Title

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Impact of parental multiple sclerosis on early childhood development: A retrospective cohort study

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Abstract

Background: Exposure to parental chronic illness is associated with several adverse developmental outcomes.

Objectives: We examined the association between parental multiple sclerosis (MS) and childhood developmental outcomes.

Methods: We conducted a population-based retrospective cohort study in Manitoba, Canada, using linked databases. The outcome was childhood development at 5 years of age, expressed as vulnerability (absent vs. present) on the Early Development Instrument (EDI). Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI).

Results: Children with an MS parent (n=153) were similar to children of unaffected parents (n=876) on all EDI domains. However, mental health morbidity was more common among MS parents compared with non-MS parents 49.5% vs. 35.3%. Among MS parents, mental health morbidity was associated with children's vulnerability on the social competence (OR, 5.73 [95% CI:1.11–29.58]) and emotional maturity (OR, 3.03 [95% CI:1.03–8.94]) domains. The duration of child's exposure to parental MS was associated with vulnerability on the physical health domain (OR, 1.49 [95%CI:1.03–2.15]).

Conclusion: Parental MS was not associated with adverse early childhood developmental outcomes. However, children of parents with mental health morbidity, and those with longer duration of exposure to parental MS, were at higher risk for early childhood developmental vulnerability.

Keywords: Child development, multiple sclerosis, developmental outcomes, parental chronic illness, child of impaired parents, population-based studies, administrative databases

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Introduction

In the Western world, approximately 10% of children and adolescents aged 18 years or under live in households where a parent has a chronic disease.[1,2] Early-life stressors such as parental chronic disease are associated with adverse developmental outcomes, including poor social and emotional functioning.[3,4] Most research in this area has focused on patients with cancer.[1] Information on other chronic illnesses and potential impacts on young children is lacking.

Multiple sclerosis (MS) is the most common non-traumatic cause of neurological disability among young adults in the Western world.[5] MS affects more women than men and typically manifests between the ages of 20 and 40 years when parenting is an important issue for many.[6] Therefore, many children are exposed to a parent coping with a potentially disabling chronic neurological condition. Owing to the broad array of potential health effects, including physical and cognitive disability, MS can cause considerable stress and anxiety to individuals and their families, and indirectly affect the developmental health of children.[7,8] Indeed, childhood anxiety is a common factor identified in the sparse literature on children of parents with MS.[9,10] The few cross-sectional studies published show that children with an MS parent are at risk of adjustment difficulties, particularly internalizing disorders and

behavioral disturbances, which are associated with later depressive disorders.[7,11]

The studies that have addressed the issue of psychosocial well-being of children with an MS parent have methodological limitations including cross-sectional design, lack of a comparison group,[12,13] self-reported data,[13] and failure to adjust for relevant confounding variables.[11] We, therefore, investigated the association between parental MS and childhood developmental health using a population-based cohort study.

Materials and methods

Study design

This was a retrospective matched cohort study in Manitoba, a province of 1.2 million people in the geographic centre of Canada. All data came from the Manitoba Population Health Research Data Repository.[14] Due to comprehensive universal health care coverage, virtually all contacts with the health care system are captured for 98% of the population.[14] All data files used in this study were anonymized, and linkage at the individual level was performed via the scrambled personal health identification number (PHIN) identifying the person who received the service.

The province-wide databases included: the Drug Programs Information Network (capturing outpatient prescription drug dispensations since 1996, including date, drug name, and drug identification number for all Manitoba residents); Physician Claims (including service date, and three-digit International Classification of Disease (ICD-9-CM) from 1 April 1984 to 31 March 2012); Hospital Discharge Abstracts (containing admission and discharge dates, and up to 16 discharge diagnoses, recorded as five-digit ICD-9-CM codes from 1 April 1984 to 31 March 2004, and from 1 April 2004 to 31 March 2012 using ICD-10-CA codes); and the Manitoba Health Insurance Registry (providing demographic information e.g. sex, age, dates of health coverage, and enabling identification of the family for all individuals registered in Manitoba). Two data sources were used to determine socioeconomic status (SES) of the child's family: the provincial Employment and Income Assistance data (identifying individuals requiring social assistance) and Census data (providing average household income in the area of residence). Finally, Early Development Instrument (EDI)[15] data, which provided information on early childhood developmental outcomes, were accessed through linkage with the Healthy Child Manitoba Office. The reliability and validity of these data sources have been well documented.[16–19]

Study cohorts

Using hospital and physician claims data from 1 April 1984 to 31 March 2012 along with prescription claims from 1 April 1996, we identified all Manitobans with MS using a case definition that was previously validated against medical records.[20] These were individuals with ≥3 records related to MS in any combination of hospital, physician, or prescription claims.[20] All persons with MS who had a child born between 1 January 1999 and 31 December 2006, with EDI data, were included in the study cohort. These birth dates allowed each child to have reached his/her fifth birthday between 2005 and 2011 and to be part of the EDI data collection. Individuals whose MS onset occurred after their child's EDI data collection, based on the date of the first health care claim for demyelinating disease (Appendix 1 – Supplementary Methods) were excluded from the study, as were individuals who had a partner who also had MS. Up to six children from the population who had EDI data were selected for each case, matched on sex, regional health authority and year of the EDI data collection, to form a comparison group. Where multiple children were eligible from the same family, one was randomly selected. Children of parents with diagnostic codes for demyelinating disease were excluded from the matched comparison cohort.

Outcomes and covariates

The primary outcome of interest was childhood development, as measured by the EDI. The EDI has routinely been administered biannually in all 37 public school divisions in Manitoba beginning in 2005/06. Teachers completed the EDI for each child in their kindergarten class, typically when children were five or close to turning 5 years, mid-way through the school year. The EDI was developed as an assessment of school readiness with the recognition that readiness should be understood as a holistic concept involving several developmental areas.[15] It consists of 104 binary and Likert-scale items designed to tap five core areas of early childhood development:[15,21] physical health and well-being; social competence; emotional maturity; language and cognitive development; and communication skills and general knowledge[15] (for more details on the EDI see Appendix 2 –Supplementary Methods). Children were considered vulnerable on a domain if their scores fell below the 10th percentile value[22] based on the national EDI

cut-off scores.[23] The EDI has been found to be a psychometrically reliable and valid tool for research.[15,24]

The main determinant of interest was the presence (vs. absence) of parental MS. SES was defined as the average household income in the child's residential area (using the EDI-derived postal codes) from the 2006 Canadian Census data, grouped into quintiles.[25] This was complemented by parental receipt of income assistance at any time from the child's birth to the EDI assessment. These categories (income quintiles and income assistance) were then collapsed to create three approximately equal-sized SES groups because of the relatively small study size: low (quintile 1 or income assistance recipients);[17] medium (quintiles 2 and 3); and high (quintiles 4 and 5).

As comorbidity is relatively common in MS,[26] our analyses included covariates for morbidity. We included comorbidities affecting ≥5% of the MS population. Parental mental health disorders (either depression or anxiety disorder[27]), diabetes, hypertension, hyperlipidemia, and chronic lung disease (e.g. asthma, bronchitis) were identified using validated algorithms, generated through hospital and physician claims and drug data.[28,29] Only parental morbidity occurring before the child's EDI assessment was considered. Other variables of interest included maternal age at time of birth, marital status, child's first language at home, age of the child at the time of EDI, and number of siblings.

Statistical analyses

Demographic and clinical characteristics of the parent–child family unit were compared between the children of MS parents and the children in the matched comparison cohort using paired *t*-tests, and the Wilcoxon signed rank test. Multivariable conditional logistic regression models were used to determine the association between parental MS and each domain of the EDI, adjusted for potential confounders. Confounders were included in the final models based on the literature[22,30] or statistical significance (p-value <0.10). The full model included the following covariates: maternal age at birth (per 5-year increase), age of the child at the time of EDI completion (years), number of siblings (1,2, ≥3 vs. 0), and parental mental morbidity (absent vs. present). As mental morbidity was the only health condition associated with the outcome or showing evidence of confounding, this was the only morbidity included in the final model. Further, to test whether the effect of MS on child developmental outcomes was modified by parental mental morbidity, we included an interaction term in the fully adjusted models.

Secondary analyses were also conducted within the MS cohort only, including assessment of the impact of parental mental comorbidity (presence vs. absence) and examining whether a 'dose-response' effect to MS existed by considering (i) the child's duration of exposure to parental MS in years (i.e. time from onset of MS or the child's birth, whichever was later, to the child's EDI assessment), and (ii) the duration of parental MS in years (i.e. time from onset of MS to the child's EDI assessment). Sensitivity analyses were also carried out with EDI considered as a continuous score in multiple linear regression models.

Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Regression model fit was assessed using the likelihood ratio test. A 2-sided $p<0.05$ was used to determine statistical significance. The University of Manitoba Health Research Ethics Board approved the study, and the Manitoba Health Information Privacy Committee approved data access. Analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

Results

Study cohorts

Of 17,009 individuals with any health claim(s) related to a demyelinating disease, 3116 individuals met the case definition of MS; of these 211 had a child with an available EDI assessment (Figure 1). This index cohort of MS parents and children was matched to a reference cohort of 1207 children and their parents who did not have MS. Children were excluded from these cohorts for the following reasons: MS onset occurred after the EDI assessment (n=27), no demographic or postal code information (n=3) and multiple eligible reference children (n=35). The final study population contained 153 children with an MS parent and 876 children and their parents in the matched comparison cohort.

Characteristics of the MS and matched comparison cohorts

The MS-affected and matched comparison cohorts were similar in terms of age at EDI collection (mean [SD] 5.7 [0.3] years), and marital status (Table 1). However, MS-affected parents were on average 3 years older at the time of the child's birth, more likely to be native English speakers, and had a higher SES than

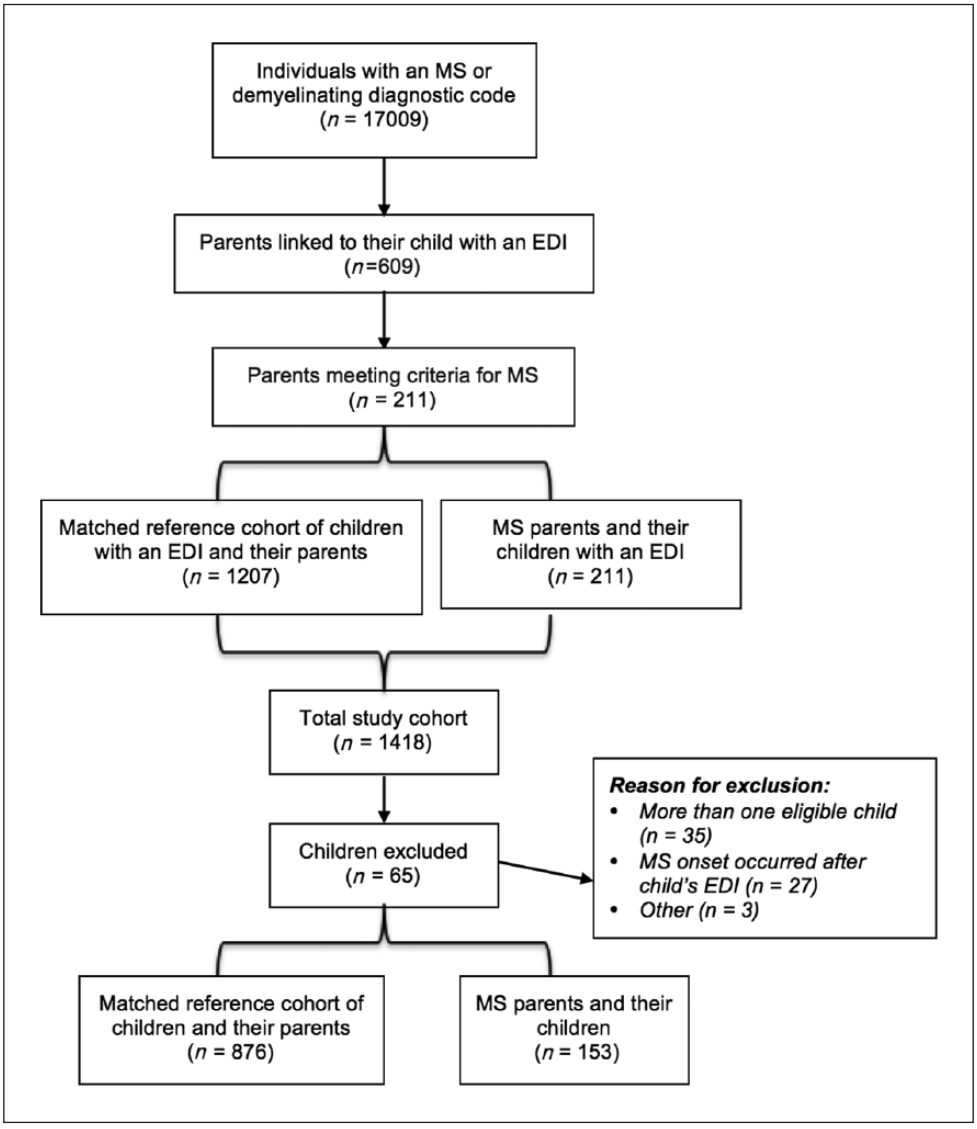

Figure 1. Schematic depiction of the process for identifying the study cohorts.

parents in the comparison group. The frequency of diabetes, hypertension and hyperlipidemia was similar between parents with MS and those in the matched comparison cohort, but MS parents were more likely to have a mental health comorbidity and chronic lung disease (Table 1). Differences in mental health morbidity were particularly striking (49.5% vs. 35.3% among MS parents and non-MS parents, respectively).

The clinical characteristics of the MS parents are shown in Table 2. The median age at MS onset was 29.4 years and 85% of MS parents were women. The median disease duration at the time of EDI completion was 6 years (range <1–25 years), and over half of the parents had received disease-modifying medication.

Developmental outcomes

In univariate analyses (Table 1), significant differences were noted in mean scores for language and cognition and communication and general knowledge, with children of MS parents receiving higher scores. However, there was no statistically significant difference regarding vulnerability on EDI domains between children in the index group and the matched comparison cohort. Findings from the multivariable conditional logistic regression analyses were similar (Table 3). Factors significantly associated with vulnerability in children of MS and non-MS parents across three or more domains included: presence of parental mental morbidity (vs. absence), low SES (vs. highest SES) and three or more

Table 1. Characteristics of multiple sclerosis (MS) affected child–parent units and the matched comparison group, Manitoba, Canada.

Characteristics	Parent with MS (n=153) no. (%)	Parent in matched comparison cohort (n=876) no. (%)	p-value
Child's age at EDI completion (years)			
Mean (SD)	5.7 (0.3)	5.7 (0.4)	0.98[a]
Maternal age at the time of birth			
Mean in years (SD)	31.3 (4.9)	28.3 (5.8)	<.001[a]
<25 years	16 (10.5)	267 (30.5)	<.001[b]
25–29	41 (26.8)	262 (29.9)	
30–34	61 (39.9)	242 (27.6)	
≥35	35 (22.9)	105 (12.0)	
Neighborhood income (SES)			
Highest SES	85 (55.6)	284 (32.4)	<.001[b]
Middle SES	42 (27.5)	253 (28.9)	
Lowest SES or income assistance	26 (17.0)	339 (38.7)	
Siblings			
None	20 (13.1)	145 (16.6)	0.03[b]
1 sibling	88 (57.5)	387 (44.2)	
2 siblings	30 (19.6)	213 (24.3)	
≥3 siblings	15 (9.8)	131 (15.0)	
Marital status			
Married	92 (60.1)	462 (52.7)	0.09[b]
Not married	61 (39.9)	414 (47.3)	
Child's first language			
English	137 (89.5)	700 (79.9)	0.01[b]
Other	16 (10.5)	176 (20.1)	
Parental mental health (depression and/or anxiety)			
Yes	76 (49.7)	309 (35.3)	<.001[b]
No	77 (50.3)	567 (64.7)	
Parental diabetes			
Yes	12 (7.8)	52 (5.9)	0.35[b]
No	141 (92.2)	824 (94.1)	
Parental hypertension			
Yes	33 (21.6)	159 (18.2)	0.29[b]
No	120 (78.4)	717 (81.9)	
Parental hyperlipidemia			
Yes	25 (16.3)	107 (12.2)	0.15[b]
No	128 (83.7)	769 (87.8)	
Parental chronic lung disease			
Yes	45 (29.4)	185 (21.1)	0.02[b]
No	108 (70.6)	691 (78.9)	
Child's EDI score			
Physical Health and Well-being			
Mean (SD)	8.7 (1.4)	8.7 (1.3)	0.88[c]
Vulnerable Yes	21 (13.7)	101 (11.5)	0.41[b]
No	132 (86.3)	775 (88.5)	
Social Competence			
Mean (SD)	8.5 (1.7)	8.2 (1.9)	0.07[c]
Vulnerable Yes	11 (7.2)	111 (12.7)	0.06[b]
No	142 (92.8)	765 (87.3)	

(Continued)

Table 1. (Continued)

Characteristics	Parent with MS (*n*=153) no. (%)	Parent in matched comparison cohort (*n*=876) no. (%)	*p*-value
Emotional Maturity			
Mean (SD)	7.9 (1.6)	7.8 (1.6)	0.41[c]
Vulnerable Yes	21 (13.7)	116 (13.4)	0.83[b]
No	132 (86.3)	760 (86.8)	
Language and Cognition			
Mean (SD)	8.6 (1.7)	8.1 (2.0)	<0.001[c]
Vulnerable Yes	12 (7.8)	102 (11.6)	0.16[b]
No	141 (92.2)	774 (88.4)	
Communication and General Knowledge			
Mean (SD)	8.1 (2.4)	7.4 (2.7)	0.003[c]
Vulnerable Yes	13 (8.5)	115 (13.1)	0.11[b]
No	140 (91.5)	761 (86.9)	

[a]Paired *t*-test.
[b]Conditional logistic regression.
[c]Wilcoxon Signed Rank Test.

siblings (vs. none). In the adjusted model, younger age of the child at completion of the EDI (years) was associated with vulnerability on the social competence domain. Maternal age at the time of birth was not associated with vulnerability on the EDI. Tests for multiplicative interaction between parental MS and mental morbidity were not statistically significant for any of the EDI domains (data not shown). Multiple linear regression analyses with EDI domains represented as continuous scores revealed similar associations between parental MS and EDI (data not shown).

Secondary analyses

Analyses within the MS cohort (*n*=153 children and 153 parents) showed that the duration of the child's exposure to parental MS was associated with vulnerability on the physical health and well-being domain of the EDI (aOR, 1.49, [95% CI, 1.03–2.15], *p*-value 0.03, Table 4). Although the duration of the child's exposure to parental MS was not significantly associated with the other four EDI domains, all these associations showed an increased risk of vulnerability with each additional year of exposure to parental MS. There was also no significant association between the parent's absolute disease duration and vulnerability on the EDI. However, children with an MS parent who also had a mental comorbidity were at a 3-fold greater odds of vulnerability on the emotional maturity domain compared with MS parents without a mental health condition (aOR 3.03, [95% CI, 1.03–8.94]) and a 5-fold greater odds of vulnerability on the social competence domain (aOR 5.73, [95% CI, 1.11–29.58]).

Discussion

Our population-based investigation of the association between parental MS and early childhood development at the kindergarten stage showed no statistically significant association between parental MS and a child's vulnerability on any developmental outcome, as measured by the EDI. However, there was a significant association between the duration of the child's exposure to parental MS and vulnerability on the physical health and well-being domain of the EDI. Although the relationships between parental MS and the remaining four EDI domains were not statistically significant, all associations showed an increased risk of vulnerability. In addition, the presence of mental health morbidity in the parent adversely influenced children's developmental health. Even though the effect of mental health morbidity on the EDI domains was no different among children of MS parents vs. the children of unaffected parents, the substantially higher rate of mental health morbidity among MS parents was striking 49.5% vs. 35.3%. Children whose parent had both MS and a mental health condition (vs. MS, but no mental health comorbidity) were at an increased

Table 2. Characteristics of the cohort with multiple sclerosis (MS).

Characteristics	MS parent no. (%)
Sex of the MS parent	
Male	23 (15.0)
Female	130 (85.0)
Ever on MS disease-modifying treatments	
Yes*	78 (51.0)
No	75 (49.0)
Age of parent at MS onset	
<20 years	10 (6.5)
20–29 years	73 (47.7)
30–39 years	65 (42.5)
≥40 years	5 (3.3)
Median [range]	29.4 [10.3–43.8]
Parental MS disease duration at the time of the EDI	
<3	37 (24.2)
3–<6 Years	35 (22.9)
6–<12 Years	44 (28.8)
≥12 Years	37 (24.2)
Median [range]	6.4 [<1.0–24.5]
Child's duration of exposure to MS parent at the time of the EDI	
<3 Years	37 (24.2)
3–<5 Years	26 (17.0)
≥5 Years	90 (58.8)
Median [range]	5.3 [<1.0–6.1]
Parental MS onset after child's birth	
Yes	90 (58.8)
No	63 (41.2)

*n=13 (16.7%) were exposed to glatiramer acetate and n=65 (83.3%) to a beta-interferon.

risk of vulnerability on emotional maturity and social competence domains of the EDI.

Our study findings highlight the complex nature of the relationship between parental MS and childhood developmental outcomes, and may help explain some of the discordant findings in the literature. Previous studies have shown that mother–daughter interactions during work and play tasks were perceived as similar, irrespective of whether the mother had MS.[31] Similarly, other studies have shown that children with an MS-affected parent did not appear to differ from the community norms for overall difficulties and externalizing problems.[6,9] However, these studies showed that parents with MS were more likely to report that their children had psychological problems.[6,9] Relying on parental perception, and other study limitations including the lack of an appropriate comparison group and failure to adjust for important confounders are other potential explanations for some of the contradictory findings with regard to parental MS and developmental outcomes in children.[13,32]

Our finding that a child's duration of exposure to parental MS was not associated with adverse developmental outcomes, except for the significant association with physical health and well-being, is not consistent with previous studies that have reported negative psychosocial behavior among children of MS parents.[33] Studies have reported a greater risk of depression, anxiety, somatization, difficulty in relating to others and greater emotional and behavioral problems in children of MS parents.[6,7,34–36] It is possible that children of MS parents have relatively normal developmental trajectories in early childhood, but that the stress of parental MS manifests with vulnerability on the physical health dimension first.[37] Our study was restricted to early childhood development and we cannot rule out effects in later childhood and adolescence.

Table 3. Adjusted and unadjusted odds ratios (95% confidence intervals) showing the effect of parental multiple sclerosis and other factors on vulnerability within the five Early Development Instrument (EDI) domains.

Factor	Unadjusted*			Adjusted †		
	OR (95% CI)		p-*value*	*OR (95% CI)*		p-*value*
Presence of parental multiple sclerosis (vs. absence)						
Physical Health and Well-being	1.24	(0.75–2.05)	0.41	1.59	(0.89–2.83)	0.12
Social Competence	0.53	(0.28–1.02)	0.06	0.51	(0.25–1.06)	0.06
Emotional Maturity	1.06	(0.63–1.76)	0.83	0.96	(0.55–1.67)	0.89
Language and Cognitive	0.64	(0.34–1.20)	0.16	0.91	(0.46–1.83)	0.80
Communication and General Knowledge	0.61	(0.34–1.12)	0.11	0.69	(0.37–1.31)	0.26
Parental mental morbidity (vs. absence of mental morbidity)						
Physical Health and Well-being	2.41	(1.57–3.69)	<.001	1.93	(1.22–3.06)	0.005
Social Competence	1.92	(1.25–2.95)	0.003	1.94	(1.21–3.11)	0.01
Emotional Maturity	1.94	(1.28–2.92)	0.002	1.74	(1.13–2.66)	0.01
Language and Cognitive	1.10	(0.70–1.72)	0.68	0.90	(0.54–1.47)	0.66
Communication and General Knowledge	0.68	(0.44–1.06)	0.09	0.60	(0.38–0.96)	0.03
Socioeconomic Status (SES)						
Lowest SES (vs. highest SES)						
Physical Health and Well-being	3.17	(1.94–5.20)	<.001	3.13	(1.73–5.69)	<.001
Social Competence	2.49	(1.54–4.02)	<.001	2.4	(1.37–4.20)	0.002
Emotional Maturity	1.38	(0.87–2.17)	0.17	1.35	(0.80–2.29)	0.26
Language and Cognitive	4.37	(2.58–7.42)	<.001	3.96	(2.18–7.20)	<.001
Communication and General Knowledge	1.67	(1.03–2.69)	0.04	1.68	(0.97–2.91)	0.06
Middle SES (vs. highest SES)						
Physical Health and Well-being	0.64	(0.34–1.19)	0.16	0.66	(0.35–1.24)	0.19
Social Competence	0.49	(0.25–0.95)	0.03	0.56	(0.29–1.10)	0.09
Emotional Maturity	0.64	(0.37–1.10)	0.10	0.67	(0.38–1.16)	0.15
Language and Cognitive	0.77	(0.40–1.49)	0.44	0.75	(0.39–1.47)	0.41
Communication and General Knowledge	0.82	(0.48–1.40)	0.46	0.73	(0.42–1.27)	0.27
Child's age at EDI completion (years)						
Physical Health and Well-being	0.63	(0.34–1.14)	0.12	0.70	(0.37–1.32)	0.27
Social Competence	0.48	(0.27–0.86)	0.01	0.51	(0.28–0.93)	0.03
Emotional Maturity	1.05	(0.59–1.86)	0.87	1.11	(0.62–2.00)	0.72
Language and Cognitive	0.44	(0.24–0.82)	0.001	0.53	(0.27–1.01)	0.05
Communication and General Knowledge	1.05	(0.60–1.85)	0.86	1.16	(0.64–2.08)	0.62
Maternal age††						
Physical Health and Well-being	0.97	(0.94–1.01)	0.13	1.01	(0.82–1.24)	0.95
Social Competence	0.98	(0.94–1.02)	0.28	1.10	(0.88–1.37)	0.41
Emotional Maturity	1.02	(0.98–1.06)	0.33	1.16	(0.95–1.42)	0.14
Language and Cognitive	0.96	(0.92–0.99)	0.03	1.00	(0.80–1.25)	0.98
Communication and General Knowledge	1.00	(0.97–1.04)	0.96	1.12	(0.91–1.38)	0.27
Siblings						
One Sibling (vs. none)						
Physical Health and Well-being	0.80	(0.43–1.48)	0.47	1.20	(0.61–2.37)	0.60
Social Competence	0.99	(0.54–1.83)	0.98	1.33	(0.69–2.55)	0.40
Emotional Maturity	0.83	(0.46–1.48)	0.53	0.90	(0.49–1.66)	0.73

Table 3. (Continued)

Factor	Unadjusted*			Adjusted †		
	OR (95% CI)		p-*value*	*OR (95% CI)*		p-*value*
Language and Cognitive	1.00	(0.53–1.91)	0.99	1.44	(0.71–2.94)	0.32
Communication and General Knowledge	1.33	(0.68–2.57)	0.40	1.50	(0.76–2.98)	0.25
Two Siblings (vs. none)						
Physical Health and Well-being	1.43	(0.73–2.77)	0.30	1.81	(0.89–3.70)	0.10
Social Competence	1.08	(0.55–2.11)	0.83	1.14	(0.55–2.35)	0.72
Emotional Maturity	0.84	(0.44–1.60)	0.60	0.91	(0.47–1.76)	0.77
Language and Cognitive	0.99	(0.48–2.06)	0.98	1.29	(0.59–2.84)	0.53
Communication and General Knowledge	1.56	(0.76–3.20)	0.23	1.77	(0.85–3.68)	0.13
Three or More Siblings (vs. none)						
Physical Health and Well-being	2.39	(1.18–4.86)	0.02	2.34	(1.10–4.96)	0.03
Social Competence	2.66	(1.29–5.48)	0.01	2.50	(1.15–5.45)	0.02
Emotional Maturity	1.75	(0.87–3.51)	0.12	1.64	(0.80–3.37)	0.18
Language and Cognitive	3.43	(1.64–7.17)	0.001	3.65	(1.63–8.15)	0.002
Communication and General Knowledge	4.17	(1.97–8.84)	<.001	4.16	(1.95–8.86)	<.001

*Unadjusted conditional logistic regression models; children in the index and reference groups were matched on child's sex, health authority, and year of EDI data collection.
†Adjusted conditional logistic regression models based on matching factors plus SES (low, middle vs. high), age at EDI (years), maternal age (per 5 years), parental mental health morbidity (vs. absence), and siblings (1,2,3 or more vs. none).
††Odds ratios express the change in EDI vulnerability per 5-year increase in maternal age.

The negative impact of parental mental health morbidity on childhood development observed in our study is consistent with findings from previous work demonstrating an association between depression in a parent with MS and poor social adjustment in children.[7,36] The broader literature on the impact of parental mental health on child health suggests that it is these co-occurring, daily problems and stressors, such as children's exposure to parental anxiety and depression, that are often the determinants of children's subsequent mental health.[3]

The strengths of our study included the ability to access comprehensive health and education-related databases at the population level, and the use of previously validated case definitions for both MS and other morbidities. Together, this allowed for a population-based cohort study, with an MS cohort matched to an appropriate comparison cohort. However, we were only able to identify morbidity among subjects who had contact with the health care system. Also, since it was difficult to distinguish between depression and anxiety disorders within our data sources,[27] the presence of either (or both) diagnoses was considered a 'mental health morbidity.'[27] We also lacked information regarding the severity of parental MS but used disease duration as a proxy of severity given the association of increasing disability with increasing disease duration. Other strengths of our study included the use of EDI to assess early childhood development, and the adjustment for potential confounders. The EDI has undergone significant psychometric testing to confirm validity and reliability as a research tool[15,18] and has been shown to be correlate to later literacy achievements[38] and psychological assessments.[39] Nonetheless, there may be some individual differences in teachers' ability to evaluate developmental outcomes on the EDI.[23] Last, although we attempted to control for a broad range of confounders, unmeasured and residual confounding may have occurred due to factors not available in our data sources or imprecise measurement of factors such as SES.

In summary, our study showed that the presence of parental MS was not independently associated with adverse developmental outcomes in kindergarten-level children. However, children whose parents also suffered from mental health morbidity and those who were exposed to parental MS for a longer period were at higher risk for developmental vulnerability. While other longitudinal studies are needed to

Table 4. Adjusted odds ratios (95% confidence intervals) showing the effect of parental disease characteristics on vulnerability in the five EDI domains, multiple sclerosis cohort (*n*=153 parents and *n*=153 children).

Factors	Adjusted		
	OR (95% CI)		p-*value*
Number of years the child was exposed to parental MS (years)[a]			
Physical Health and Well-being	1.49	(1.03–2.15)	0.03
Social Competence	1.22	(0.79–1.91)	0.37
Emotional Maturity	1.17	(0.87–1.57)	0.31
Language and Cognitive	1.25	(0.82–1.92)	0.31
Communication Skills and General Knowledge	1.13	(0.81–1.59)	0.48
Parental disease duration (years)[b]			
Physical Health and Well-being	1.05	(0.98–1.14)	0.17
Social Competence	0.98	(0.88–1.09)	0.69
Emotional Maturity	1.00	(0.92–1.08)	0.92
Language and Cognitive	1.01	(0.91–1.11)	0.88
Communication Skills and General Knowledge	1.00	(0.91–1.10)	0.99
Parental mental morbidity (vs. absence of mental morbidity) [c]			
Physical Health and Well-being	1.75	(0.60–5.09)	0.30
Social Competence	5.73	(1.11–29.58)	0.04
Emotional Maturity	3.03	(1.03–8.94)	0.04
Language and Cognitive	1.76	(0.49–6.30)	0.38
Communication Skills and General Knowledge	1.73	(0.50–5.98)	0.39

Logistic regression models adjusted for: child's sex (male vs. female), age of the child at EDI (years), and: **a.** parental mental health morbidity (vs. absence), SES (low, Middle vs. high), siblings (1,2,3 or more vs. none); **b**: parental mental health morbidity (vs. absence); **c.** child's exposure to parental MS (years), SES (lowest, Middle vs. high), siblings (1, 2, 3 or more vs. none).

confirm our findings, health professionals need to be aware of the effects of mental health morbidity commonly associated with MS, and their impact on childhood development. Mental illness such as anxiety and depression among MS parents should suggest the need for appropriate support for children (and their families) who are potentially at risk for adverse early developmental outcomes.

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Conflict of interest

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