementia differed with level of education came from population studies. Prevalence of dementia was greater among those with low or no education, and prevalence of dementia was less among those with higher education. For example, in the Shanghai study (Zhang et al., 1990), illiteracy predicted higher rates of dementia. In the Canadian Study of Health and Aging (1994), those with 6 or fewer years of education had higher rates of Alzheimer's disease than did those with 10 or more years. Other population studies of prevalent cases have confirmed this relationship (Dartigues et al., 1991; Kokmen, Beard, O'Brien, & Kurland, 1993; Ott et al., 1995; Precipe, Casini, Ferretti, Lattanzio, Fiorelli, & Culasso, 1996; Yamada et al., 1999), and various case-control series have replicated the observation that low education is a significant risk factor (e.g., Mortel, Meyer, Herod, & Thornby, 1995).

More recently, there have been follow-ups of several large population-based samples to identify incident dementia cases, and education has again been examined as a risk factor. For example, in a longitudinal follow up in East Boston, Massachusetts, Evans and colleagues (1997) reported that low education was a significant predictor of incident Alzheimer's disease, and Nielsen, Lolk, Andersen, Andersen, and Kragh-Sorensen (1999) found low education predicted incident Alzheimer's disease in the Odense study. In the pooled EURODEM analyses of incident cases, lower education was a significant risk factor, especially in women (Launer et al., 1999). Several authors of incidence studies have reported similar findings (Ott, Van Rossum, Van Harskamp, Van de Mheen, Hofman, & Breteler, 1999; Stern, Gurland, Tatemichi, Tang, Wilder, & Mayeux, 1994; Zhang, Katzman, Yu, Liu, Xiao, & Yan, 1998).

Other findings imply a more complex relationship between education and dementia. Some studies—both of prevalent cases and of incident cases—have found education to be a risk factor for some dementias but not all dementias. In the Kungsholmen study in Sweden, Fratiglioni et al. (1991) found low education to be a significant risk factor only for all dementias combined, but not for Alzheimer's disease alone. In the Framingham study, Cobb, Wolf, Au, White, and D'Agostino (1995) found that education was a significant risk factor for incidence only of dementias other than Alzheimer's disease, largely vascular dementia. The authors speculated that the critical mechanism revolved around bad health habits associated with lower education, such as smoking and poor diet, because these bad health habits would be risk factors for stroke and for vascular dementias.

Some reports have suggested that the education effect depends on which levels of education are compared. For example, in an Italian study, DeRonchi, Fratiglioni, Rucci, Paternico, Graziani, and Dalmonte (1998) found that having no formal education was a significant risk, but there was no significant difference in dementia or Alzheimer's disease prevalence when comparing those with up to 3 years of education with those with 3 or more years.

Other studies—largely incidence studies or prevalence studies in developing areas of the world—have found no relationship between dementia and education. In the Rochester Epidemiology Project, which was based on incident cases identified from medical records, there was no signifi-

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cant association between dementia and education when comparing those with less than 9 years of education to those with 9 years or more (Kokmen, Beard, O'Brien, & Kurland, 1996). In the Indo-US study (Chandra, Ganguli, Pandav, Johnston, Belle, & DeKosky, 1998), there was no association between prevalence of dementia and illiteracy, nor did dementia prevalence relate to education in the Assiut-Upper Egypt study (Farrag, Farwiz, Khedr, Mahfouz, & Omran, 1998) or in Nigeria (Hall et al., 1998).

The conclusion across these projects is that low education is most relevant to predicting dementia in studies of prevalent cases in populations that include people with quite low or no education, especially if low education is compared with high education. The education effect is reduced if age is controlled for, is less in incidence studies than in prevalence studies, and is generally less for Alzheimer's disease alone than for all dementias.

There are four views about the reason that education might be related to dementia: cognitive reserve, "use it or lose it," education as a proxy for other exposures, and diagnostic bias.

Cognitive Reserve

The construct of cognitive reserve (see, e.g., Mortimer, 1997; Satz, 1993) offers a conceptual framework for discussing the education–dementia relationship. In this view, dementia is observed clinically after cognitive reserve is depleted to some threshold. Less initial cognitive reserve would imply that smaller changes would be required to bring the individual to the threshold at which impairment would be evident, whereas greater cognitive reserve would presumably afford greater protection against dementia. In this theory, cognitive reserve could reflect either innate differences in cognitive capacities or better early brain maturation (for example, in relation to maternal and infant nutrition). In either event, educational attainment would be an indicator of greater cognitive reserve.

Bidzan and Ussorowska (1995) looked at unfavorable environmental factors during childhood, such as low family income, that they posited to indicate negative influences on early brain development and found that these factors were more prominent among groups with dementia than among control groups. Mortimer and colleagues (Mortimer, Fortier, Rajaram, & Gauvreau, 1998) found that, among adults who had siblings with dementia, those who grew up in socioeconomically disadvantaged circumstances had a higher risk of Alzheimer's disease themselves. More recently, Moceri, Kukull, Emanuel, van Belle, and Larson (2000) reported that various indicators of early-life socioeconomic level (greater number of siblings, area of residence as a child) were related to greater risk of Alzheimer's disease. The cognitive-reserve line of thinking is also supported by findings from the Nun study (Snowdon, Kemper, Mortimer, Greiner, Wekstein, & Markesbery, 1996), in which the complexity of thought in essays written in their early 20s predicted which nuns later developed Alzheimer's disease. Other research results have also supported the idea that intelligence might function as cognitive reserve (Stern, Alexander, Prohovnik, & Mayeux, 1992). These authors showed that, after they controlled for dementia severity, higher education and estimated premorbid intellectual ability were associated with greater impairment on tests of cerebral metabolism. Although at first this finding might appear counterintuitive, the authors' interpretation is that intelligence moderates clinical manifestation of cerebral pathology.

A further prediction based on the cognitive reserve model is that the education–dementia relationship should be weaker in cultures or cohorts for whom level of education is less directly reflective of intellectual capacities or, hence, of cognitive reserve. For example, Hall et al. (1998) found that low education was a risk factor in Indianapolis, Indiana, but not in Nigeria, and Harwood and colleagues (1999) found that low education was a risk factor for Whites but not for Hispanics.

Use It or Lose It

Some writers have discussed the possibility that mental activity throughout adulthood can increase synaptic density, whether through formal educational activities or through cognitively challenging occupations or cognitively stimulating leisure activities (e.g., Katzman, 1993). The idea that high education might be a protective factor has also received support from animal studies associating mental stimulation with dendritic complexity (Lucassen, Van Someren, & Swaab, 1998) and from proposals of plausible neurobiological mechanisms by which neuronal activation might slow amyloid deposition (Friedland, 1993). In a finding consistent with this line of reasoning, Fabrigoule, Letenneur, Dartigues, Zarrouk, Commenges, and Barberger-Gateau (1995) found incidence of dementia was lower among those who had participated in leisure activities such as traveling or gardening. It is, of course, appealing to think that older individuals might be able to prevent or to postpone onset of dementia through remaining mentally active (see Orrell & Sahakian, 1995).

Education as a Proxy

There has also been an interest in the possibility that education might be indicative of other risk factors such as occupational exposures or bad health habits, for example, alcohol use (Fratiglioni et al., 1991). However, DeRonchi et al. (1998) found a residual education effect after controlling for age, occupation, and smoking. Similarly, Evans and colleagues (1997) found independent contributions from education and from low occupational prestige and low income. Thus, whereas these other risk factors may increase odds of developing dementia, they do not entirely explain the education effect.

Diagnostic Bias

Finally, education might serve to teach the individual the sorts of reasoning skills that are required by neuropsychological tests used in dementia assessments (Gilleard, 1997). Here, education is sometimes regarded as a confounding factor, requiring that norms on tests be adjusted for education for the test to be a valid measure across different groups of people (Stockton, Cohen-Mansfield, & Billig, 1998). This explanation of the education–dementia relationship receives support from the observation that those with lower education tend to have lower scores on neuropsychological tests used in dementia assessment but not greater functional deficits (Swanwick et al., 1999).

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Twin Methods

Twin studies provide a vehicle for helping to sort out the alternative mechanisms that might be involved in the association between education and dementia. A matched-pair analysis takes twin pairs who are discordant for a disease and evaluates whether the twin who was exposed to a given risk factor is more often the twin with the disease. This design has the advantage of controlling for genetics, insofar as identical twins share 100% of their genes and fraternal twins share 50% of their segregating genes. In addition, cases and controls are the same with respect to age and gender (for like-sexed pairs), and they are similar with respect to their environmental history. We know that twins are very similar with respect to intellectual abilities, with up to 80% of the variance in intellectual abilities explained by genetic effects (Pedersen, Plomin, Nesselroade, & McClearn, 1992). Thus, twins should be similar in their baseline cognitive reserve.

In one twin study that has examined education and dementia, Räihä, Kaprio, Koskenvuo, Rajala, & Sourander (1998) used twin pairs who were discordant for Alzheimer's disease, determined by matching the Finnish Twin Registry with a registry of diagnoses. Across 25 identical and 25 fraternal pairs, higher education was related to reduced risk of Alzheimer's disease.

The key question of interest in the present study was to contrast a classical case-control analysis with a matched-pair analysis. A classical case-control approach recruits cases with dementia and controls without dementia from a similar population. The analysis tests relative proportions of cases compared with controls who experience a particular risk factor, for example, low education. We hypothesized that low education would be a significant risk factor in a classical case-control analysis, replicating previous findings, whereas in the matched-pair analysis, by controlling for familial influences on intellectual ability, we would not find low education to be a significant risk factor. If this hypothesis is supported, it is consistent with a cognitive-reserve interpretation of the education–dementia relationship.

A third, more exploratory set of analyses was conducted to provide suggestions with respect to possible meanings of the education variable. Here we drew on twins' self-reported comparisons of who got better grades in school, who read more books, and who found learning to be easier. If these variables differed between cases and their partners, it would provide evidence for early differences in intellectual involvement. Such a pattern would be consistent with an environmentally mediated cognitive-reserve interpretation, but also with use it or lose it.

In these analyses, we did not directly test whether education relates to adult environmental exposures, and the role of diagnostic bias is minimized insofar as diagnoses are not based directly on test results but on functional deficits as well.

Methods

Sample

Participants in the present study include members of the Study of Dementia in Swedish Twins (Gatz et al., 1997) and members of the OCTO-Twin study (McClearn et al., 1997). Both studies represent defined subsamples of the population-based Swedish Twin Registry. The Study of Dementia in Swedish Twins identified dementia cases from the Swedish Adoption/Twin Study of Aging (SATSA; Pedersen et al., 1991). SATSA includes all pairs from the twin registry who indicated having been reared apart and a matched sample who were reared together. Members of SATSA have been surveyed by mail-out questionnaires every 3 years since 1984, and complete pairs aged 50 and older have participated in in-person cognitive and health assessments on a 3-year rolling schedule. For purposes of the dementia study, all twins identified for the SATSA sample born in 1935 or previously were included, if one or both members of the pair were alive in 1987, whether or not they had responded to SATSA data collection efforts (N = 1,978). Baseline screening took place in 1987 and 1988, with the final 20% completed by 1991, and incident cases were identified at each additional data collection.

The OCTO-Twin study enrolled all twin pairs 80 years old and older if both members of the pair were alive during the first wave of data collection in 1991–1994 (N = 702). Four subsequent waves of in-person assessment were scheduled at 2-year intervals. Cases of dementia were identified at the first three waves.

The present study included all cases, both those identified initially (prevalent cases) and new cases of dementia identified longitudinally (incident cases).

Procedures.—Case ascertainment from the SATSA sample used a two-stage process (see Gatz et al., 1997). Participants were screened for dementia using either the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) during an in-person visit or a telephone screening protocol (Gatz, Reynolds, Nikolic, Lowe, Karel, & Pedersen, 1995) for those not seen in person. Those scoring below established cutoffs were identified as suspected cases of dementia and referred for evaluation by an assessment team employing a nurse, a psychologist, and a physician. The protocol parallels Consortium to Establish a Registry for Alzheimer's Disease (CERAD) procedures for physical and neurological evaluations, laboratory tests, neuropsychological testing, and neuroimaging (Morris et al., 1989). Findings were presented at a consensus diagnosis conference, attended by the clinicians and chaired by a psychologist who had not met the twin. Diagnoses were assigned following *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., rev. (American Psychiatric Association, 1987) criteria for dementia, NINCDS/ADRDA criteria for probable and possible Alzheimer's disease (McKhann et al., 1984), and—once available—NINDS–AIREN criteria for vascular dementia (Roman et al., 1993). Twin partners of participants were given an identical clinical work-up. If the partners were deceased, their diagnostic assessment included informant interviews and review of medical records, including death certificates. Cases and partners were followed longitudinally every 18 months, with postmortem neuropathological examination for any who died. Autopsy confirmation of diagnosis was available for 24 cases.

Case ascertainment from the OCTO-Twin sample entailed a review of MMSE scores and cognitive performance information collected from all twins, whether or not de-

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mented. The battery paralleled that used with the suspected dementia cases from SATSA. For those suspected of dementia, informant interviews were conducted using the same protocol as for the SATSA twins, medical records were reviewed, and a consensus diagnosis assigned by a physician and a psychologist (Boo Johansson). Boo Johansson also chaired the diagnostic conferences for both samples.

Differences in case ascertainment between the two samples include the following: (a) SATSA twins include pairs reared apart as well as pairs reared together, whereas OCTO twins were reared together; (b) in OCTO-Twin, both members of the pair had to be alive at age 80, whereas SATSA twins were included if dementia status could be established for both members of the pair; (c) nonresponders to OCTO-twin cognitive testing were lost to dementia study, whereas nonresponders to SATSA data collection were telephoned for dementia screening; and (d) a SATSA twin whose in-person MMSE was below cutoff could refuse further work-up, whereas an OCTO twin whose cognitive testing was impaired could be presented for consensus diagnosis. These differences could result in disparate, competing, but unknown diagnostic biases across twin pairs, although few differences that should be differential within twin pairs.

Longitudinal follow up of both the SATSA and OCTO-Twin samples provided additional waves of screening and a means to identify incident cases. One individual who screened negative was found to be demented at a later wave and was deemed a false negative because age of onset was earlier than the baseline screening. This pair is not in the matched-pairs analysis.

Sample for Matched-Pairs Analysis

The prevalent matched-pair analyses included pairs discordant for dementia at first assessment, excluding pairs whose co-twin died before the participant's age of onset.

For incident matched-pairs analysis, we identified a baseline sample of pairs in which both members of the pair were cognitively intact at the first data collection, either the screening of the SATSA sample for dementia or the first wave of OCTO-Twin. Incident cases are those new cases of dementia from within these pairs. Pairs were defined as discordant if one member of the pair developed dementia while the other member of the pair remained intact through the same duration of follow up, or longer. To assure that incident cases were truly incident and were not false negatives at baseline screening, we obtained age at onset of incident cases without knowledge of prior screening date or outcome. These ages were checked to ensure that onset occurred subsequent to baseline screening.

Using these procedures, we found 143 pairs discordant for dementia—77 prevalent and 66 incident. Forty-eight pairs (62%) were discordant for prevalent Alzheimer's disease (the participant had had definite, probable, or possible Alzheimer's disease, whereas the partner was cognitively intact). The other cases were diagnosed with vascular dementia or mixed Alzheimer's and vascular pathology (29%), secondary dementia (4%), or dementia of uncertain etiology (5%). Zygosity was originally determined by a questionnaire and then confirmed serologically. All pairs were of the same sex. Zygosity, gender, and age of onset for prevalent and incident cases are shown in Table 1.

Sample for Classical Case-Control Analysis

The classical case-control analysis compared dementia cases with unrelated controls. If both members of a pair were demented, one was randomly included. The pool from which controls were drawn was obtained by selecting one member of each twin pair in SATSA or OCTO-Twin for which both members of the pair were cognitively intact. Two unrelated controls were selected for each case, matching for gender and age, within 5-year agebands. Age was based on age of onset for cases and age at visit for controls. For these purposes, there were a total of 131 prevalent cases of dementia who were compared with a control sample of 262; 77 of these cases constituted the Alzheimer's disease sample. We compared a total of 90 incident cases of dementia with a control sample of 180; 54 of these cases constituted the Alzheimer's disease sample. Throughout this process, all dependencies were removed from the data. Zygosity, gender, and age of onset for prevalent and incident cases are shown in Table 1.

Measures

Education.—Education was collected as a five-category variable: (1) elementary school, meaning 6 years, (2) secondary school, (3) vocational school or adult high school, (4) "gymnasium," and (5) university. For all of our analyses, we collapsed education into two categories: elementary or less schooling compared with greater than elementary schooling. In Sweden in the early 20th century, 6 years of education was mandatory, so virtually no one had less than

Table 1. Demographic Characteristics of Cases

	Zygosity (% MZ)	Gender (% women)	Diagnoses (% Alzheimer's disease)	Age of onset		
				M	*SD*	Range
Matched pairs sample						
Prevalent cases (N = 77 pairs)	29.9%	62.3%	67.6%	78.5	9.1	50–92
Incident cases (N = 66 pairs)	36.4%	65.2%	73.9%	82.0	5.6	63–92
Case control sample						
Prevalent cases (N = 131)	30.5%	70.2%	58.8%	76.2	7.8	50–92
Incident cases (N = 90)	38.9%	63.3%	60.0%	82.8	5.4	63–93

Note: MZ = monozygotic.

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6 years of education, and the vast majority of the population stopped school at this point. Information about education was collected for the SATSA panel from the 1984 questionnaire or, for those who did not answer the questionnaire, from the individual or a proxy at the time of the clinical workup. For OCTO-Twin, information about education came from the 1992 interview. We also were able to fill in missing data and cross-check against information in the Swedish Twin Registry collected in 1963. Thus, in the sample of 134 discordant pairs, information about education was available for both members of 129 pairs.

Comparative risk.—We obtained answers to five questions about grades in school and reading for pleasure from the twins in the SATSA sample only, using a comparative report format in which twins were asked, "Before age 20, who read more books or read more frequently?" "As an adult, who read more books or read more frequently?" "Who had better grades in school?" "Who found learning in school to be easier?" and "Whose ability to find their way in unfamiliar surroundings was better?" Response options included "me," "my twin," "equally as much," and "don't know." This strategy, devised by Mack (Hamilton & Mack, 2000), avoids some of the pitfalls of recall measures, as it is easier for siblings to remember who did something more than it is to remember absolute numbers. Data were either collected at the time of the dementia assessment, only from the cognitively intact member of the pair, or in 1992 from all members of the SATSA sample, including those who might later be included in the Study of Dementia in Swedish Twins. Information was available from 17 cases and 37 partners. Twin pairs who were reared apart tended not to answer this questionnaire. For 12 of the cases, information came from both case and partner. There were no instances in which the twins disagreed, for example, both saying "me" or both saying "my twin." Information from cases and partners was therefore combined and scored for whether case or control had greater exposure. In other words, if either twin answered, the data were used. If both twins answered, the consensus answer was used. For these purposes, answers of "equally as much" or "don't know" were treated the same as missing data.

Analyses

For the classical case-control analysis, we estimated the association between education and disease through the odds ratio, comparing proportion with low education in cases and in controls. In addition, a logistic regression model was used to adjust for ageband and gender. For the matched-pair analysis, odds ratio estimates of relative risk were calculated using McNemar's test, with 95% confidence intervals. The odds ratio indexes the magnitude by which low education magnifies risk. An odds ratio near 1.0 would indicate that education was not a significant risk factor.

For the analyses using comparative reports, the result took the form of percentage of cases and percentage of partners experiencing an exposure, and 95% confidence intervals were constructed around the percentage of cases. A finding that significantly less than 50% of cases experienced the exposure would be evidence of a protective effect associated with the activity.

Results

Classical Case-Control Analysis

Results are summarized in Table 2 for the odds ratios. In prevalent cases, low education is a significant risk for Alzheimer's disease but not for all dementias. Logistic regression results (in the far right column of Table 2) show that including ageband, gender, and education in the model indicated no age or gender effect, but the significant effect remained for low education as a risk factor for Alzheimer's disease alone. For incident cases, however, neither the odds ratio for all dementias nor for Alzheimer's disease alone was significant.

Matched-Pair Analyses

Results, summarized in Table 3, show that no odds ratio was statistically significant. The conclusion here is that there is not a significantly greater chance for the less educated partner to have either dementia in general or to have Alzheimer's disease. If there is a trend in the data, it is a greater effect for low education with respect to Alzheimer's disease than to the combined dementia category.

Results did not differ when examined separately by gender, rearing status, or zygosity (not included in Table 3). The only suggestive difference with respect to zygosity was that in the analysis of incident Alzheimer's disease, three of the four pairs for whom the case had lower education were monozygotic, and there were no monozygotic pairs for whom the partner had lower education. Thus, it appears that that inclusion of dizygotic pairs was not the explanation for the larger than expected odds ratios for Alzheimer's disease.

Table 2. Case-Control Analyses: Low Education as a Risk Factor

	Proportion of cases with low education	Proportion of controls with low education	Odds ratio (95% confidence intervals)[a]	Odds ratio adjusted for age and gender (95% confidence intervals)[a]
Prevalent cases				
All dementias	112/131 (85.5%)	210/262 (80.2%)	1.46 (0.82, 2.59)	1.47 (0.82, 2.62)
Alzheimer's disease only	68/77 (88.3%)	119/154 (77.3%)	2.22 (1.02, 4.84)	2.26 (1.02, 5.02)
Incident cases				
All dementias	78/90 (86.7%)	151/180 (83.9%)	1.25 (0.60, 2.58)	1.25 (0.60, 2.60)
Alzheimer's disease only	50/54 (92.6%)	92/108 (85.2%)	2.17 (0.70, 6.73)	2.17 (0.69, 6.86)

[a]95% confidence intervals correspond to $p < .05$. If the confidence interval does not include 1.0, then the risk factor is significant.

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Table 3. Matched-Pairs Analyses: Low Education as a Risk Factor

	% cases with low education	% partners with low education	Total no. of pairs	Pairs discordant for education		Odds ratio (95% confidence intervals)[a]
				Case lower	Partner lower	
Prevalent cases						
All dementias	80.5	81.8	77	7	8	0.88 (0.32, 2.41)
Alzheimer's disease only	87.5	83.3	48	4	2	2.00 (0.37, 10.92)
Incident cases						
All dementias	84.8	84.8	66	6	6	1.00 (0.32, 3.10)
Alzheimer's disease only	92.9	85.7	42	4	1	4.00 (0.45, 35.79)

[a]95% confidence intervals correspond to $p < .05$. If the confidence interval does not include 1.0, then the risk factor is significant.

Twins' Comparative Reports of Intellectual Involvement

The comparative risk results provided in Table 4 showed a pattern suggesting that the twin who later became demented had less intellectual involvement earlier in life. There were statistically significant differences with respect to reading fewer books as an adult and finding one's way in unfamiliar surroundings less well. There were no significant differences with respect to grades or ease of learning.

Discussion

Analyses were conducted to test the prediction that low education would be a significant risk factor for dementia using a classical case-control design, whereas a matched-pairs analysis would not find low education to be a significant risk factor. The basis for such a prediction is the assumption that educational attainment largely reflects cognitive reserve, in particular, genetic influences on cognitive abilities. This prediction, however, received equivocal support. Our ability to resolve alternative explanations of the meaning of low education was, in turn, limited by restricted power that essentially reflected twin similarity in cognitive reserve.

The findings from the prevalent, or cross-sectional, case-control analyses comport with the conclusion from many previous studies that low education is a risk factor for dementia, whereas higher education is associated with protection. Some previous reports have suggested that the education effect is more pronounced for all dementias or for dementias other than Alzheimer's disease (e.g., Cobb et al., 1995). This was not found in our material, in which results were significant only for Alzheimer's disease considered alone and not for all dementias. Consistent with Kokmen and colleagues (1996) and Ott and colleagues (1999), but not with Launer and colleagues (1999), low education was not a significant risk factor when incident cases of Alzheimer's disease or all dementias were considered. However, we observed similar odds ratios for prevalent and incident Alzheimer's disease, and differences in confidence intervals in part reflect sample size.

In our material, the 2.22 odds ratio for prevalent Alzheimer's disease was statistically significant but smaller than has been observed in other studies. For example, an odds ratio of 4.00 was reported for a Canadian sample (Canadian Study of Health and Aging, 1994), an odds ratio of 3.49 for a sample from Indianapolis, Indiana (Hall et al., 1998), and an odds ratio of 4.7 for an Italian sample (DeRonchi et al., 1998). Of these, only the Canadian sample had a larger number of cases than the Swedish sample. The difference may reflect rather small amount of variability in education among Swedish adults born before 1925. Also, the country was at that time very poor economically, and these social circumstances meant that few were allowed to obtain an education that might correspond with their intellectual abilities. Although speculative, this outcome is compatible with the cognitive reserve model, which would predict a weaker education–dementia relationship in a population or cohort in which education was less directly reflective of intellectual capacities.

The comparison built into this study is between these case-control results and the matched-pairs analyses. Matched-pairs analyses control for genetic and other familial influences. As predicted, we found that education was not significantly different in cases compared with their twin partners. For all dementias, the odds ratio for both prevalent and inci-

Table 4. Comparative Risk Results in Twin Pairs Discordant for Dementia

	All dementias			Alzheimer's disease		
Exposure	*N* of pairs	% cases with exposure	95% confidence intervals[a]	*N* of pairs	% cases with exposure	95% confidence intervals[a]
Read more books before age 20	19	31.6	10.7, 52.2	15	33.3	9.5, 57.1
Read more books as an adult	20	25.0	6.0, 44.0	16	25.0	3.8, 46.2
Better grades in school	17	41.2	17.8, 64.6	14	50.0	23.8, 76.2
Found learning in school easier	14	42.9	17.0, 68.8	12	50.0	21.7, 78.3
Found one's way better in unfamiliar places	21	28.6	9.3, 47.9	15	20.0	0.0, 40.2

[a]95% confidence intervals correspond to $p < .05$. If the confidence interval does not include 50.0%, then the percent of cases with the exposure is significantly less than chance whereas their twin partners were more likely to have engaged in the activity.

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dent pairs was close to 1.0. For prevalent cases of Alzheimer's disease, however, the proportion of cases with low education was greater than the proportion of partners with low education, with about the same point estimate for the odds ratio as was found for the case-control design. The odds ratio was not significant because of a lack of statistical power. In other words, in the few pairs in which there was a difference in attained education, the matched-pairs results suggest an effect of education that is not explained by genetic or shared environmental influences.

From our previous work with the Swedish twin samples, we know that twins are highly similar on a composite of cognitive abilities, and that this similarity reflects a large proportion of genetic influences (Pedersen et al., 1992). We have previously reported in a larger sample of nondemented twins that the correlation between education and MMSE scores can be best explained by common genetic factors shared with cognitive abilities, and that, in turn, these genetic factors also explain the correlation between cognitive abilities and education and MMSE scores (Pedersen, Reynolds, & Gatz, 1996). However, for women, there was greater environmental than genetic mediation of the MMSE–education correlation. This observation and the results from the present study point to nongenetic as well as genetic contributors to cognitive reserve.

There has been one prior report of education as a risk factor for Alzheimer's disease in a twin sample. Results from the present study appear comparable to those previously reported by Räihä and colleagues (1998) from the Finnish Twin Registry. In the Finnish study, there are unknown selection effects, as information about education was obtained from only two-thirds of the discordant pairs and cases were ascertained only by record linkage, which is likely to miss up to half of cases (Gatz & Pedersen, 1996). There were more pairs in the Swedish sample, but less discordance for education.

The comparative-risk findings in the present study lead to the interpretation that differences in intellectual involvement already present earlier in life are important for dementia. These findings are consistent with the Nun study (Snowdon et al., 1996), in which differences in linguistic complexity were obvious earlier in life between those who later became demented and those who did not. Our results cannot rule out the idea that lifelong intellectual engagement—use it or lose it—can make a difference. We would, however, hazard that those individuals already higher in cognitive reserve may also be more likely to engage intellectually. Thus, if there are two processes, they may work in tandem, and cognitive reserve might be viewed as a joint and probably interacting function of both genetic and environmental influences.

Key limitations to this study are the small number of pairs discordant for education and the limited amount of variability on education. It has previously been reported that twin pairs in SATSA tend to be similar for education (Lichtenstein, Pedersen, & McClearn, 1992). In the sample in the present study, pairs were highly alike for education (tetrachoric correlation = .71). Those pairs who were dissimilar for education did not differ from other pairs with respect to whether they were reared together or apart. In addition, 74% had low education, making it quite probable that any two individuals would be comparable for education. The matched-pairs analyses were based on the pairs discordant for both education and disease. Thus, the great similarity for education reduced the number of pairs available for comparison. Although the odds ratio was not affected, confidence intervals became large.

In addition, these matched pairs could be regarded as "overmatched," as twin pairs are similar on many other variables, for example, choice of occupation. Thus, the matched-pair design may be overcontrolling for other variables for which education is a proxy.

Additionally, the discordant pairs included both monozygotic and dizygotic pairs; thus, genetic effects were imperfectly controlled for. There were not a sufficient number of monozygotic pairs for an analysis based on them alone. For the matched-pair design, there must be twin pairs discordant for both the disease and the exposure of interest. In the prevalent sample, for example, there was only one monozygotic pair discordant for both Alzheimer's disease and education. For this reason, it should be emphasized that the matched-pair design controls for familial effects, including some genetic and some shared rearing influences.

The comparative-risk analyses have the same sample size considerations as the matched-pairs analyses. In addition, there could be concern about retrospective bias, in which twins would tend to avoid attributing an unfavorable quality to themselves, or in which cognitively intact twins would tend to attribute negative intellectual qualities to the member of the pair who became demented. We were able to determine within this sample that, if both members of the pair did reply to the questionnaire, they did not disagree on these items. The data included some questionnaires that were completed before onset of dementia in either twin; unfortunately, not all of the data were prospective. Moreover, the items that did significantly discriminate were, if anything, less loaded with social desirability than the items that did not discriminate.

In conclusion, in applying a case-control design with unrelated controls, the results provided a replication of low education as a risk factor for Alzheimer's disease but not for all dementias. A matched pairs design that controls for familial effects, including genetically mediated characteristics, showed similar estimates of risk, but these were nonsignificant because of lack of power. The lack of power stemmed from high heritability of cognitive abilities and high similarity of educational attainment in twin pairs, with similarity of educational attainment to a great extent reflecting similarity in cognitive abilities. In the few pairs discordant for education, there was a nonsignificant tendency for twins with Alzheimer's disease to have less education than their cognitively intact partners. The comparative twin findings also suggest that intellectual involvement contributes to cognitive reserve. Taken together, these findings support threshold theories that emphasize the relevance of cognitive reserve as protecting from dementia.

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