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Education, Occupation, and Dementia: The Bavarian School Sisters Study

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Key Words
Dementia · Reserve capacity · Risk factor · Natural experiment

Abstract
Background/Aims: An inverse association of educational level with the occurrence of dementia has been repeatedly demonstrated. The mechanism of this relationship is not yet clear. Studies on populations with different educational and occupational levels but uniform living conditions throughout adult life may serve as a natural experiment and may help to rule out lifestyle and environmental factors as possible explanations. ***Methods:*** We studied the relationship of education, occupational training, and appointment to a leading position with dementia in a cross-sectional study of older female members of a religious order. ***Results:*** Out of 517 eligible sisters, 442 (85.5%) with an average of 54 years membership in the order participated in the study, among which 104 cases of dementia were identified. We found a strong association of low educational and occupational attainment with dementia. The increased risk of dementia was attributable to sisters being poorly educated (age-adjusted OR = 4.5; 95% CI: 2.0–9.9), not having received any vocational training (OR = 9.1; 95% CI: 3.9–20.9), and never having been appointed to a leading position (OR = 3.7; 95% CI: 2.0–7.0). ***Conclusion:*** In a setting which largely excludes the influence of lifestyle and environmental factors, we observed a strong association between educational variables and dementia. Our findings support the hypothesis of a reserve capacity against the consequences of brain diseases.

Introduction

In western countries, where life expectancy is long, nearly a third of all elderly individuals develop dementia towards the end of their lives [1, 2]. Individuals with better formal education, however, appear to have a lower susceptibility for dementia than less-educated subjects. A significant inverse association of educational level with prevalence and incidence of dementia and Alzheimer disease (AD) has been demonstrated in various cultural environments [3, 4]. The mechanism underlying this relationship is not clear. If spurious associations caused by selection or detection biases [5] can be ruled out, at least 3 explanations remain:

Firstly, education and higher lifelong mental stimulation may exert a direct protective effect by enhancing the brain's reserve capacity, e.g. by increasing neocortical synapse density [6–8].

Secondly, education may be a marker of intelligence and undisturbed brain maturation [9–11]. Adverse conditions for neurocognitive development in early life may lower cognitive ability, reduce the likelihood of higher

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educational attainment, and increase the susceptibility to neurodegenerative disease in old age.

Thirdly, an increased risk of dementia may be mediated by education-associated lifestyle and environmental factors in adulthood. Lower levels of education may simply be an indicator of other risk factors for dementia, such as cardiovascular diseases, smoking, or occupational hazards [12–14].

These possible mechanisms of association are intimately connected, mutually non-exclusive, inaccessible to experimental manipulation, and difficult to distinguish in observational studies. To differentiate between these effects, investigations on special populations, such as religious orders, which can feature high variability of education and low variability of lifestyle and environment, may be of value. If an association between education and dementia were demonstrable in populations of this type, then lifestyle factors would not be a likely explanation. With the use of this approach, some aspects of the relationship of education or education-related variables, such as linguistic ability and occupational achievement, with dementia have been examined in small samples [15–18]. We had the opportunity to study this relationship in a large community of Roman Catholic sisters. We hypothesized that there would be a significant negative association of formal education and vocational training with the presence of dementia in this special population despite homogeneous living conditions throughout adult life.

Method

Study Population

All participants of the study were members of the Congregation of the School Sisters of Notre Dame, and lived in Bavaria, Germany. The Order was founded in 1833 in Bavaria. Its original mission was to provide school tuition and religious education to girls and young women in poor rural areas. Today, the Order runs children's homes, kindergartens, and schools in 35 countries and is engaged in pastoral work. North American members of the Order are participating in the 'Nun Study', which also focuses on dementia research [15, 18]. In 2001, the Order in the province of Bavaria comprised 750 members, of whom 550 were 65 years of age or older. Whereas these sisters had shared a very homogeneous environment during their entire adulthood, there was a large variability with regard to level of education, type of vocational training, and position attained in the Order. This enabled us to examine the association between these variables and the prevalence of dementia.

Recruitment

The motherhouse of the Order in Munich provided a complete list of all sisters who lived in the Bavarian province. The data set included year of birth, place of residence, and current or previous occupation. Sisters aged 65 years or older were informed about the study by a letter from the Provincial Leader, which included a detailed description of the protocol. If a sister declared interest in participation, a personal visit was scheduled. These visits were performed consecutively over a period of 18 months. After a complete description of the study to the subjects, written informed consent was obtained. The study protocol was approved by the institutional review board of the Medical Faculty at Technical University of Munich.

Assessment Procedures

Study participants were examined by an experienced clinician who had been trained at our memory clinic. A standardized diagnostic protocol was employed, which included the following assessments and instruments: cognitive evaluation (Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery, CERAD-NP [19], incorporating the Mini-Mental State Examination, MMSE [20]), assessment of activities of daily living (Barthel index) [21], and self-rating of depressive symptoms (Geriatric Depression Scale) [22]. For all participants, informant interviews with knowledgeable sisters were performed to ascertain their ability to carry out activities of daily living (25-item Bayer Activities of Daily Living Scale, B-ADL) [23], to determine deterioration of cognitive ability from a previous level (16-item short version of the Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE) [24] and to assess the grade of severity of cognitive impairment and dementia (Clinical Dementia Rating Scale, CDR) [25]. Physical and neurological examinations were also performed. Fasting blood samples were drawn for a laboratory screening for measurement of blood lipids, HbA_{1c}, homocysteine, and estrogen levels, and for apolipoprotein E *(APOE)* genotyping.

Dementia was diagnosed according to DSM-IV criteria. Etiological diagnoses of dementia were established using NINCDS-ADRDA criteria for AD and NINDS-AIREN criteria for vascular dementia (VD).

Information on the participants' educational and occupational attainment was obtained from the provincial archive by an independent rater who was blind to the clinical assessments. Education was classified into low (compulsory elementary education, $\leq$8 years), intermediate (secondary general qualification, ~10 years), and high levels (college or equivalent, university, $\geq$13 years). Occupation was categorized according to the highest level of vocational training reached. With a few exceptions, the sisters pursued the occupation in which they had been trained for their whole lives. Study participants were allocated to 1 of 5 groups: (1) domestic workers, who had no formal vocational training and did the housework for the community; (2) skilled workers (dressmakers, gardeners); (3) nurses and educators in kindergartens and children's homes; (4) teachers for needle work and home economics; (5) teachers in primary schools, secondary schools, and high schools, or other professions with academic degrees. Information was also obtained from the archive on the appointment of leading positions within the Order. These positions were held for an average duration of 12 years. The father's occupation type was used as an index of the participants' socioeconomic background.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 15.0). Differences between educational and occupational

Table 1. Characteristics of the study participants in relation to their educational level

	Educational level			p value
	low (n = 172)	intermediate (n = 170)	high (n = 100)	
Sociodemographic variables				
Age, years	81.1 ± 8.2	76.6 ± 9.7	77.0 ± 9.1	<0.001
Any occupational training, %	50.6	98.8	99.0	<0.001
Leading position, %	14.5	39.4	68.0	<0.001
Laboratory variables and vascular factors				
Body mass index	26.4 ± 5.4	25.4 ± 5.2	26.3 ± 6.1	0.23
Systolic blood pressure, mm Hg	151.3 ± 26.0	152.8 ± 23.8	152.8 ± 23.2	0.81
Diastolic blood pressure, mm Hg	79.3 ± 13.5	80.5 ± 12.1	80.8 ± 11.7	0.59
Total cholesterol, mmol/l	6.0 ± 1.1	6.1 ± 1.2	6.0 ± 1.2	0.78
LDL cholesterol, mmol/l	3.7 ± 1.0	3.9 ± 1.0	3.8 ± 1.0	0.37
Triglycerides, mmol/l	1.4 ± 0.7	1.4 ± 0.6	1.2 ± 0.5	0.26
HbA_{1c}, %	6.0 ± 0.8	5.9 ± 0.7	5.8 ± 0.3	0.05
Homocysteine, μmol/l	9.9 ± 7.6	8.8 ± 5.8	7.9 ± 4.0	0.05
Estradiol, pg/ml	16.5 ± 12.2	15.8 ± 9.3	15.6 ± 8.9	0.74
Apolipoprotein E ε4 carriers, %	21.5	23.0	21.6	0.94
Mental and physical characteristics				
Dementia, %	39.0	14.7	12.0	<0.001
MMSE score	23.4 ± 7.4	27.1 ± 3.9	27.2 ± 4.9	<0.001
IQCODE score	3.6 ± 0.8	3.3 ± 0.5	3.3 ± 0.6	<0.001
Depression score (GDS)	2.6 ± 2.0	2.3 ± 1.7	2.4 ± 2.0	0.32
Care dependency, %	23.3	8.2	12.0	<0.001
Barthel index	79.8 ± 28.9	89.7 ± 21.4	90.2 ± 20.5	<0.001
Bayer ADL scale	3.8 ± 3.6	2.2 ± 2.5	2.1 ± 2.7	<0.001

groups were examined using χ^2 tests on categorical variables and ANOVA on continuous variables. Correlations between test performance and proxy information were analyzed by calculating Pearson correlations.

The association between educational or occupational level and the presence of dementia was evaluated using binary logistic regression analysis, with the highest levels of education and occupation as the reference. Results are presented as unadjusted and age-adjusted odds ratios (OR) and 95% CI. Father's occupation type, APOE genotype, depression score, blood pressure, blood levels of cholesterol, HbA_{1c}, and homocysteine were tested for confounding effects. Since the inclusion of these variables did not influence the association between dementia and educational variables, the adjustment for confounders was restricted to the age of the sisters.

To examine whether the associations of education or occupation with dementia were dependent on nosological category, we performed subgroup analyses on sisters with AD and on sisters with other dementias, comparing them separately with non-demented participants. There is a possibility that the level of education has an influence on the diagnosis in the sense that a diagnosis of dementia is more likely in less educated than in better educated individuals. One would expect that such a bias particularly affects the diagnostic classification of subjects with borderline levels of cognitive impairment. To test whether the associations were robust against this type of diagnostic bias, additional sensitivity analyses were performed excluding CDR stages of questionable (CDR = 0.5) or mild dementia (CDR = 1) or both.

In order to exclude possible age cohort effects, we performed separate analyses for the age group over 85 years. In addition, we created a simple total index of the educational and occupational qualification from 0 to 3 points by dichotomizing the 3 indicators education, vocational training, and position of leadership, and in each case gave 1 point for intermediate or high educational level, for some vocational training, and for the position of leadership. No points were given if only an elementary school education had been achieved, no occupational training had occurred, and no position of leadership was attained. The association of this index with the presence of dementia was analyzed as well.

Results

Sample Description

Out of the 550 sisters, 33 were ineligible; 21 of these had died before contact was established, 5 were abroad, and 7 were undergoing inpatient treatment. Of the remaining 517 sisters, 442 (85.5%) were examined in per-

Table 2. Characteristics of the study participants (n = 442) according to severity of cognitive impairment (CDR)

	n and %	Age, years	MMSE[a]	B-ADL[b]	IQCODE[c]
No dementia (0)	300 (67.9)	74.9 ± 8.1	28.4 ± 1.5	1.1 ± 0.4	3.0 ± 0.1
Questionable (0.5)	38 (8.6)	83.0 ± 7.6	25.8 ± 2.0	2.5 ± 1.8	3.3 ± 0.4
Mild (1)	37 (8.4)	85.3 ± 7.2	22.3 ± 3.8	5.1 ± 2.0	4.0 ± 0.4
Moderate (2)	27 (6.1)	87.7 ± 5.2	15.8 ± 4.5	8.8 ± 1.3	4.9 ± 0.2
Severe (3)	40 (9.0)	88.4 ± 4.8	8.6 ± 5.8	9.8 ± 0.7	5.0 ± 0.0
Total	442 (100)	78.7 ± 9.2	25.7 ± 5.9	2.9 ± 3.2	3.4 ± 0.7

[a] Range from 0 to 30. Higher scores indicate better cognitive ability; missing data for 17 sisters.
[b] Range from 1 to 10. Higher scores indicate worse performance (1 = subject never has difficulties with everyday activities, 10 = subject always has difficulties with everyday activities).
[c] Range from 1 to 5. Scores >3 indicate cognitive decline (3 = not much change, 4 = a bit worse, 5 = much worse as compared with 10 years ago); missing data for 1 sister.

son, and 75 (14.5%) refused to participate. The 442 participants and the 108 non-participants did not significantly differ with respect to occupational attainment ($\chi^2 = 7.8$, d.f. = 4, p = 0.097).

The mean age of the participants was 78.7 years (SD 9.2 years, range 65–100 years), whilst the mean duration of membership in the Order was 54 years (range 33–81 years). The participants' fathers were farmers (53.8%), blue-collar workers (18.9%), employees or officials (14.3%), and craftsmen or other self-employed individuals (13.1%). Study participants had a higher level of education compared to the general German female population of the same age. The level of education in women older than 65 years was low in 81.5% of the cases, intermediate in 12.4%, and high in 6.1% according to German population data (www.gbe-bund.de). In contrast, the distribution of the respective educational levels was 38.9, 38.5, and 22.6% among study participants. With respect to occupation, 19.9% of the sisters had had no occupational training, 3.4% had been trained in skilled work, 22.9% were educators or nurses, 26.5% were teachers of needle work or home economics, and 27.4% were teachers or had graduated from other academic studies. In addition, 36.2% of the participants had been appointed to a leading position within the Order.

Table 1 represents the distribution of baseline characteristics in the sample according to the 3 educational groups. Sisters with lesser education were significantly older, had less often received occupational training, and had less often been in leading positions in the course of their lives than the better educated sisters. Body mass index, blood pressure, concentration of the blood lipids, estradiol level, and APOE ε4 carriership did not differ with respect to the level of education: only HbA_{1c} and homocysteine showed slightly significant differences. Furthermore, the sisters with lesser education had a significantly higher percentage of dementias, achieved poorer cognitive performance, had greater difficulty in dealing with everyday activities according to the assessment of informants, and showed the strongest cognitive decline.

Table 3. Age-specific prevalence of total dementia and Alzheimer disease

Age group years	Sample size, n	Total dementia n and %	AD n and %
65–69	120	2 (1.7)	1 (0.8)
70–74	65	1 (1.5)	1 (1.5)
75–79	47	6 (12.8)	3 (6.4)
80–84	83	25 (30.1)	7 (8.4)
85–89	75	39 (52.0)	27 (36.0)
90+	52	31 (59.6)	21 (40.4)
65+	442	104 (23.5)	60 (13.6)

Presence of Dementia

We identified 104 cases of dementia, of which 60 (57.6%) met the diagnostic criteria for AD and 21 (20.2%) for VD, whereas 23 (22.1%) remained unclassified. Age, cognitive performance, and informant-rated activities of daily living and cognitive decline are displayed according to severity of dementia (CDR rating) in table 2. Across CDR categories, there were highly significant differences on all variables ($p < 0.001$). The informant interviews (B-

Table 4. OR for total dementia according to educational and occupational variables

	Total n	Dementia n	Unadjusted OR and 95% CI	Age-adjusted OR and 95% CI
Age	442	104	1.20 (1.15–1.25)	–
Educational level				
Low	172	67	4.7 (2.4–9.2)	4.5 (2.0–9.8)
Intermediate	170	25	1.3 (0.6–2.6)	1.3 (0.5–3.0)
High	100	12	1.0 (reference)	1.0 (reference)
Occupational training				
No occupational training	88	47	8.8 (4.4–17.6)	9.1 (3.9–20.9)
Handicraft training	15	1	0.6 (0.1–4.5)	1.5 (0.2–13.7)
Educator, nurse	101	18	1.7 (0.8–3.5)	1.5 (0.6–3.7)
Teacher (home economics)	117	24	2.0 (1.0–4.0)	1.9 (0.8–4.4)
Teacher	121	14	1.0 (reference)	1.0 (reference)
Leading position				
No	282	84	3.0 (1.7–5.1)	3.7 (2.0–7.0)
Yes	160	20	1.0 (reference)	1.0 (reference)

Table 5. OR for dementia according to occupational training and appointment to a leading position in the subgroup of sisters with low education

Variable combination	Total n	Dementia n	Unadjusted OR and 95% CI	Age-adjusted OR and 95% CI
Low education/no leading position	147	63	3.9 (1.3–12.0)	9.6 (2.2–41.7)
Low education/leading position	25	4	1.0 (reference)	1.0 (reference)
Low education/no occupational training	85	45	3.3 (1.7–6.3)	4.4 (1.8–10.4)
Low education/any occupational training	87	22	1.0 (reference)	1.0 (reference)

ADL and IQCODE scores) showed close correlations to the MMSE scores of r = 0.88 and r = 0.86, respectively.

Age-specific prevalence rates for total dementia and AD are presented in table 3. Prevalence increased with age and amounted to 23.5% for all types of dementia in the present sample combined and to 13.6% for AD.

Associations of Education and Occupation with Dementia

Unadjusted and age-adjusted negative associations of educational level, occupational training, and appointment to a leading position within the Order with the presence of dementia were highly significant (table 4). A significantly higher presence of dementia was observed above all in participants with the lowest level of educational or occupational qualification. In contrast, sisters with intermediate levels of education and sisters who had received some type of vocational training did not differ significantly from the reference groups. These associations remained unchanged when APOE genotype, the father's occupational category, and the remaining potential confounders (depression score, blood pressure, blood levels of cholesterol, HbA_{1c}, and homocysteine) were included in the regression model. Furthermore, the pattern and magnitude of the associations between education, occupation, and presence of dementia remained basically unchanged when diagnostic subgroups (AD, other dementias) were analyzed, and when mild dementia (CDR = 1) or questionable dementia (CDR = 0.5) or both were excluded from the analysis.

Dementia clearly clustered in sisters with low education; 67 out of 172 (39.0%) sisters in this category were diagnosed with dementia, but only 37 of the remaining 270 sisters (13.7%) were demented. Within this group, however, the risk of disease was heterogeneous (table 5). Poorly educated sisters had a significantly increased risk

Table 6. OR for total dementia and AD according to a summary index for educational level, occupational training, and leading position

Summary index	Total n	Dementia n	AD n	Unadjusted OR for total dementia and 95% CI	Age-adjusted OR for total dementia and 95% CI	Age-adjusted OR for AD and 95% CI
0 points	84	44	23	8.2 (4.2–16.1)	9.3 (4.0–21.6)	11.5 (3.8–34.3)
1 point	67	22	17	3.6 (1.8–7.5)	4.4 (1.8–10.6)	7.6 (2.5–23.3)
2 points	156	22	12	1.2 (0.6–2.4)	1.3 (0.6–2.8)	1.5 (0.5–4.4)
3 points	135	16	8	1.0 (reference)	1.0 (reference)	1.0 (reference)

Index from 0–3 points; 1 point each for higher education than elementary, for any occupational training, and for appointment to a leading position.

of dementia if they had never been appointed a leading position (OR = 9.6; 95% CI: 2.2–41.7) or if they had not received any vocational training (OR = 4.4; 95% CI: 1.8–10.4). In contrast to this, for sisters with intermediate or high educational levels, dementia was not significantly more frequent if they had never occupied a position of leadership (OR = 1.5, 95% CI: 0.7–3.3). The association between dementia and occupation could not be studied in this subgroup due to the low number of sisters without occupational training.

According to the simple 4-stage summary index for education and occupation, 52.4% of the sisters with 0 points, 32.8% with 1 point, 14.1% with 2 points and 11.9% with 3 points suffered from dementia (table 6). Sisters on the lower 2 rungs of the index also had more cases of dementia than the reference group (highly significant). The associations were even closer for AD than for total dementia. In the comparison of the 2 groups with 2 and 3 points, there was no significant difference in the occurrence of dementia. Position of leadership or higher level of education did not additionally reduce the risk of dementia if the other 2 qualifications were fulfilled.

Most of the total of 104 dementias, namely 70 cases (67.3%), were diagnosed in the >85-year age group of the sisters. The mean age of the 127 sisters over 85 years was 89.8 years (SD = 3.4), and showed no difference between the education groups. Among the oldest old, 46 out of 57 sisters (80.7%) with low education suffered from a dementia, whereas, of the sisters with intermediate or high education, a dementia was found in only 24 of 70 (34.3%) cases (age-adjusted OR = 7.7; 95% CI: 3.8–17.7). Out of the 34 sisters without occupational training, 30 (88.2%) were afflicted by a dementia, compared with 40 out of 93 (43.0%) who had some form of occupational training (age-adjusted OR = 10.1; 95% CI: 3.2–31.2). Finally, out of the 88 sisters who had never had any leading position in their entire lives, 58 (65.9%) had contracted a dementia; out of the 39 sisters with leading positions, this figure was only 12 (30.8%; age-adjusted OR = 5.3; 95% CI: 2.2–12.7).

Compared to the reference group of the sisters over 85 who attained 3 points in the total index for education and occupation, the age-adjusted OR of a dementia amounted to OR = 20.5 (95% CI: 5.4–77.7) for 0 points, to OR = 13.8 (3.4–55.3) for 1 point and to OR = 1.9 (0.7–5.4) for 2 points. For AD, the age-adjusted odds ratio, after exclusion of the non-AD dementias, amounted among the oldest old to OR = 27.6 (95% CI: 6.0–126.4) for 0 points, to OR = 22.9 (95% CI: 4.8–109.6) for 1 point, and to OR = 2.0 (95% CI: 0.6–7.3) for 2 points.

Discussion

In this study of 442 members of a single religious order, who lived for more than 5 decades together under very similar external conditions, we found a strong and highly significant association of educational attainment, occupational training, and appointment of a leading position with the prevalence of dementia and AD in old age. The increased prevalence of dementia was mainly attributable to a subgroup of sisters who were poorly educated, had not received any vocational training, and were never appointed to a leading position within the Order. Whereas occupational training and appointment of a leading position were also closely associated with the occurrence of dementias at the lowest educational level, we found no significant relationship between dementia and education, occupational attainment, or leading position among the sisters with intermediate or high educational levels. Several alternative explanations must be considered, which may account for these findings.

It is unlikely that the association is due to a selection or an ascertainment bias [5, 26]. All members of the Order in the appropriate age group were identified at the beginning of the study, and 85.5% of the eligible sisters agreed to participate. According to information from the Order, there was no significant difference in participation rates in relation to occupational attainment. An overdiagnosis of mild dementia in poorly educated sisters relative to better educated participants is also improbable since the prevalence of dementia in the former group was still significantly increased when mild dementia or MCI or both were excluded from the analysis. Furthermore, the formal diagnoses were quite consistent with informant ratings.

Sisters with low education were significantly older than the better educated sisters. In order to exclude a confounding of the association between education and dementia through a birth cohort effect, which can arise through older participants having received less education than the younger ones, we performed separate analyses of the over 85 group [26]. In this age group, we found the same close and highly significant associations as in the total sample, although the oldest sisters with different educational and occupational qualifications did not differ from one another in age.

Life in the Order may be viewed as a natural experiment which affords uniquely homogeneous living conditions throughout adulthood. Study participants shared the same type of accommodation, had meals from the same kitchens, and had the same access to medical care for more than 5 decades on average. They also had the same daily routines, did not smoke, had negligible alcohol consumption, and no obviously different workplace hazards. Moreover, since they were under the vow of poverty they were not able to purchase any personal items. Notably, there were no strong differences across educational and occupational groups with regard to cardiovascular risk factors. Therefore, it appears improbable that the association between education and dementia which we found in the present sample is brought about mainly by an education-associated lifestyle or environmental factors in adult life. This result is in agreement with studies which were able to show that the association between education and dementia persists even after adjustment for differences in socioeconomical status, in lifestyle, and in other risk factors for dementia [10, 27].

An effect of education which is unaffected by methodological bias and independent of other risk factors for dementia is compatible with the hypothesis of a cognitive reserve capacity [7]. According to the reserve hypothesis, education represents an indicator of the resistance and compensation ability of the brain against neurodegenerative changes. Support for the reserve hypothesis comes from studies which show that the association between neuropathological changes and manifest dementia is modified by the level of education [28–31]. It remains unclear, however, whether education is the result of a greater innate reserve capacity or one which is acquired during brain maturation, or whether education per se and the lifelong intellectual stimulation which is associated with education and occupation contribute to the strengthening of the cognitive reserve.

There is empirical evidence for each of the 2 mutually non-exclusive explanations. Numerous studies found that cognitive activity is associated with a lower risk of dementia even in old age [32–34], and complex intellectually demanding work may have a protective effect [35, 36, 37]. On the other hand, a number of studies have demonstrated that developmental markers, including height [38, 39], limb length [40], and head circumference or total intracranial volume as measures of pre-morbid brain size, are related to cognitive impairment and dementia in late life [41]. In addition, associations have been found between cognitive ability in childhood [9] and linguistic performance in young adults and dementia [15, 18], which may be mediated through variability of brain development in early life [42]. These observations point to the possibility that poor education could reflect a lack of cognitive ability that is innate or acquired in early life [43–45]. Neurocognitive development and brain maturation in early childhood may be compromised by lack of mental stimulation, nutritional deficits, or toxic exposures. These disadvantages may limit an individual's access to higher school grades in youth and increase the susceptibility to neurodegeneration in old age.

Two observations from the present study appear to be more simply explained by the influence of such early factors than by the results of increased mental activity in school, work, and leisure time. First of all, if a protective effect were primarily to be ascribed to an increased intellectual activity, one would expect that a longer and more demanding educational and vocational training should result in lower rates of dementia. No such dose-response relationship was seen among sisters with higher levels of qualifications, however. Neither a better schooling, a more demanding occupational activity, nor the appointment of a leading position was associated with an additional protective effect for sisters with intermediate or high education. Secondly, one would expect that among the sisters with lower education, those who have better

cognitive abilities would be particularly likely to seek occupational training and be selected for a leading position. In fact, there were large differences in the subgroup with low education regarding the risk of dementia depending on further qualifications, whereas even sisters with low education did not suffer more frequently from dementia in comparison with better educated sisters, insofar as they had had occupational training and occupied a leading position.

Potential limitations of the present investigation need to be acknowledged. Prevalence of dementia was chosen as the dependent variable. A length bias due to shorter duration of disease in better educated sisters cannot be completely excluded [46]. A recent review of 22 studies, however, found no association between education and survival with dementia [47]. As a consequence of the highly selected study population, the external validity and generalizability of the findings is possibly limited. Unmeasured confounders such as psychological stress which might be distributed unequally across the different levels of educational or occupational attainment could affect associations [48]. The study is lacking in a measurement of the cognitive ability of the sisters at early age. For this reason, it is difficult to decide whether individual talent or whether other factors such as poverty and social background primarily determined their educational and occupational qualifications. Due to the strong interrelation between education, occupation, and appointment to a leading position, it was not possible to determine their specific effects simultaneously in multivariate analyses.

The study has also a number of strengths. The likelihood of a selection bias was minimized by complete enumeration of all sisters in the Bavarian province and by a high participation rate. The lifestyle and environment of the participants were highly homogeneous, which excludes the influence of many known and probably also of unknown confounders. The quality of data on education and occupation over the participants' life course was excellent, since it was extracted separately from archived staff files and not derived from self-reports with questionable validity. Furthermore, a diagnostic bias is probably negligible because expert diagnosis was highly consistent with proxy information. The reliability of the main results was confirmed by different additional analyses of subsamples and through consideration of many potential confounders.

The main conclusion that can be drawn from this study is that a low level of educational and occupational attainment in early life is strongly associated with dementia in old age, even in a sample with highly uniform living conditions over the entire adult life course. Our findings are compatible with the view that educational attainment and susceptibility for dementia in old age may both be influenced by yet unidentified early-life factors or that the higher lifelong cognitive activity of the better educated may protect against the consequences of brain diseases.

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