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Education and Dementia: A Meta-Analytic Study

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Dementia · Education · Alzheimer's disease · Cognitive reserve

Abstract
Considerable controversy exists about the role of education in the risk of dementia. Individual studies have not been conclusive so far. To examine the hypothesis that lower education is associated with a higher risk of dementia, we carried out a meta-analysis. Observational studies published as of October 2005 that examined the association between education and risk of dementia were systematically reviewed. Relative risks (RRs) and odds ratios were extracted from cohort and case-control studies. We first compared the risk of dementia in subjects with high level of education with the risk of dementia in those with low educational level. In a subsequent analysis, we compared the risk of persons with high education with the risk of subjects with education level other than high (medium, low). We weighted log RRs for cohort studies or odds ratios by the inverse of their variances. Nineteen studies were included in our meta-analysis (13 cohort and 6 case-control studies). RRs for low versus high education level were: Alzheimer's disease (AD) 1.80 (95% CI: 1.43–2.27); non-AD dementias, 1.32 (95% CI: 0.92–1.88), and all dementias 1.59 (95% CI: 1.26–2.01). For low and medium versus high education level, the RRs were: AD 1.44 (95% CI: 1.24–1.67); non-AD 1.23 (95% CI: 0.94–1.61), and all dementias 1.33 (95% CI: 1.15–1.54). These results confirm that low education may be a risk factor for dementia, especially for AD.

Introduction

Over the last decade, several studies have shown an association between education and dementia.

This relation has been evaluated through cross-sectional and longitudinal studies, in clinical and general settings and in different cultures. Most of them have shown an increase in the risk of dementia among subjects with low level of education [1–3], but others have failed to find any association [4, 5].

Several mechanisms have been invoked to explain this relation. First, it has been argued that the results could be due to bias related to the tools used in the diagnosis. The distortion effect exerted by education on the performance of some cognitive tests such as Mini-Mental State Examination (MMSE) and Geriatric Mental State (GMS) used in the measurement of the cognitive function is well

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known. Usually, patients with low educational level score worse in those tests than patients with high educational level. Dementia is then overestimated in those populations. However, this explanation was ruled out in studies that used other measurement tools such as Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases, 10th edition (ICD-10), tools that take into account the social and occupational status of the patient [6].

A second explanation has been advanced in which the educational level could be an independent risk factor for the disease, either by exerting a direct effect or by delaying the clinical expression of the disease. The latter is known as the 'cognitive reserve' hypothesis. This hypothesis [7, 8], initially proposed to explain the lack of a direct relation between the severity of brain damage and its clinical expression, postulates that there are some personal characteristics that may delay the clinical expression of the disease in subjects with brain damage. These characteristics are innate, acquired or both. Education is a good candidate as it provides strategies to solve the cognitive requirements and represents a stimulus that could modify the neural connectivity and plasticity, a fact that has been proved in animal studies [9].

The aim of this systematic review and meta-analysis was to examine the hypothesis that lower education is associated with higher risk of dementia.

Methods

Search Strategy

We systematically searched Medline (between 1966 and October 2005 for both English and non-English language articles by entering '(dementia OR Alzheimer*) AND education* AND (cohort OR case control OR follow-up OR epidemiol* OR prospective OR retrospective)'. In a subsequent search, we introduced the same terms as free text words and subject heading. We used similar strategies to search Embase, PsycInfo and Scopus databases. Further, we manually searched the bibliographic references of the articles retrieved electronically to find other potentially relevant studies.

Data Extraction

We included studies if they: (1) used clear diagnosis criteria for dementia, i.e. DSM-III and updates [10–13], NINCDS-ADRDA [14], ICD-10 [15]; (2) provided information about education of subjects (level of education, years of school); (3) controlled for potential confounders by using risk adjustment in the analysis or matching in the study design; (4) provided odds ratios or relative risks (RRs) and 95% confidence intervals or provided enough data to calculate these figures.

Data Analysis

In a first analysis, we compared the risk of dementia in subjects with high level of education with the risk of dementia in those with low educational level. Subsequently, we compared the risk of persons with high education with the risk of subjects with education level other than high (medium or low).

We considered three different outcomes: Alzheimer's disease (AD), non-Alzheimer's dementia and all dementias.

We weighted log RRs for cohort studies or odds ratios by the inverse of their variances to obtain a pooled measure of the RRs. We assumed that the odds ratios from case-control studies approximate RRs in cohort studies. In general, the reference category for education in the individual studies was 'high level of education'. However, when studies used 'low educational level' as the reference category, for pooling purposes we recalculated the individual RR estimates using high educational level as the reference. We combined cohort studies and case-control studies in the absence of statistical heterogeneity and calculated fixed effects and random effects pooled RRs. When results from the fixed and random effects models were different, we presented the second as it represents a more conservative approach. We tested for heterogeneity by using the DerSimonian and Laird Q statistic. We also measured heterogeneity by using the Ri statistic, which quantifies the proportion of the total variance that is due to between study variance [16]. We assessed publication bias graphically by using a funnel plot. In order to measure the potential effect of publication bias on the pooled RRs, we carried out a sensitivity analysis using three assumptions: published studies included in our meta-analysis represent only half of the studies ever conducted; the remaining unpublished studies have found null associations (that is, RR = 1); the unpublished studies included as many cases and controls as the average of the published studies. We used HEpiMA version 2.1.3 for all analyses [17].

Results

Nineteen studies were finally included in our meta-analysis: 13 cohort studies [1, 2, 18–28] (table 1) and 6 case-control studies [4, 29–33] (table 2). Overall, our results show that the risk of dementia is moderately increased in subjects with low education (table 3). This increase is consistent throughout designs (case-control or cohort studies) and outcomes (AD, non-Alzheimer's dementia and all dementias).

Figure 1 presents a forest plot of the individual studies of AD as well as the pooled estimate of the RR. AD was considered in 14 studies (9 cohort and 5 case-control studies). These studies suggest that the risk of AD is increased in people with low education and that this risk is higher than for the rest of outcomes. For low versus high level of education, the risk was 1.80 (95% CI: 1.43–2.27). For low and medium levels versus high level, the risk was 1.44 (95% CI: 1.24–1.67).

Figure 2 shows the funnel plot for these studies where no evidence of publication bias was detected.

Table 1. Relative risks of dementia according to level of education (cohort studies)

Study	Country	Cohort size	Population/ restriction	Level of education	RR (95% CI)			Dementia criteria	Adjustment variables
					AD	non-AD	all dementias		
Li, 1991 [18]	China	1,090	general population, >59 years	literate[1] illiterate			1 3.18 (1.01–6.10)	DSM-III	none (no adjusted RR available)
Paykel, 1994 [19]	UK	1,195	general population, >75 years	>8 years[1] ≤8			1 1.33 (0.71–2.51)	MMSE, CAMDEX	age
Stern, 1994 [2]	USA	593	general population, 60–99 years	≥8 years[1] <8	1 2.02 (1.33–3.06)			DSM-III-R, NINCDS-ADRDA	age, sex
Cobb, 1995 [20]	USA	3,330	general population, 55–88 years	high school or beyond[1] < high school grade < grade school	1 1.01 (0.71–1.44) 1.04 (0.62–1.74)	1 0.94 (0.61–1.44) 1.75 (1.03–2.98)	1 0.98 (0.74–1.29) 1.31 (0.90–1.90)	DSM-III, NINCDS/ ADRDA	age
Yoshitake, 1995 [21]	Japan	828	general population, >64 years	high education[1] lower high education	1 1.18 (0.61–2.27)	1 0.82 (0.41–1.62)		DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	age
Schmand, 1997 [22]	Netherlands	2,176	general population, 65–85 years	high level[1] general intermediate lower vocational extended primary incomplete primary			1 0.77 (0.32–1.86) 2.31 (1.06–5.01) 2.19 (0.93–5.14) 2.19 (1.05–4.59) 1.76 (0.48–6.36)	GMS	age, sex
Ott, 1999 [23]	Netherlands	6,827	general population, >54 years	high education[1] medium low	1 1.09 (0.57–2.01) 1.41 (0.8–2.47)		1 1.29 (0.77–2.13) 1.24 (0.42–3.64)	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	age, sex
Letenneur, 1999 [1]	France	2,881	general population, >64 years	high education[1] low	1 1.78 (1.27–2.45)		1 1.82 (1.36–2.42)	DSM-III-R, NINCDS-ADRDA, Hachinski score	age, sex
Scarmeas, 2001 [24]	USA	1,772	medicare beneficiaries, >64 years	low education[1] high education	1 0.81 (0.58–1.12)			DSM-III-R, NINCDS-ADRDA	age, ethnic group, occupation, leisure
Kukull, 2002 [25]	USA	2,356	general population, >64 years	<12 years[1] 12–15 years >15 years	1 0.73 (0.47–1.14) 0.48 (0.27–0.84)	1 0.98 (0.48–2.02) 0.92 (0.42–2.02)	1 0.85 (0.58–1.24) 0.64 (0.40–1.00)	DSM-IV, NINCDS-ADRDA	age, sex, APOE
Di Carlo, 2002 [26]	Italy	3,208	general population, 65–84 years	0–5 years[1] 6–10 years ≥11 years	1 0.32 (0.12–0.89) 0.34 (0.12–0.96)	1 0.33 (0.08–1.37) 0.47 (0.14–1.58)	1 0.39 (0.20–0.77) 0.44 (0.23–0.85)	DSM-III-R, NINCDS-ADRDA, ICD-10	age, sex
Tuokko, 2003 [27]	Canada	838	general population, >64 years	>11 years[1] 0–6 years			1 1.11 (1.04–1.18)	DSM-III, NINCDS-ADRDA, ICD-10	age, sex, occupation
Karp, 2004 [28]	Sweden	931	general population, >74 years	>10 years[1] 8–10 years 2–7 years	1 0.6 (0.2–1.6) 2.6 (1.3–5.2)		1 0.8 (0.4–1.8) 2.2 (1.2–4.0)	DSM-III-R, NINCDS-ADRDA	age, gender, vascular disease index, alcohol

[1] Reference category.

Table 2. Odds ratios of dementia according to level of education (case-control studies)

Study	Country	Type of study	Cases: controls	Population/ restriction	Level of education	Odds ratio (95% CI)		Dementia criteria	Adjustment variables
						AD	all dementias		
Beard, 1992 [4]	USA	population C/C	241:241	not given	>9 years[1] < 9 years	1 1.13 (0.69–1.85)		Rochester Epidemiology Project	age, sex, length of medical record
Canadian Study, 1994 [29]	Canada	population C/C	258:535	>64 years	≥ 10 years[1] 7–9 years 0–6 years	1 1.72 (1.12–2.61) 4.0 (2.49–6.43)		DSM-III-R, NINCDS-ADRDA	age, sex, residence
Bonaiuto, 1995 [30]	Italy	population C/C	48:96	>59 years	over 4th grade[1] no formal or up 4th grade illiterate		1 1.7 (0.4–7.6) 1.8 (0.4–9.0)	DSM-III	age, sex, occupation
Gatz[2], 2001 [31]	Sweden	twins C/C	221:442		>6 years[1] <6 years	1 2.17 (0.69–6.86)	1 1.25 (0.60–2.60)	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	age, sex
Lindsay, 2002 [32]	Canada	population C/C	194:3,894	>64 years	≥ 13 years[1] 9–12 years 0–8 years	1 1.37 (0.91–2.06) 1.90 (1.25–2.90)		DSM-III, NINCDS-ADRDA, DSM-IV, NINDS-AIREN	age, sex
Harmanci, 2003 [33]	Turkey	population C/C	57:127	>70 years	no schooling[1] primary education secondary education higher education	1 0.90 (0.38–2.12) 0.72 (0.23–1.37) 0.10 (0.02–0.50)		DSM-III-R, NINCDS-ADRDA	residence, occupation, alcohol use, tuberculosis, stroke, general anesthesia, NSDAID use

[1] Reference category.
[2] This study presented two different analyses: case-control analysis and matched-pair analysis. Only the former was considered in this meta-analysis.

Table 3. Pooled RRs of dementia stratified by dementia type

		Studies	RR (95% CI)	Ri[1]	p value[2]
Lowest education level versus highest education level					
AD	Cohort studies	9	1.59 (1.35–1.86)	0.33	0.1570
	Case-control studies	5	2.40 (1.32–4.38)	0.79	0.002
	All studies	14	1.80 (1.43–2.27)	0.61	<0.0001
Non-AD	Cohort studies	4	1.32 (0.92–1.88)	0.22	0.2816
All dementias	Cohort studies	10	1.62 (1.26–2.09)	0.91	<0.0001
	Case-control studies	2	1.33 (0.68–2.59)	0.00	0.6870
	All studies	12	1.59 (1.26–2.01)	0.88	<0.0001
Any education level other than highest versus highest level					
AD	Cohort studies	5	1.32 (1.09–1.59)	0.61	0.0550
	Case-control studies	3	1.66 (1.30–2.10)	0.00	0.5150
	All studies	8	1.44 (1.24–1.67)	0.47	0.0730
Non-AD	Cohort studies	3	1.23 (0.94–1.61)	0.21	0.3030
All dementias	Cohort studies	6	1.45 (1.16–1.81)	0.59	0.0350
	Case-control studies	1	1.75 (0.58–5.23)		
	All studies	7	1.33 (1.15–1.54)	0.51	0.0740

[1] Proportion of the total variance due to between study variance. Large values (>0.75) indicate large heterogeneity between studies; small values (<0.4) indicate lack of heterogeneity.
[2] DerSimonian and Laird Q statistic.

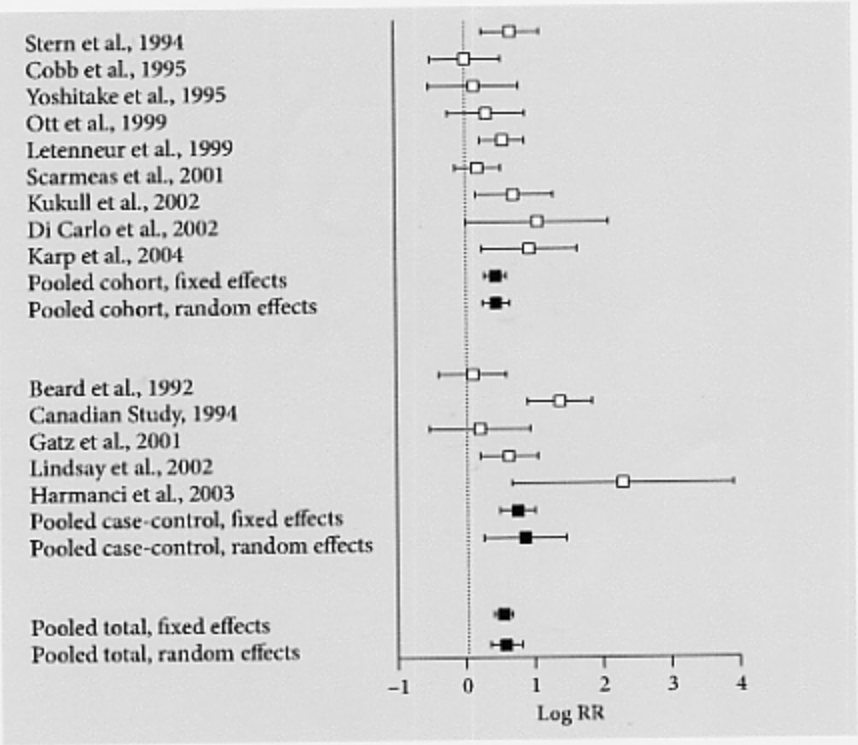

Fig. 1. Forest plot of the studies of education and AD.

Non-AD was considered in 4 studies (all of them cohort studies). Results suggest larger risk of dementia for low level of education, although these results did not reach statistical significance. For low versus high level of education, the risk was 1.32 (95% CI: 0.92–1.88). For low and medium versus high education comparison, the risk was 1.23 (95% CI: 0.94–1.61).

Twelve studies provided data for all dementias without further specification of the classification of the disease (10 cohort and 2 case-control studies). As in the previous analysis, these studies suggest that the risk of dementia is increased in people with low education. For low versus high level of education, the risk was 1.59 (95% CI: 1.26–2.01). For low and medium versus high level of education, the risk was 1.33 (95% CI: 1.15–1.54).

The sensitivity analysis shows that our findings are robust to extreme assumptions concerning unpublished studies. The low level of education remains a risk factor for all dementias (RR = 1.27; 95% CI: 1.11–1.45) after having assumed that published studies included in our meta-analysis represented only half of the studies ever conducted and that the remaining unpublished studies have found null associations.

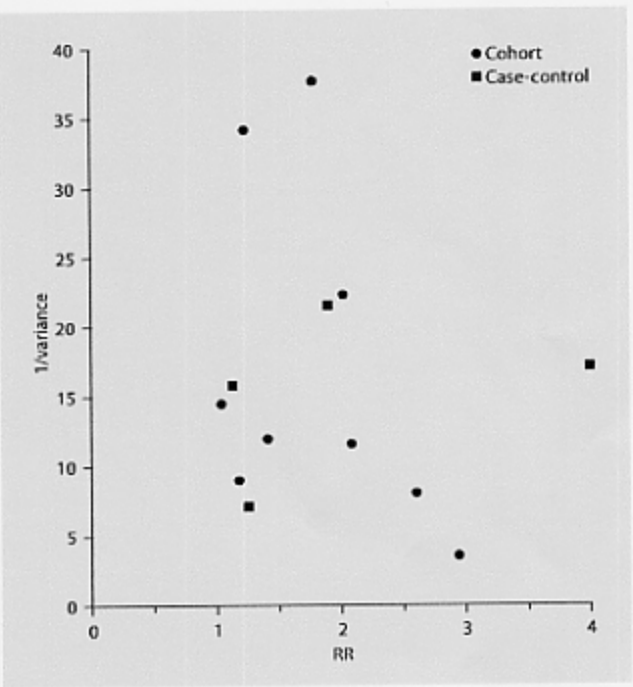

Fig. 2. Funnel plot of RR versus inverse variance of RR. (The study of Harmanci et al. [33] is out of range.)

Discussion

The results of our study suggest that low level of education may be an independent risk factor for AD. The magnitude of this risk varies between 1.44 and 1.79 depending on the categories of comparison. In relation to the type of dementia, our results show that low education represents a stronger risk factor for AD than for non-AD. Finally, case-control studies provided slightly larger risks than cohort studies. However, these differences were not statistically significant.

Causal relation between education and dementia has been discussed in the psychological literature. Our results show that the association fulfils the Bradford-Hill's criteria of causation: the incidence of dementia is higher among subjects with low education than subjects with high education (strength of association); the risk of dementia increases when level of education decreases (dose-response relationship); the association has been observed in longitudinal studies (temporality); studies using different methods and in different populations have provided findings that go in the same direction; furthermore, funnel plots and sensitivity analysis show that publication bias is not likely to explain the results (consistency); the direction of the association is the same for all dementias (analogy), and finally the results could be explained by 'the reserve' hypothesis (biological plausibility).

The burning question in the field is whether low education is a risk factor for the occurrence of the disease itself or for the expression of its clinical features. There is some evidence that the second alternative is more plausible. AD subjects with postmortem confirmed brain damage, who had had intellectual performances that were as good as those of subjects without brain damage, had heavier brain weights and higher number of neurons, a proxy of brain reserve capacity, when compared to control subjects [34, 35]. Positron emission tomography studies in AD patients have reported that subjects with severe brain damage (important parietotemporal perfusion deficit) and high educational level present similar clinical impact of the disease as those AD patients with less severe brain damage and lower educational level [36]. Furthermore, time between diagnosis and death is shorter in subjects with higher educational and occupational achievement. This suggests that the progression of the disease is not delayed [37]. This could explain the difference in risk between cohort and case-control studies. The delay of the clinical expression of the disease involves delay in the diagnosis process, so that at follow-up some of the subjects classified as 'nondemented' might be developing the dementia but do not manifest clinical symptoms yet.

The fact that education could be a factor that delays the onset of the symptoms and not an independent risk factor does not decrease its importance in the prevention strategy. Increasing the education level maintains an acceptable quality of life during a longer period and reduces the costs associated with the management of demented patients. Furthermore, it is remarkable that education may be modified by the society [38].

Our meta-analysis is subject to several limitations inherent to the design or analysis of the individual studies. The most important one is the measurement and categorization of the independent variable. The studies that we reviewed showed important heterogeneity in measurement of education. Categories used included illiterate versus literate subjects, grade school versus high school and lower versus upper 8 or 9 years of education. Some studies included two categories, while others used three or four. Also, most studies considered high level of education as the reference category, but some considered low education as a reference. However, possible bias was addressed in the analysis phase of this study and potential for distortion was low.

In conclusion, our results confirm that low education may be a risk factor for dementia, especially for AD. Results are in accordance with the cognitive reserve hypothesis that postulates that some aspects of life experience may protect against the clinical manifestations of dementia.

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