J Neurol (2016) 263:2229–2237
DOI 10.1007/s00415-016-8255-4

ORIGINAL COMMUNICATION

Educational achievements of children of parents with multiple sclerosis: A nationwide register-based cohort study

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Received: 18 June 2016 / Revised: 1 August 2016 / Accepted: 2 August 2016 / Published online: 19 August 2016

Abstract Little is known about the impact of parental multiple sclerosis (MS) on offspring's educational attainment. The objective of the study was to examine educational achievements in offspring of parents with MS compared with matched children of parents without MS in a nationwide register-based cohort study. Children of all Danish-born residents with onset between 1950 and 1986 were identified by linking the Danish Multiple Sclerosis Registry with the Civil Registration System. Twins, children with MS, and emigrated persons were excluded. The reference cohort consisted of randomly drawn individuals from the Civil Registration System without parental MS matched 8:1 to the MS offspring by sex and year of birth. Information about education was linked to the cohorts from nationwide educational registries. We included 4177 children of MS parents and 33,416 reference persons. Children of MS parents achieved statistically significant higher average grades than the reference cohort in their final exam of basic school with a mean grade difference of 0.46 (95 % CI 0.22–0.69; $p = 0.0002$). We found no difference in achievement of educational level above basic school (OR 1.04; 95 % CI 0.98–1.10; $p = 0.20$). There was a trend toward more MS offspring attaining health-related educations (OR 1.10; 95 % CI 1.00–1.21; $p = 0.06$). In conclusion, children of MS parents showed a small advantage in grade point average in final examinations in basic school, and they more often tended toward health-related educations. This study revealed no negative consequences of parental MS on grades and highest educational level achieved.

Keywords Cohort studies · Education · Epidemiology · Multiple sclerosis · Parental chronic illness · Risk factors

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Introduction

Multiple sclerosis (MS) is a neurological chronic disease in the central nervous system [1]. Clinical onset of MS averages 30 years with a female:male ratio of >2:1 [2, 3]. Physical and cognitive symptoms of MS, e.g. impaired mobility, fatigue, and deterioration of cognitive abilities, often affect the level of activity, work and social life, including partnership and children [4, 5].

Children of parents with MS have previously been reported to experience primarily negative psychosocial impact of parental MS, e.g., emotional distress, isolation, and stressful caregiving responsibilities [6–13]. However, some studies also reported positive impact of parental MS, e.g., stronger family bonds, higher maturity, and empathy [14, 15].

Previous studies favored qualitative methods or self-reports and focused on young children [8, 14]. Only two interview/questionnaire studies [16, 17] have examined adults who were caregivers as children to parents of various chronic illnesses. Thus, our study will be the first nationwide population-based register study to examine children of parents with MS.

Education is usually a prerequisite for employment and income which influences core opportunities in life, e.g., housing, neighborhood, and health care [18–20]. Therefore, education is important to examine when researching impact of parental MS on offspring [21, 22]. In addition, the outcome of obtaining a health-related education was included, because previous studies suggested that many had chosen caregiving jobs as adults [16, 17].

The objective of this population-based cohort study is to examine the impact of having a parent with MS on (1) grade achieved in basic school; (2) probability of education above basic school level; and (3) probability of health-related education.

Methods

Study design

We conducted a cohort study in which individuals with parental MS 'the MS offspring cohort' constituted the exposed cohort, and randomly chosen individuals from the background population without parental MS 'the reference cohort' constituted the unexposed cohort, matched by sex and year of birth to each of the MS offspring. Both cohorts were examined regarding educational outcomes in adolescence or in adulthood in nationwide Danish population-based registers.

Cohorts

All 7409 Danish-born residents with a confirmed MS diagnosis and clinical onset between 1950 and 1986 were retrieved from the nationwide Danish Multiple Sclerosis Registry [23]. Of them, 2879 were childless. The Danish Multiple Sclerosis Registry comprises cases with MS diagnoses classified as clinically definite by the registry's staff neurologists according to the current diagnostic criteria: Allison and Millar [24] until 1994, Poser [25] until 2004, and McDonald from 2005 [26, 27]. The offspring of persons with MS were identified through the Civil Registration System [28]. They should have only one parent with MS and should be born between 1955 and 1998. The Civil Registration System also provided the matched reference children of parents without MS. Both MS offspring and reference persons were excluded if they were twins, had MS themselves, or had emigrated. Only one child within sibships was included randomly in both cohorts to avoid clustering effect. Members of the reference cohort were selected by matching to the individuals of the MS offspring cohort by sex and year of birth. We sampled eight reference persons per MS offspring.

We stratified the age of MS offspring at the time of parental MS diagnosis into three age groups: 12 years or less (including persons for whom parental MS were diagnosed before their birth), 13–18 years, and $\geq$19. The children of parents without MS were used as reference groups within each of the age groups, continuing the match of one MS offspring person to eight reference persons. For the analyses of basic school grades and highest completed educational levels achieved, we included only MS offspring persons who were aged 12 years or less at the parent's MS diagnosis. For the analysis of health-related educations, we accepted a maximum age of 18 years at the time of the parent's MS diagnosis.

Data sources

The Danish Multiple Sclerosis Registry

The Danish Multiple Sclerosis Registry was established in 1956 and comprises all prevalent MS cases in 1948 and incident cases with onset after 1947 [23].

The Civil Registration System

The Civil Registration System contains all Danish residents, tracks their history of residency, and keeps identity of cohabitants, children, and parents [29]. It provides individual person identification to all residents. This number is life-long and is used by all public authorities and registers including educational systems.

The School Grade Register

The School Grade Register contains grade points in basic school in the 9th class which is the minimum required school level by Danish law. Subsequent education is optional. Students finish the 9th class when they are 15 years old. It was established in 2002, and we had access to the grades from 2002 to 2013. The School Grade Register uses the European Credit Transfer and

Accumulation System grading scale: −3, 0, 2, 4, 7, 10, and 12. The first two grades indicate failure. An officially appointed external examiner reviewed the student in written examinations and co-examined the student in verbal examinations. The outcome was calculated as the grade point average (GPA) per pupil.

The Population's Education Register

The Population's Education Register contains individual-level information on all educational achievements from preschool up to PhD level and was established in 1981. We had access to educational data from 1981 to 2013. The Population's Education Register has a high validity and coverage (96.4 % in 2008) [30]. We determined the highest completed educational levels of the cohorts and their parents both dichotomized in 'basic school level or above basic school level' and in four categories at follow-up in 2013. We defined the health-related educations as an attained degree in physiotherapy, occupational therapy, nursing, public health, psychology, and medicine. The health-related educational outcome was dichotomized in 'achieving an health-related education or not' at follow-up.

The number of individuals available in the analyses depended on the time frames of the registers concerned and on the MS offspring's age at the time of the parent's MS diagnosis.

Covariates

Parental age at childbirth

We hypothesized that the parental age at childbirth might be a confounder dependent on the parent's maturity and social circumstances when raising a child. The sex of the MS parent was matched with the reference parent within each matching group. The parents were not matched by age. The parental age at the birth of the included child was categorized: <20; 20–29; 30–39; ≥40.

Parental educational level

We categorized the parents' highest achieved educational levels into four categories: basic school; secondary school; vocational educational training, short or medium higher education, BA; and long higher education, PhD.

Statistical methods

The GPA was analyzed using an independent two-samples *t* test; and a general linear model (GLM) was used both unadjusted and adjusted for parental covariates.

Educational levels were analyzed with the Cochran–Armitage trend test when specified into four levels. Dichotomized levels of education (basic school alone versus higher education) and whether the MS offspring completed health-related educations were analyzed using an unadjusted and adjusted logistic regression with reported odds ratio (OR), 95 % confidence interval (CI), and *p* value. A sensitivity test was performed for children aged 30–58 years to analyze their probability of achieving above basic school level. We also used the study subjects' year of birth in a logistic regression to test for a possible calendar year effect on the children's probability of achieving above basic school. Finally, we stratified their year of birth into three categories: 1955–1964, 1965–1979, 1980–1998 for descriptive purposes.

Additional analyses compared the number of persons attaining an educational objective by stratifying by sex. Those analyses were calculated with a Chi-squared test. Death in the two cohorts was also analyzed using a Chi-squared test.

All statistical tests were performed using SAS software version 9.4.

Results

The study database comprised 37,593 persons in total. The MS offspring cohort amounted to 4177 children (Fig. 1), and the matched reference cohort amounted to 33,416 persons (Table 1). Before January 1, 2016, 157 (3.8 %) MS offspring died compared with 1248 (3.7 %) reference children which was non-significant ($\chi^2 = 0.006$; $df = 1$; $p = 0.94$). In 2013 at follow-up, the median age of the included persons was 44 years, and 88 % were between age 30 and 58.

Among the MS offspring, 2149 (51.5 %) were not yet born or were below age 13 at their parent's MS diagnosis. The proportion of females in the MS offspring cohort was 47.6 % ($n = 1987$). Among the parents with MS, the female:male ratio was 1.6:1 (Table 2). The mean age of the MS parent at birth of offspring was 27.9 years (SD 5.4). The educational levels of the MS parents and the reference parents were similar (Table 3). In a Cochran–Armitage trend test of the four categories of highest educational levels achieved by the parents of the cohorts, the MS parents attained similar educational levels as the reference parents ($p = 0.54$).

Grade achieved in basic school

We included 2672 persons (300 MS offspring and their matched 2372 reference persons) after exclusion of 28 who fell outside the time frame of the registers. They

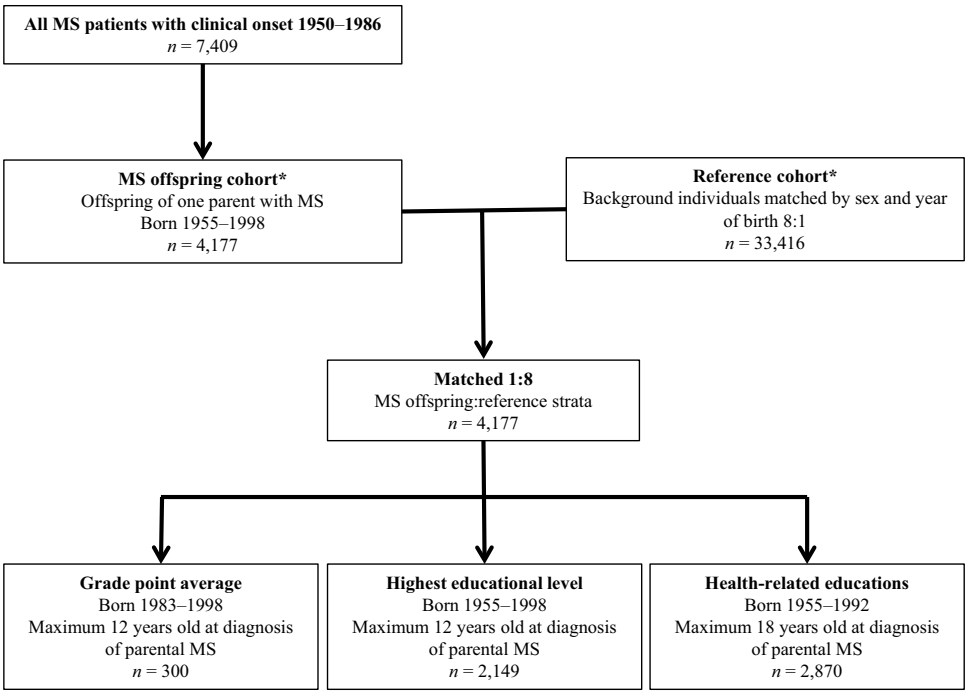

Fig. 1 Study subject disposition. *MS* multiple sclerosis. * indicates one child was randomly selected from each sibship. Twins, emigrated, and children with MS were excluded. One MS offspring child was matched randomly by sex and year of birth with eight reference children of parents without MS

Table 1 Age and sex distribution of MS offspring of a parent with MS ($n = 4177$) and matched reference persons of parents without MS ($n = 33,416$)

	MS offspring[a]	Reference cohort[a]
n	4177	33,416
Women, *n* (%)	1987 (47.6)	15,896 (47.6)
Year of birth, median (range)	1969 (1955–1998)	1969 (1955–1998)
Year of birth, *n* (%)		
1955–1963	1273 (30.5)	10,184 (30.5)
1964–1973	1535 (36.7)	12,280 (36.7)
1974–1983	878 (21.0)	7024 (21.0)
1984–1993	413 (9.9)	3304 (9.9)
1994–1998	78 (1.9)	624 (1.9)
Deceased 1970–2015, *n* (%)	157 (3.8)	1248 (3.7)
MS offspring's age at parent's MS diagnosis, *n* (%)		
Before birth to 12	2149 (51.5)	N/A
13–18	824 (19.7)	N/A
≥19	1204 (28.8)	N/A

MS multiple sclerosis, *N/A* not applicable

[a] One child was randomly selected from each sibship. Twins, emigrated, children with MS, and offspring of two parents with MS were excluded. Then, each MS offspring child was matched randomly by sex and year of birth with eight reference children of parents without MS

were born between 1983 and 1998 (median year of birth was 1990) and not more than 12 years old at the time of the parent's MS diagnosis. On average, MS offspring achieved 6.55 GPA (95 % CI 6.29–6.80) and reference persons 5.98 GPA (95 % CI 5.89–6.06) in their final examinations in basic school (Table 4). The grading difference of 0.57 was statistically significant (95 % CI 0.31–0.83; $p < 0.0001$). This difference was true for both MS offspring sexes: for MS offspring women versus reference women, the grading difference was 0.52 (95 % CI 0.16–0.88; $p = 0.005$), and for men, the difference was 0.61 (95 % CI 0.25–0.97; $p = 0.0008$). When we adjusted the GLM for the two covariates of parental age at childbirth and the parental educational level, the mean GPA continued to be significantly higher in the MS offspring persons than in the reference persons [estimate

Table 2 Age and sex distribution of MS parents and reference parents

	MS parents[a]	Reference parents[a]
n	4177	33,416
Women, *n* (%)	2581 (61.8)	20,648 (61.8)
Year of birth, median (range)	1942 (1908–1974)	1943 (1895–1970)
Age at childbirth, median (range)	27 (15–54)	26 (13–60)
Parental age at childbirth, *n* (%)		
<20	168 (4.0)	1901 (5.7)
20–29	2520 (60.4)	21,107 (63.1)
30–39	1371 (32.8)	9620 (28.8)
≥40	118 (2.8)	788 (2.4)

MS multiple sclerosis

[a] The sex of the MS parent determined which of the reference parents to include within each 1:8 matching group, only one parent for each child was included

Table 3 Distribution of educational levels of children and parents stratified into two and four categories

Educational level	Years of education	Children *n* (%)		Parents *n* (%)[a]	
		MS offspring	Reference cohort	MS parents	Reference parents
Two categories					
Basic school	9	850 (20.3)	7246 (21.7)	1756 (42.0)	13,773 (41.2)
Above basic school	12–20	3274 (78.4)	25,534 (76.4)	2314 (55.4)	17,258 (51.7)
Missing data		53 (1.3)	636 (1.9)	107 (2.6)	2385 (7.1)
Four categories					
Basic school	9	850 (20.3)	7246 (21.7)	1756 (42.0)	13,773 (41.2)
Secondary school	10–12	1866 (44.7)	14,584 (43.6)	1537 (36.8)	11,381 (34.1)
VET, short or medium higher education, BA	13–16	966 (23.1)	7740 (23.2)	649 (15.5)	4732 (14.2)
Long higher education, PhD	13–20	442 (10.6)	3210 (9.6)	128 (3.1)	1145 (3.4)
Missing data		53 (1.3)	636 (1.9)	107 (2.6)	2385 (7.1)

BA bachelor's degree, *MS* multiple sclerosis, *VET* vocational educational training, *PhD* doctor of philosophy

[a] The sex of the MS parent determined which sex of the reference parent to include within each 1:8 matching group, only one parent for each child was included

0.46; standard error (SE) 0.12; 95 % CI 0.22–0.69; $p = 0.0002$] (Table 4).

It made no significant difference for the MS offspring's GPA whether it was the father or the mother who had MS ($\chi^2 = 0.75$; $df = 1$; $p = 0.39$).

Probability of education above basic school level

We included 19,341 persons (2149 MS offspring and their matched 17,192 reference persons) after exclusion of 352 who fell outside the time frame of the registers. They were 15–58 years old at follow-up in 2013 (median year of birth 1972) and not yet born or maximum 12 years old at the time of parent's MS diagnosis. We found no difference in the proportions who achieved higher education than basic school: 77.4 % among the MS offspring and 76.8 % of the reference population (OR 1.03; 95 % CI 0.93–1.15; $p = 0.58$) neither when adjusted for the parent's age at birth of the included child nor the parent's educational level (OR 1.04; 95 % CI 0.98–1.10; $p = 0.20$) (Table 4). Analyzing the highest educational achievement categorized into four levels in a trend test revealed no significant difference ($p = 0.42$). A sensitivity analysis adjusted for the covariates and including children aged 30–58 at follow-up showed no difference regarding probability of educational level above basic school (OR 1.00; 95 % CI 0.94–1.06; $p = 0.99$).

To test for a possible calendar year effect, we adjusted for the cohort's year of birth as well as the former two covariates but found no significant effect on their probability of achieving above basic school (OR 1.01; 95 % CI 0.95–1.07; $p = 0.73$). For study persons born 1955–1964,

Table 4 Grade achieved in basic school, probability of educational level above basic school, and probability of health-related education comparing children of an MS parent with reference children of parents without MS

Grade achieved in basic school[a]								
	n	Mean	SD			95 % CI		*p* value
Reference cohort	2372	5.98	2.12			5.89–6.06		
MS offspring	300	6.55	2.26			6.29–6.80		
Difference		0.57	2.14			0.31–0.83		0.0001
	Unadjusted GLM				Adjusted GLM[b]			
	Estimate[c]	SE	95 % CI	*p* value	Estimate[c]	SE	95 % CI	*p* value[b]
Reference cohort	0.00				0.00			
MS offspring	0.57	0.13	0.31–0.83	0.0001	0.46	0.12	0.22–0.69	0.0002
Age at attainment of highest educational level aged 15–58 in 2013								
Reference cohort, median (range)				22 (13–56)				
MS offspring, median (range)				22 (13–55)				
Probability of education above basic school for cohorts aged 15–58 years in 2013								
	Unadjusted OR[d]		95 % CI	*p* value	Adjusted OR[d]		95 % CI	*p* value[b]
Reference cohort	1.00				1.00			
MS offspring	1.03		0.93–1.15	0.58	1.04		0.98–1.10	0.20
Health-related education attained for cohorts aged 21–58 years in 2013								
	Unadjusted OR[d]		95 % CI	*p* value	Adjusted OR[d]		95 % CI	*p* value[b]
Reference cohort	1.00				1.00			
MS offspring	1.21		1.00–1.45	0.05	1.10		1.00–1.21	0.06

CI confidence interval, *GLM* general linear model, *MS* multiple sclerosis, OR odds ratio, *SD* standard deviation, *SE* standard error

[a] Unadjusted independent two-samples *t* test

[b] Adjusted for parental age at childbirth and parental educational level

[c] Estimate denotes the difference between the cohorts' mean grade point average in 9th class in basic school

[d] Logistic regression

26.6 % of the MS offspring cohort and 26.2 % of the reference cohort achieved higher education than basic school. For the 1965–1979 and 1980–1998 birth cohort, the figures were 51.9 %/51.9 % and 21.5 %/21.9 %, respectively. The proportions for the 1980–1998 birth cohorts are low because of short follow-up.

Neither did we find a statistically significant difference regarding achieved educational level above basic school between the cohorts in the GPA subgroup of 300 MS offspring and the 2372 reference persons who had recorded grades in basic school (OR 0.98; 95 % CI 0.87–1.11; $p = 0.78$). The sex of the MS parent did not influence the probability of the MS offspring attaining above basic school level ($\chi^2 = 0.08$; $df = 1$; $p = 0.78$).

Probability of health-related education

We included 25,830 persons (2870 MS offspring; 22,960 reference persons) after exclusion of 480 who fell outside the time frame of the registers. They were 21–58 years old at follow-up in 2013, median year of birth was 1970, and they were maximum 18 years old at parent's MS diagnosis. MS offspring persons showed a trend toward completing health-related educations: 4.8 % (135/2695) compared with 4.0 % (897/21,623) reference persons ($\chi^2 = 3.99$; $df = 1$; $p = 0.05$). When adjusted for covariates of parental age at childbirth and parental educational level in a logistic regression, the MS offspring children still showed a trend toward attaining health-related educations (OR 1.10;

95 % CI 1.00–1.21; $p = 0.06$) (Table 4). The difference was solely attributed to women among whom 8.7 % (119/1248) of the MS offspring persons and 7.0 % (759/10,130) of the reference persons completed health-related educations ($\chi^2 = 5.50$; $df = 1$; $p = 0.02$). Among men, 1.1 % (16/1447) of the MS offspring persons and 1.2 % (138/11,493) of the reference persons completed health-related educations ($\chi^2 = 0.10$; $df = 1$; $p = 0.76$).

The sex of the MS parent had no significant influence on the MS offspring who attained health-related educations ($\chi^2 = 0.14$; $df = 1$; $p = 0.71$).

Discussion

In this population-based register study, we found that the children of parents with MS achieved a statistically significant higher GPA in basic school than the reference children, but the difference was small. A possible explanation of the difference could be that a parent with MS possibly spent more time at home with the children which may facilitate homework [17]. Some parents with MS encouraged the children to excel in school and aided them [17], and some children viewed school as a positive change from the responsibilities at home and were highly self-motivated to do well educationally [16].

Another study [31] reached the opposite result regarding GPA among 10–20-year-old children of parents with various chronic illnesses as those self-reporting children had a lower GPA than controls. We exclusively investigated children of MS parents, whereas their study also included a number of other chronic illnesses which might have other clinical manifestations than MS and thereby other living conditions and educational challenges. Another difference is that their study was based on self-reports, whereas ours is based on public records in nationwide registries. Also, their GPA self-reports span an age difference of 10 years, whereas our GPA is restricted to national final examinations in the 9th class exclusively, where the student is generally 15 years old.

Surprisingly, the higher GPA in MS offspring than in the reference cohort was not reflected in the final educational level. It could be argued that because the School Grade Register was not established until 2002, the GPA could only be calculated for 2672 persons. Hence, persons with a GPA are young with a median year of birth in 1990, and many of them have not yet attained their highest educational level in 2013.

We found no statistically significant difference between the highest achieved educational level between MS offspring and reference persons aged 15–58 years at follow-up in 2013. The result remained non-significant when categorizing the educational levels into four categories and also when testing for possible calendar year effect. The educational level of parents with and without MS was also similar in a trend test.

Interestingly, more children of parents with MS tended toward attaining health-related educations, and the difference resulted only from women. An explanation for the sex difference could be that daughters are often expected to be more caring and perform caregiving tasks to a potentially fatigued or disabled parent than sons, suggested by previous studies [7]. Years of performing caregiving tasks, helping, and supporting provided the women meaning and skills in this area, so they continued in this field educationally [16, 17].

A major strength of the study is that all data are population-based, using nationwide Danish registers where the population is thoroughly registered from fertility through socioeconomic life and unto death, linked individually by the unique personal identification number [23, 30]. The registers provide information independent of the subjects' responsiveness and memory. The Danish welfare state grants relatively equal access to free education and health care [32, 33]. Additional strength comprises the free access to education from basic school to university in Denmark, and the possibility for students to receive The Danish Students' Grants and Loans Scheme makes them independent of their parents' income to pay for education and basic living expenses [32]. This means that there is no direct economic confounding from the parent's income level. The only limitation regarding the free education is the level of admittance GPA, which many educations above secondary school employ as a sorting mechanism. The most expensive or coveted educations have the highest GPA required for admittance.

We stratified the MS offspring into three age groups dependent on their age at the time of parental disease diagnosis. We included children who were not yet born or who were maximum 12 years old at the time of the parent's MS diagnosis to allow time for the parental MS to exert potential influence on the child regarding grades achieved in basic school and achieving the highest educational level. In the analyses of probability of achieving health-related educations, we included children who were maximum 18 years old at parent's MS diagnosis, because a Dane is minimum 21 years old when attaining a medium higher health-related education. We included different age groups dependent on the outcomes and the registers available for the main analyses. The grades in basic school were calculated at age 15, and the highest educational levels achieved were calculated at ages 15–58 in 2013. Both cohorts attained their highest educational level at the same median age of 22 years, and their range was similar. The health-related education outcome had an age group of 21–58 years at follow-up in 2013, because 21 years is the

youngest age we expected a Dane to attain a medium higher education.

We have not adjusted for parental employment or income, since it is known that MS patients have lower employment rates and income in the course of their disease [34]. The childhood exposure to these socioeconomic consequences of parental MS cannot be distinguished from the effect of parental MS per se.

Potential effect modifiers are the clinical characteristics of the parental MS, e.g., relapse rate, type of MS course, and grade of disability, but these data were not available at specific years, since the MS Registry is primarily an epidemiological registry. In addition, a recent study found that the children's adjustment to parental MS was not correlated with the disability or the progression of MS but instead with the parent's coping and depression [9], although another study found that the children's adjustment was correlated with parental disability, MS progression as well as parental coping and depression [35].

By matching the MS offspring to the reference cohort by sex and year of birth, we have accounted for the most important confounders. We are aware that many other conditions and circumstances influence socioeconomic variables. We had no data on urban or rural residency at birth. This could theoretically be associated with both MS and employment, but this possible confounding may be reduced by our adjustment for parental educational level.

The external validity of the study is limited to countries with comparable educational and health care systems.

In conclusion, this study revealed no negative consequences of parental MS in terms of the offspring's grades in basic school and highest achieved educational level. On the contrary, the MS offspring showed a small advantage in grade point average in final examinations in basic school, and they more often tended toward attaining health-related educations.

Compliance with ethical standards

Ethics The personal identification numbers from the various registers were encrypted by Statistics Denmark where the datasets were stored, and we linked the datasets using the encrypted personal identification numbers. The study was approved by The Danish Data Protection Agency for research and statistical usage [reference numbers 30-1141 and 2008-54-0482]. Ethical committee approval was not necessary by Danish law, since the study was entirely register-based and non-interventional.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding This work was supported by The Danish Multiple Sclerosis Society [grant numbers A25533 and A27983] and The Karen A. Tolstrup Foundation [grant number 300.106–008].

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