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Family health conditions and parental occupational status modify the relationship between pediatric-onset multiple sclerosis and parental health-related quality of life

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Abstract

Background: The health-related quality of life (HRQoL) of children with multiple sclerosis (MS) is mediated by the HRQoL of their parents. Understanding factors that modify the relationship between the child's MS diagnosis and parental HRQoL would inform interventions to improve the HRQoL of both parents and children living with MS.

Objective: We evaluated whether the association between an MS diagnosis during childhood and parental HRQoL is modified by the presence of a family health condition or low socioeconomic position (SEP).

Methods: Parents of children with MS or the transient illness, monophasic-acquired demyelinating syndromes (monoADS), were enrolled in a prospective Canadian study. Multivariable models evaluated whether the association between a child's MS diagnosis (vs. monoADS) and parental HRQoL was modified by ⩾1 family health conditions or low SEP.

Results: Two hundred seven parents and their children with MS ($n=65$) or monoADS ($n=142$) were included. We found a synergistic effect of an MS diagnosis and a family health condition on parental HRQoL. We also found a synergistic effect of having MS and a low SEP on parental HRQoL.

Conclusion: Parents of children with MS who have another family health condition or a low SEP are at particularly high risk for low HRQoL.

Keywords: Pediatric, multiple sclerosis, demyelination, health-related quality of life, quality of life, caregiver, parent

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Introduction

Pediatric-onset multiple sclerosis (MS) is a potentially life-altering diagnosis for affected children and their parents. Parents of children with MS report lower health-related quality of life (HRQoL) when compared to parents of children with the transient illness, monophasic-acquired demyelinating syndromes (monoADS).[1] Poor parental HRQoL is associated with poor outcomes in children facing chronic diseases, such as poor HRQoL, treatment adherence, and health.[2–4] Previously, we found that parental HRQoL mediated the relationship between the child's MS diagnosis and the child's HRQoL.[5] Therefore, interventions to improve the HRQoL of parents of children with MS may benefit parents and their affected children. It is unknown whether any factors modify the relationship between the diagnosis of MS during childhood and parental HRQoL. Such information would inform interventions to improve parental HRQoL and potentially the HRQoL of affected children.

Few studies have evaluated the relationship between parental illness and socioeconomic position (SEP), and the HRQoL of caregivers to children facing chronic health conditions. SEP refers to the social and economic factors that influence which positions individuals hold within society,

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including employment and education.[6] Studies that have evaluated the relationship between parental illness and HRQoL in families facing other childhood diseases have reported conflicting results.[7–9] Moreover, studies of caregivers to children with other chronic diseases have found low SEP is associated with poor caregiver HRQoL.[9–11] It is unknown whether parents' prior experience facing chronic health conditions within their family or their SEP modify the relationship between the diagnosis of pediatric-onset MS and parental HRQoL.

We evaluated whether the association between an MS diagnosis during childhood and parental HRQoL is modified by the presence of a family health condition or low SEP. We hypothesized that the presence of familial health conditions or low SEP would have a greater than additive (i.e. synergistic) effect on the association between the child's MS diagnosis and parental HRQoL.

Methods

Source population

As part of a prospective cohort study, we enrolled children aged <16 years with MS or monoADS within 90 days of their first clinical signs (herein "symptom onset") at 23 Canadian sites between 2004 and 2013.[5,12] Inclusion criteria were modified when the study objectives were updated with a new phase of funding, allowing enrollment of children <18 years within 180 days of symptom onset at two enrollment centers between 2015 and 2018. Study visits occurred at enrollment, 3, 6, and 12 months after symptom onset, and annually thereafter.

Study population

As described previously, we enrolled parents or legal guardians (herein termed "parents") concurrently with participating children.[5] We compared parents of children with MS to parents of children with monoADS to ascertain the effect of the diagnosis MS on parental HRQoL. We excluded parents of children with neuromyelitis optica or relapsing demyelination (including those with clinical relapses with antibodies to myelin oligodendrocyte glycoprotein) who did not meet the diagnostic criteria for MS because we were interested in the effect of an MS diagnosis relative to a non-chronic condition (monoADS).

We obtained ethics approval at all sites and obtained informed consent or assent from participants.

Sociodemographic information

Parents reported the sex, birth date, and place of their child with MS or monoADS, and the number of children in the family during interviews with trained research coordinators at the time of study enrollment. Changes in the number of children in the family were queried during follow-up. As described previously, SEP was ascertained using the Barratt Simplified Measure of Social Status (BSMSS) Occupation Score at the first study visit occurring after it was introduced to the study protocol in 2015.[5,13] BSMSS Occupation Scores are based on the employed status and occupation of each parent. Scores range from 5 to 45, with higher scores indicating higher social status. We classified participants with a BSMSS Occupation Score in the lowest tertile as having a low SEP.

Clinical characteristics of children

Diagnoses of MS were conferred to children according to the McDonald 2017 criteria. MonoADS was defined by the absence of relapses or new lesions on serial brain MRI.[14–16] Relapses were defined as new neurological impairments persisting >24 hours in the absence of acute fever or illness and confirmed by clinical exam. Neurological findings were evaluated and recorded on case report forms by trained site investigators. For this analysis, participants were considered to have normal or mild neurological impairment (EDSS ⩽ 2.5) if they had normal gait, no encephalopathy, did not experience difficulties with bowel or bladder control, corrected visual acuity better than 20/30 bilaterally, had normal or minimal pyramidal dysfunction, and normal or mild decreases in sensory function in <3 limbs.

Health conditions

Children and their parents reported all diagnoses within the family at enrollment and provided updates at follow-up visits. Families were classified as having a health condition if they reported any of the conditions listed on a comorbidity scale among either parent, any sibling irrespective of cohabitation status or degree of relation (e.g. full, half, or step), or the child with MS or monoADS.[17,18] Children with MS or monoADS were considered to have a comorbidity if they reported any of the conditions listed on the comorbidity scale.

Health-related quality of life

Self-reported HRQoL of the child was ascertained using the PedsQL™ Inventory (Child Report) between 2010 and 2018 at all study visits >30 days

from symptom onset or relapses. Similarly, parental HRQoL was ascertained concurrently using the Family Impact Module (Appendix e1). We assessed HRQoL of one parent (mother or father) per participant, not necessarily the same parent evaluated at each assessment. Overall scores were calculated according to PedsQL™ scoring guidelines with higher scores indicating better HRQoL (100 best health and 0 worst health).

Analyses

We characterized the study population using median (interquartile range (IQR)) and frequency (percent) as appropriate. We compared the MS versus monoADS groups using χ^2, Wilcoxon, or Kruskal–Wallis tests. We performed bivariate analyses with respect to the HRQoL of the parent, accounting for clustering at the individual level using random effects specifications (Appendix e1).[19]

We constructed three multivariable regression models using random effects to evaluate whether familial health conditions or SEP modified the relationship between the child's MS diagnosis (vs. monoADS) and parental HRQoL. Using random effects specifications, we calculated the variance in parental HRQoL that is due to within-participant variation (time-variant factors that fluctuate between HRQoL assessments) separate from the variance in parental HRQoL due to between-participant variation (time-invariant factors that do not change within participants). For each multivariable model, the outcome of interest was parental HRQoL. Model 1 assessed the effect of an MS diagnosis and $\geqslant$1 family health condition(s). Model 2 assessed the effect of an MS diagnosis and $\geqslant$1 comorbidity among the child with MS or monoADS. Model 3 assessed the effect of an MS diagnosis and low SEP. For each model, we created a categorical variable with four levels combining the two dichotomous predictors of interest to ascertain the joint effect separate from the individual effects. For example, the categories for Model 1 were: MS and a family health condition, MS without a family health condition, monoADS with a family health condition, and monoADS without a family health condition (reference group).[20,21] We adjusted for the following time-invariant covariates: number of children in the family (count), sex of the child (male as reference group, binary), age of the child at symptom onset (years, continuous), length of stay in hospital for first attack (days, continuous), child's birth country (born outside Canada as reference group, binary). Number of children in the family was modeled as time-invariant because few changes were reported. We also adjusted for time-variant covariates: the child's age at the time of HRQoL assessment (years; continuous), the child's HRQoL (continuous), and the presence of functional neurological impairments (normal or mild impairments as reference group; binary). We adjusted for country of birth to account for the large proportion of internationally educated immigrants in Canada who report working in occupations for which they are over-qualified.[22] We also adjusted for low SEP (high SEP as the reference group, binary; Models 1 and 2), health conditions among the parents or siblings (no health conditions as the reference group, binary; Model 2), and family health conditions (no health conditions as the reference group, binary; Model 3) as time-invariant covariates. Tests for reverse causality between the parent and child's HRQoL were negative.[23] The joint effect of the predictors was categorized as synergistic when it was greater than the sum of the individual effects and statistically significant. We report R2 values to assess the proportion of variability in parental HRQoL explained by the independent variables.

Since our multivariable modeling methods excluded participants for whom covariates are missing or not applicable, we did not include variables unique to children with MS (e.g. relapses and exposure to disease-modifying therapies (DMTs)); these variables are reported to support generalizability of our findings.

Results

Children with MS or MonoADS

As detailed previously, between 2004 and 2018, 207 families (65 MS and 142 monoADS) met the inclusion criteria for analysis (Table 1).[5] Versus children with monoADS, children with MS were more likely to be female, older at symptom onset and first HRQoL assessment, to have shorter hospitalizations at initial attack, and be born outside of Canada (Table 1). Most children were unaffected by functional neurological impairments at the time of HRQoL assessment. Children with MS reported lower HRQoL than children with monoADS. During the period of HRQoL observation, 17% of participants with MS experienced relapses and 75% were treated with DMTs.

Parental HRQoL

Parents completed a median (IQR; min–max) of 4 (3–6; 1–8) HRQoL assessments 5.11 (3.09–7.24) years after the onset of their child's symptoms (Table 1). We observed minimal change in parental HRQoL

Table 1. Characteristics of the pediatric cohort.

Characteristic	monoADS ($n=142$)[1]	MS ($n=65$)[1]	p value
Characteristics of the child at symptom onset			
Female, *n* (%)	64 (45)	43 (66)	**0.005**
Age (years), median (IQR), min–max	8.67 (4.62–12.34), 0.46–15.89	14.49 (11.75–15.72), 1.90–17.86	**<0.001**
Length of stay for first attack (days), median (IQR)	7 (5–11)	3 (0–7)	**<0.001**
Born in Canada, *n* (%)	130 (92)	52 (80)	**0.02**
Characteristics of the child and family at First HRQoL assessment			
Child's age at questionnaire (years), median (IQR)	12.99 (8.86–16.34)	17.19 (14.85–19.52)	**<0.001**
Functional neurological impairments, median (IQR)	13 (9)	7 (11)	0.71
Disease duration (years), median (IQR)	4.15 (3.02–6.09)	3.13 (0.46–6.05)	**0.02**
Child with MS or monoADS and ⩾1 comorbidity, *n* (%)	25 (18)	14 (22)	0.56
Family with ⩾1 health condition, *n* (%)	76 (54)	43 (66)	0.09
Characteristics of the family at symptom onset			
Number of children in the family, median (IQR)	2 (2–3)	2 (2–3)	0.74
[2]Low socioeconomic position, *n* (%)	50 (35)	25 (38)	0.65
PedsQL™ HRQoL results			
Number of questionnaires per participant, median (IQR)	3 (2–4)	2 (2–4)	0.77
[3]HRQoL parent	89.58 (78.58–97.29)	78.13 (62.92–92.12)	**<0.001**
[3]HRQoL child	86.25 (77.17–92.66)	79.12 (65.22–89.86)	**<0.01**

P values <0.05 were considered statistically significant and are presented in bold text.
MS: multiple sclerosis; IQR: interquartile range; HRQoL: health-related quality of life.
[1]Of the 443 families enrolled, 207 had a child with the condition of interest and the remaining 236 participants were excluded because they were no longer being followed for the study when HRQoL assessments were introduced to the study protocol ($n=80$), they did not complete the HRQoL questionnaires ($n=75$), they did not complete the BSMSS ($n=27$), or they did not meet the diagnostic criteria for MS or monoADS ($n=54$). Children of families included in this analysis had a longer length of follow-up when compared to children of families who were excluded, but did not differ in terms of MS diagnosis, age at onset, or sex.
[2]Low SEP defined as a Barratt Simplified Measure of Social Status (BSMSS) Occupation Score in the lowest tertile.
[3]PedsQL™ Questionnaire scores are continuous from 0 (worst health) to 100 (best health).

(median (IQR) change of 10 (0–23) across observations. Parents of children with MS reported lower HRQoL than parents of children with monoADS (Table 1). Families of children with MS or monoADS did not differ regarding the number of family health conditions or SEP.

On bivariate analyses, having a child with MS, a health condition within the family, a child with a comorbidity plus MS or monoADS, a child with worse HRQoL, or a low SEP were associated with lower parental HRQoL (Tables 2 and 3).

The difference in median parental HRQoL between families who did or did not have a comorbid family health condition was much greater when the child had MS (17.29 points) than when the child had monoADS (5.41 points; Table 2). Similarly, the difference in parental HRQoL between families where the child did or did not have a comorbidity was greater when the child had MS (20.06 points) than when the child had monoADS (2.5 points). The difference in parental HRQoL between families with MS who had a low versus high SEP was 9.79 points compared to a difference of 4.47 points among monoADS families.

Multivariable analyses

We observed statistically significant positive associations between the child's HRQoL and parent's HRQoL in all three multivariable regression models.

The effect of having both MS and a family health condition on parental HRQoL (–10.90) was greater than would be expected by the sum of their individual effects ($p<0.001$; effect of having MS without a family health condition: –3.28 and effect of having a family health condition without MS: –5.37; Figure 1). We also found an adverse synergistic effect ($p<0.001$) on parental HRQoL of having a child with MS who also has a comorbidity (Figure 2). Finally, we found an adverse synergistic effect ($p<0.001$) on parental HRQoL of having a child with MS and a low SEP (Figure 3).

Discussion

We evaluated whether family health conditions or SEP modified the relationship between the diagnosis of MS during childhood and parental HRQoL in a large prospective cohort study with repeated

Table 2. Parental HRQoL by diagnosis, family health conditions, and SEP.

	MS ($n=65$)	monoADS ($n=142$)
Family health condition	71.25 (61.25, 86.88) 72.99 (16.71)	86.88 (77.26, 95.88) 84.04 (13.84)
No family health condition	88.54 (68.75, 95.63) 83.09 (15.62)	92.29 (85.63, 98.13) 88.54 (12.66)
Child comorbidity	65.36 (61.25, 71.88) 65.37 (12.49)	87.50 (72.68, 92.81) 80.49 (16.33)
No child comorbidity	85.42 (68.75, 92.92) 79.44 (16.81)	90.00 (80.63, 97.92) 87.34 (12.50)
[1]Low SEP	72.50 (62.92, 86.88) 73.42 (16.66)	86.25 (71.88, 96.25) 82.61 (14.91)
[2]High SEP	82.29 (63.49, 92.71) 78.28 (17.03)	90.72 (82.19, 97.50) 88.05 (12.24)

MS: multiple sclerosis; SEP: socioeconomic position.
[1]Low SEP defined as a Barratt Simplified Measure of Social Status (BSMSS) Occupation Score in the lowest tertile.
[2]High SEP defined as a Barratt Simplified Measure of Social Status (BSMSS) Occupation Score in the highest two tertiles.

Table 3. Bivariate analyses of associations between the parent's HRQoL and covariates.

Predictor	Beta coefficient (95% CI)	Test statistic	*p* value
Time-invariant predictors			
MS diagnosis	–9.30 (–13.54, –5.06)	–4.30	**<0.001**
Health condition in the family	–6.90 (–10.95, –2.85)	–3.34	**0.001**
Health condition parent	–2.85 (–6.99, 1.29)	–1.35	0.18
Child with comorbidity	–9.58 (–14.68, –4.47)	–3.68	**<0.001**
Sibling with health condition	–8.78 (–15.15, –2.42)	–2.70	**<0.01**
Low [1]socioeconomic position	–5.24 (–9.50, –0.99)	–2.42	**0.02**
Child female sex	–3.40 (–7.49, 0.69)	–1.63	0.10
Child's age at symptom onset	–0.19 (–0.64, 0.25)	–0.86	0.39
Length of stay for first attack	0.10 (–0.11, 0.31)	0.94	0.35
Child born in Canada	1.57 (–4.64, 7.77)	0.49	0.62
Number of children in the family	0.84 (–1.06, 2.73)	0.86	0.39
Child's HRQoL	0.44 (0.35, 0.53)	9.57	**<0.001**
Child's age at HRQoL questionnaire	–0.02 (–0.38, 0.33)	–0.12	0.91
Functional neurological impairments	–4.42 (–9.29, 0.44)	–1.78	0.08

P values <0.05 were considered statistically significant and are presented in bold text.
CI: confidence interval; MS: multiple sclerosis.
[1]Low SEP defined as a Barratt Simplified Measure of Social Status (BSMSS) Occupation Score in the lowest tertile.

HRQoL observations and long-term follow-up. We found synergistic effects between the MS diagnosis and the presence of family health conditions or low SEP on parental HRQoL, such that parents who had a child with MS and either of these additional risk factors were at particularly high risk for low HRQoL. Families of children with MS versus monoADS did not differ in number of health conditions or SEP, but they did differ in terms of the effects of these factors.

We could not identify prior studies examining whether family health conditions modified the association between parenting a child with chronic disease and parental HRQoL. Prior studies did, however, evaluate the basic relationship between parental health conditions and parental HRQoL. These studies yielded conflicting results, possibly due to differences in caregiving burden. A cross-sectional study of 543 parents of chronically ill children from 10 different diagnosis groups found that parental chronic illness was associated with worse parental HRQoL.[7] A study of 170 caregivers to children with a range of disabilities found that caregiver illness was associated with higher mental, but lower physical HRQoL.[9] However, another study of parents of children with metabolic

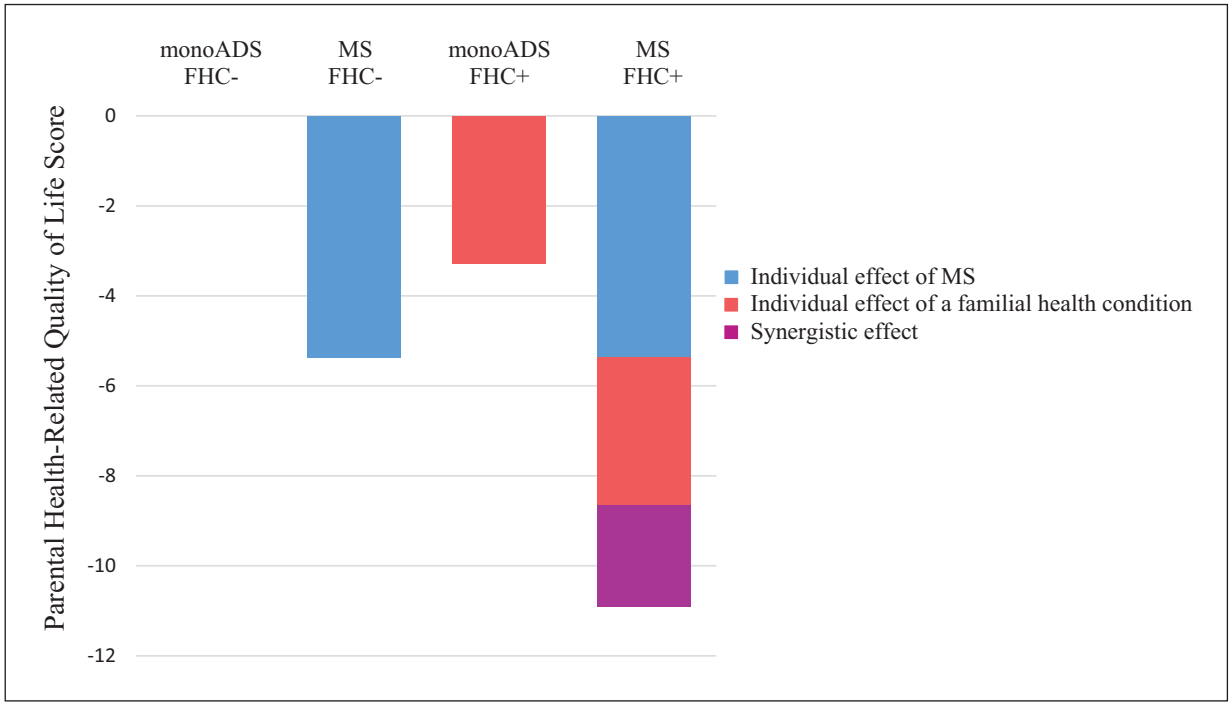

Figure 1. Individual and combined effects of MS and a familial health condition on parental health-related quality of life (HRQoL).
MS: multiple sclerosis; FHC: familial health condition; monoADS FHC–: participants with monoADS without a familial health condition; MS FHC–: participants with MS without a familial health condition; monoADS FHC+: participants with monoADS with a familial health condition; MS FHC+: participants with MS and a familial health condition.
The individual effect of having MS on parental HRQoL (MS FHC–) was –5.37; the individual effect of having a familial health condition on parental HRQoL (monoADS FHC+) was –3.28; and the effect of having both MS and a familial health condition on parental HRQoL (MS FHC+) was –10.90. We concluded that the effect of having MS and a familial health condition on parental HRQoL was synergistic because the combined effect (–10.90) was greater than the sum of the individual effects (–3.28 + –5.37 = –8.65).
R^2 within = 0.03; R^2 between = 0.40; R^2 overall = 0.25.

disorders found no association between parental chronic illness and parental HRQoL.[8]

We could not identify prior studies examining whether low SEP modified the association between parenting a child with chronic disease and parental HRQoL. Prior studies consistently reported associations between low SEP and lower HRQoL among caregivers to children with other chronic diseases; these studies did not evaluate synergy.[9–11] The child's MS diagnosis affected parental HRQoL differently for families with low versus high SEP although all participants had access to Canada's universal health care. Low SEP is recognized to be associated with poor health outcomes among children and adults who have access to universal health care.[24,25] A greater effect of low SEP on parental HRQoL might be observed in countries with smaller social safety nets.

We can speculate as to why we observed synergistic effects of family health conditions or SEP. A qualitative study of the experiences of parents of children with MS found that a primary concern among parents was their worry for how to care for their child in the future; parents with health conditions may have greater concerns about their child's future.[26] Parents with less education and lower occupational statuses perceived the HRQoL of their children with complex chronic conditions to be worse than parents with higher occupational statuses.[27] Parents with less education or lower occupational levels may have lower expectations for their children's outcomes. A study of caregivers from the Canadian General Social Survey found that participants with greater caregiving responsibilities were more likely to report feelings of loneliness and social isolation, although this appeared to be mitigated by greater income.[28] Similarly, a study of parents of chronically ill children who reported low levels of social support and worse HRQoL had lower education and were chronically ill themselves.[7] Individuals with lower SEP may have less ability to navigate the health care system or worse health literacy, which is associated with worse HRQoL.[29]

There are known strategies to mitigate the effects of low SEP on health outcomes. Parents of children

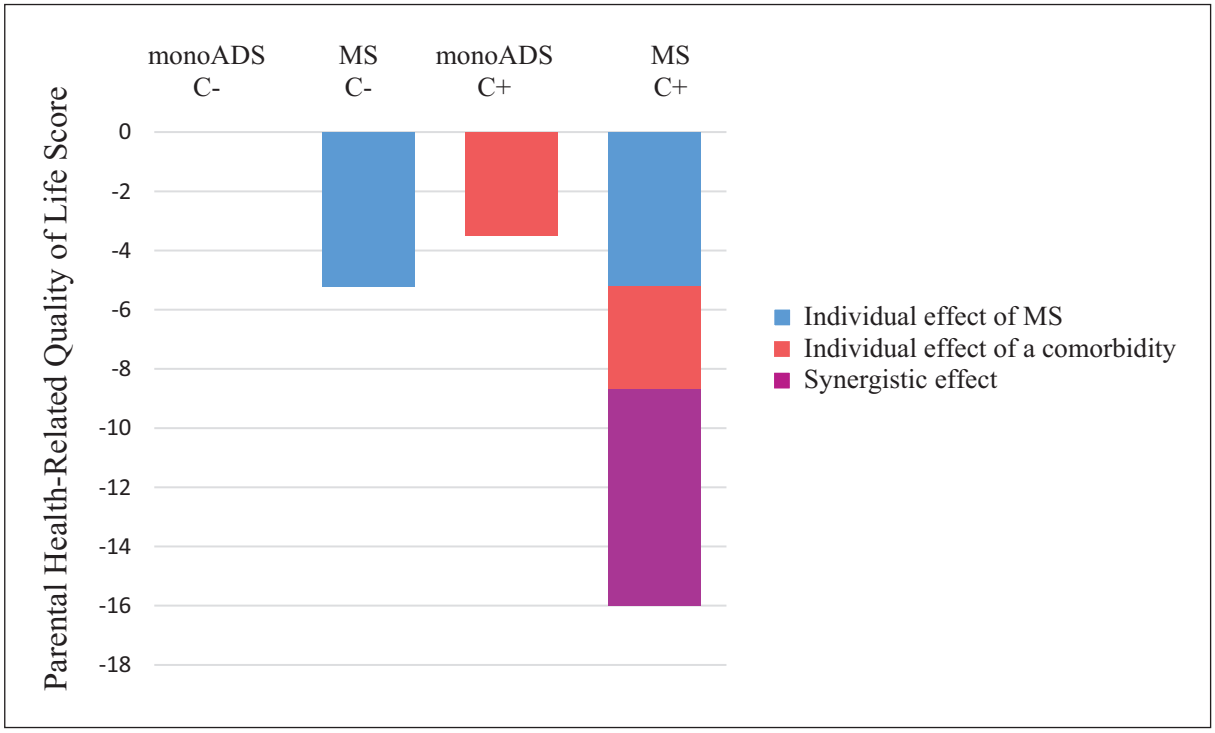

Figure 2. Individual and combined effects of MS and a comorbidity on parental health-related quality of life (HRQoL).
MS: multiple sclerosis; C: child's comorbidity; monoADS C-: participants with monoADS without a comorbidity; MS + C–: participants with MS without a comorbidity; monoADS C+: participants with monoADS with a comorbidity; MS + C+: participants with MS and a comorbidity.
The individual effect of having MS on parental HRQoL (MS + C–) was –5.21; the individual effect of having a child with MS or monoADS and a comorbidity on parental HRQoL (monoADS C+) was –3.49; and the effect of having both MS and a child with MS or monoADS and a comorbidity on parental HRQoL (MS + C+) was –16.02. We concluded that the effect of having MS and a child with MS or monoADS who has a comorbidity on parental HRQoL was synergistic because the combined effect (–16.02) was greater than the sum of the individual effects (–5.21 + –3.49 = –8.70).
R^2 within = 0.03; R^2 between = 0.41; R^2 overall = 0.27.

with MS have previously reported the importance of financial subsidies for medications available through the American National MS Society. Making parents aware of such resources may help to mitigate the effect of low SEP on their HRQoL. Social prescribing programs that address income security, legal needs, health literacy, social isolation, employment, housing, transportation, and food security have been shown to improve well-being, health outcomes, and are cost-effective.[30]

We previously found that parental HRQoL mediates the effect of the child's MS diagnosis on the child's HRQoL. Together with our present findings, this suggests that bidirectional relationships between HRQoL of children with MS and their parents. To our knowledge, no psychosocial care guidelines exist for improving the HRQoL of children with MS and no studies have evaluated psychosocial interventions for children with MS or their parents. Prior studies of psychosocial interventions involving children with other chronic disorders and their parents found improvements in the HRQoL of both children and parents.[31] Future studies targeted at improving the HRQoL of parents of children with MS or affected children should involve parents and children together.

Given the role of parental HRQoL in mediating the effect of the child's MS diagnosis on the affected child's HRQoL, pediatric care providers may need to focus more on optimizing parental HRQoL.[5] Among women with a health condition attending pediatric primary care clinics for their child, most indicated that they would welcome screening and referrals for their own health by pediatric providers.[32] Pediatric care providers have identified their own time, inadequate training, and legislation as current barriers to addressing parental health.[33]

Our findings should be considered in the context of study limitations. This was not a population-based study, so that, our findings may not be generalizable to all families of children with MS. We did not account for the type, severity, or number of pre-existing familial health conditions, and this might have affected the magnitude of the association

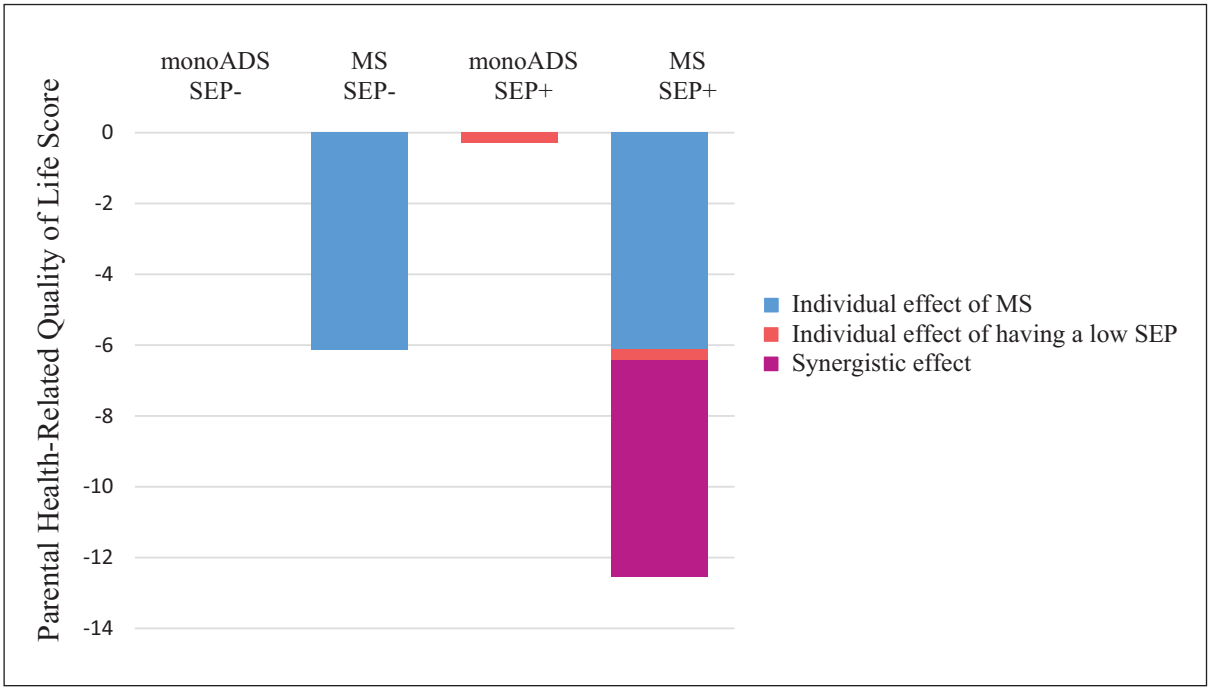

Figure 3. Individual and combined effects of MS and a low socioeconomic position (SEP) on parental health-related quality of life (HRQoL).
MS: multiple sclerosis; SEP: socioeconomic position; monoADS SEP–: participants with monoADS and a high SEP; MS + SEP–: participants with MS and a high SEP; monoADS SEP+: participants with monoADS and a low SEP; MS + SEP+: participants with MS and a low SEP.
The individual effect of having MS on parental HRQoL (MS + SEP–) was –6.13; the individual effect of having a child with MS or monoADS and a comorbidity on parental HRQoL (monoADS SEP+) was –0.29; and the effect of having both MS and a child with MS or monoADS and a comorbidity on parental HRQoL (MS + SEP+) was –12.54. We concluded that the effect of having MS and a low SEP on parental HRQoL was synergistic because the combined effect (–12.54) was greater than the sum of the individual effects (–6.13 + –0.29 = –6.42).
R^2 within = 0.04; R^2 between = 0.40; R^2 overall = 0.26.

observed. By treating all health conditions as equal, we may have underestimated the effect of specific health conditions on the relationship between the diagnosis of MS and parental HRQoL. We do not know whether the same parent responded to the HRQoL questionnaires over time; however, we observed minimal change in parental HRQoL over time. Although participants with monoADS included in this analysis were followed for a median (IQR) of 7 (5–9) years after symptom onset, it is possible that some participants categorized as having monoADS might later be diagnosed with MS; this would bias our results toward the null. By querying SEP at a single study visit, we may have misclassified participants whose SEP changed over time; however, SEP scores for this analysis are likely to remain static because they were assigned based on vocation rather than income. We adjusted for country of birth of participants to account for misclassification of SEP among internationally educated immigrants in Canada who work in occupations for which they are over-qualified;[22] however, this adjustment might not fully account for potential misclassification.

In families of pediatric-onset MS patients, lower SEP and the presence of other health conditions within the family further aggravate the already negative impact on parental HRQoL. As we consider optimal health management for children and youth living with MS, we must remember that MS lives within a family, and that caring for our pediatric MS patients requires supporting the entire family unit.

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Declaration of Conflicting Interests

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Supplemental Material

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References

1. O'Mahony J, Marrie RA, Laporte A, et al. Pediatric-onset multiple sclerosis is associated with reduced parental health-related quality of life and family functioning. *Mult Scler* 2019; 25(12): 1661–1672.
2. Defenderfer EK, Rybak TM, Davies WH, et al. Predicting parent health-related quality of life: Evaluating conceptual models. *Qual Life Res* 2017; 26(6): 1405–1415.
3. Drotar D and Bonner MS. Influences on adherence to pediatric asthma treatment: A review of correlates and predictors. *J Dev Behav Pediatr* 2009; 30(6): 574–582.
4. Dobbels F, Decorte A, Roskams A, et al. Health-related quality of life, treatment adherence, symptom experience and depression in adolescent renal transplant patients. *Pediatr Transplant* 2010; 14(2): 216–223.
5. O'Mahony J, Banwell B, Laporte A, et al. The health-related quality of life of children with multiple sclerosis is mediated by the health-related quality of life of their parents. *Mult Scler* 2022; 28(8): 1299–1310.
6. Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health* 2006; 60(1): 7–12.
7. Hatzmann J, Maurice-Stam H, Heymans HS, et al. A predictive model of health related quality of life of parents of chronically ill children: The importance of care-dependency of their child and their support system. *Health Qual Life Outcomes* 2009; 7: 72.
8. Hatzmann J, Valstar MJ, Bosch AM, et al. Predicting health-related quality of life of parents of children with inherited metabolic diseases. *Acta Paediatr* 2009; 98(7): 1205–1210.
9. Xia C, Sun M, Li X, et al. Health-related quality of life and related factors among primary caregivers of children with disabilities in Shanghai, China: A cross-sectional study. *Int J Environ Res Public Health* 2020; 17(24): 9299.
10. Ten Hoopen LW, de Nijs PFA, Duvekot J, et al. Caring for children with an autism spectrum disorder: Factors associating with health- and care-related quality of life of the caregivers. *J Autism Dev Disord* 2022; 52(11): 4665–4678.
11. Etemad K, Heidari A, Setoodeh A, et al. Health-related quality of life of parents of children with

phenylketonuria in Tehran Province, Islamic Republic of Iran. *East Mediterr Health J* 2020; 26(3): 331–339.

12. Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: A prospective national cohort study. *Lancet Neurol* 2011; 10(5): 436–445.
13. Barratt W. The Barratt simplified measure of social status (BSMSS), 2012, http://socialclassoncampus.blogspot.com/2012/06/barratt-simplified-measure-of-social.html
14. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: Revisions to the 2007 definitions. *Mult Scler* 2013; 19(10): 1261–1267.
15. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17(2): 162–173.
16. Fadda G, Brown RA, Longoni G, et al. MRI and laboratory features and the performance of international criteria in the diagnosis of multiple sclerosis in children and adolescents: A prospective cohort study. *Lancet Child Adolesc Health* 2018; 2(3): 191–204.
17. Sangha O, Stucki G, Liang MH, et al. The Self-Administered Comorbidity Questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis Rheum* 2003; 49(2): 156–163.
18. Horton M, Rudick RA, Hara-Cleaver C, et al. Validation of a self-report comorbidity questionnaire for multiple sclerosis. *Neuroepidemiology* 2010; 35(2): 83–90.
19. Burton P, Gurrin L and Sly P. Extending the simple linear regression model to account for correlated responses: An introduction to generalized estimating equations and multi-level mixed modelling. *Stat Med* 1998; 17(11): 1261–1291.
20. Knol MJ, van der Tweel I, Grobbee DE, et al. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *Int J Epidemiol* 2007; 36(5): 1111–1118.
21. Richardson DB and Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. *Am J Epidemiol* 2009; 169(6): 756–760.
22. Ahn JJ, O'Mahony J, Moshkova M, et al. Puberty in females enhances the risk of an outcome of multiple sclerosis in children and the development of central nervous system autoimmunity in mice. *Mult Scler* 2015; 21(6): 735–748.
23. Woolridge J. *Econometric analysis of cross section and panel data*. Cambridge, MA: MIT Press, 2010.
24. Brownell M, Martens P and Kozyrskyj A. Assessing the health of children in Manitoba: A population-based study. Winnipeg, MB, Canada: Manitoba Centre for Health Policy and Evaluation, 2001.
25. McMaughan DJ, Oloruntoba O and Smith ML. Socioeconomic status and access to healthcare: Interrelated drivers for healthy aging. *Front Public Health* 2020; 8: 231.
26. Hinton D and Kirk S. Living with uncertainty and hope: A qualitative study exploring parents' experiences of living with childhood multiple sclerosis. *Chronic Illn* 2017; 13(2): 88–99.
27. Pérez-Ardanaz B, Pelaez-Cantero MJ, Morales-Asencio JM, et al. Socioeconomic factors and quality of life perceived by parents and children with complex chronic conditions in Spain. *Children* 2021; 8(10): 931.
28. Ysseldyk R, Kuran N, Powell S, et al. Original quantitative research—Self-reported health impacts of caregiving by age and income among participants of the Canadian 2012 General Social Survey, 2021, https://www.canada.ca/en/public-health/services/reports-publications/health-promotion-chronic-disease-prevention-canada-research-policy-practice/vol-39-no-5-2019/self-reported-health-impacts-of-caregiving-age-and-income-among-participants.html
29. Svendsen MT, Bak CK, Sorensen K, et al. Associations of health literacy with socioeconomic position, health risk behavior, and health status: A large national population-based survey among Danish adults. *BMC Public Health* 2020; 20(1): 565.
30. Bloch G and Rozmovits L. Implementing social interventions in primary care. *CMAJ* 2021; 193(44): E1696–E1701.
31. Seid M, Varni JW, Gidwani P, et al. Problem-solving skills training for vulnerable families of children with persistent asthma: Report of a randomized trial on health-related quality of life outcomes. *J Pediatr Psychol* 2010; 35(10): 1133–1143.
32. Kahn RS, Wise PH, Finkelstein JA, et al. The scope of unmet maternal health needs in pediatric settings. *Pediatrics* 1999; 103(3): 576–581.
33. Olson AL, Kemper KJ, Kelleher KJ, et al. Primary care pediatricians' roles and perceived responsibilities in the identification and management of maternal depression. *Pediatrics* 2002; 110(6): 1169–1176.