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Lifetime stressors relate to invisible symptoms of multiple sclerosis

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Abstract

Aim: Childhood stressors can increase adult stress perception and may accumulate over the lifespan to impact symptoms of multiple sclerosis (MS). Growing evidence links childhood stressors (e.g., abuse, neglect) to fatigue, pain, and psychiatric morbidity in adults with MS; yet literature in this area is lacking a comprehensive lifespan approach. The aim of this cross-sectional study was to examine contributions of childhood and adulthood stressor characteristics (i.e., count, severity), on three individual outcomes: fatigue, pain interference, and psychiatric morbidity in People with MS (PwMS).

Methods: An online survey was distributed through the National MS Society. Hierarchical block regression modeling was used to sequentially assess baseline demographics, childhood stressors, and adult stressors per outcome. We hypothesized that child and adult stressors would significantly contribute to fatigue, pain interference, and psychiatric morbidity.

Results: Overall, 713 PwMS informed at least one final analytic model. Both childhood and adult stressors significantly contributed to pain interference and psychiatric morbidity. Adult stressor severity independently correlated with psychiatric morbidity ($P < 0.0001$). Childhood stressors significantly contributed to fatigue (LR test $P < 0.0001$). Childhood stressor severity independently significantly correlated with both fatigue likelihood ($P = 0.03$) and magnitude ($P < 0.001$).

Conclusions: This work supports a relationship between stressors across the lifespan and fatigue, pain, and psychiatric morbidity in PwMS. Stressor severity may have an important role which may not be captured in count-based trauma measurement tools. Clinicians and researchers should consider lifetime stress when addressing fatigue, pain, and psychiatric morbidity among PwMS.

Keywords

Adverse childhood experiences, stressors, multiple sclerosis, fatigue, pain, psychiatric morbidity

Introduction

Traumatic childhood stressors (e.g., abuse, neglect) are associated with many negative biopsychosocial health outcomes including immune-mediated diseases and symptoms [1–3]. Research on adverse childhood experiences (ACEs) and multiple sclerosis (MS) is a quickly growing field, yet the focus has primarily been on the risk for developing MS and not disease burden or chronic symptoms which heavily impact the lives of people with MS (PwMS) [4, 5]. The few studies that have focused on common "invisible symptoms" of MS have found that childhood maltreatment was associated with adult MS fatigue [6, 7], pain catastrophizing [8], anxiety [9], and psychiatric morbidity (e.g., anxiety, depression) [10].

Additionally, stressor measurement is inconsistent and still evolving. For example, most studies use count-based scales (e.g., ACEs), or tools that include severity of only a few stressors [e.g., Childhood Trauma Questionnaire (CTQ)] [5]. There is also a lack of consensus regarding what qualifies as a stressor. Indeed, with increased recognition of the importance of social determinants of health [11], additional factors such as unstable housing and discrimination have been incorporated into newer measures. For example, the CTQ only captures five core stressors of physical abuse/neglect, emotional abuse/neglect, and sexual abuse; while newer measures like the Stress and Adversity Inventory (STRAIN) capture experiences of unstable housing and being excluded because of personal factors like race or gender [12]. Recently, the STRAIN was used to evaluate only the stressors aligning with expanded ACE criteria, which revealed associations between emotional and physical stressors (e.g., abuse severity/duration) and invisible symptoms of fatigue, pain interference, and psychiatric morbidity in adults with MS [7]. However, limiting stressor measurement to only childhood provides limited insight, especially given that life stressors continue into adulthood, and that more childhood stress has been correlated with increased adult stress perception [13]. Consequently, studies that don't include exposure to stress across the lifespan may miss predictive adult information and overestimate relationships with childhood stressors [14].

A lifetime approach can help address the literature gap between child and adult stressor research, has the added value of potentially elucidating when stressors have the most impact on MS, and is more applicable to adult healthcare settings. The purpose of this study was to evaluate comprehensively measured lifetime stressors (e.g., cumulative child, adult, count, severity), to answer the research question of whether these stressors relate to three common invisible features of MS—fatigue, pain interference, and psychiatric morbidity, in a large national sample of PwMS. We used a hierarchical block modeling approach to highlight the importance of stressor timing (childhood *vs.* adulthood) and optimize future preventative and mitigation efforts. We hypothesized that successive models with a cumulative childhood stressor block and a cumulative adult stressor block would contribute significantly more predictive variance over the previous nested models, and thus, significantly associate to each outcome.

Materials and methods

The current study is a secondary data analysis of the Stress-MS dataset created by Polick et al., 2023 [7, 14]. Online surveys were distributed to US-based adults with MS in October 2021 via the National MS Society (NMSS) listserv including nearly 80,000 PwMS. STROBE guidelines were followed to strengthen reporting and transparency of observational studies [15]. Ethical approval was obtained from the University of Michigan and participants gave implied consent.

Measures

Stressors

The STRAIN encompasses 55 lifetime stressors including abuse, neglect, household dysfunction, housing instability, neighborhood safety, infertility, financial strain, and feeling excluded based on personal factors like race or gender [12]. If a participant endorsed a stressor, follow up questions captured the age at which

it happened and stressor severity. Stressor severity items are scored on a 0–5 Likert scale from "very slightly or not at all" to "extremely". Stressors were assessed as cumulative childhood count/severity and cumulative adult count/severity; higher scores represent higher stress.

Outcomes

Patient Reported Outcome Information System (PROMIS) tools were used to measure pain interference and fatigue. PROMIS-Pain Interference is a validated 8-item questionnaire measuring the impact of pain on the mental, physical, and social aspects of life in the past week [16], which has been used with PwMS [17]. Likert scale scoring from 1 (not at all) to 5 (very much), indicates higher pain interference with higher scores. Reliability was very high in this study (Cronbach's alpha = 0.98).

The PROMIS-Fatigue MS Short Form is a validated 8-item questionnaire measuring fatigue in the last week specific to PwMS [18, 19]. Likert scale scoring from 1 (never) to 5 (always); indicates higher fatigue with higher scores. Reliability was very high in this study (Cronbach's alpha = 0.95).

Psychiatric morbidity is a composite count score including elements of self-reported diagnoses and symptoms, focused primarily on the most common challenges for PwMS (e.g., anxiety, depression). This approach aligns with how this concept has previously been measured in an MS sample in the child stress literature and used here to promote better comparisons to bolster the lifetime stressor literature [7]. This approach captures both PwMS who may be symptomatic but not diagnosed and those who may be diagnosed but no longer symptomatic. Four item PROMIS-Anxiety and PROMIS-Depression tools were used to measure symptoms. For parsimony in already complex modeling, PROMIS anxiety and depression scores were each dichotomized into symptomatic (1) (i.e., any positive score) and not symptomatic (0), and then summed with other dichotomous variables including an anxiety diagnosis (0/1), depression diagnosis (0/1), or presence of other diagnoses [e.g., bipolar, schizophrenia, post-traumatic stress disorder (PTSD), 0/1]. Summed scores ranged from 0–6; higher scores indicated higher psychiatric morbidity.

Covariates

Demographic and MS covariates were used in each analysis (i.e., age, gender, education, MS subtype). Treatments, such as disease modifying therapy (DMT) and a count of different types of medications that can impact pain (e.g., opiates, antidepressants), were used in pertinent analyses (Table 1).

Table 1. Predictors per hierarchical block modeling approach

Sequential modeling	Predictors per each model
Base model 1: demographics and MS covariates	Age, gender, education, MS subtype, DMT[a], pain medication count[b]
Model 2 adds childhood stressors	Base model 1 + childhood stressor count, childhood stressor severity
Model 3 adds adult stressors	Model 2 + adult stressor count, adult stressor severity

[a] DMTs not included in psychiatric morbidity analysis; [b] pain medication count only included for pain interference and psychiatric morbidity analyses

Data screening and pre-processing

Raw PROMIS scores were transformed to normalized *t*-scores (https://www.healthmeasures.net/). Scores representing "no pain" or "no fatigue" were replaced with zeros to evaluate these outcomes appropriately using a two-part statistical model described below. Structural and social stressors disproportionately occur among minoritized populations, inhibiting our ability to disentangle race and racism. Thus, race and ethnicity variables were not included in the main analyses to not violate statistical principles (e.g., collinearity). These efforts align with our goal to thoughtfully reconsider attributing statistical onus on race, *versus* what social and health system structural factors contribute to outcomes for PwMS [20, 21].

Analytic strategy

Aligning with previous work that evaluated lifetime stressors and physical outcomes [14], our analytic approach aimed to assess fit of increasingly complex models that include blocks of related predictors (i.e., collinear variables representing latent constructs) to determine if their collective contributions improve

model fit. Of note, this type of analysis focuses on establishing whether there is a relationship between the latent constructs (e.g., blocks) and the outcomes, and not necessarily the change or individual variable contributions because they could be underestimated. Successive models were compared to prior models using likelihood ratio (LR) testing, and Akaike Information Criterion (AIC) as an index of relative model fit, with lower AIC indicating better fit. If a block of predictors did not significantly improve the model, it was removed from final analytic modeling. Table 1 shows the predictors and covariates in each of the three blocks, with each model nested within the next higher-level model.

The base model encompassed covariates to determine baseline contributions. Model fit of the base model was then compared to Model 2 which added childhood stressor predictors to assess if these contribute over and above the base model. For Model 3, adult stressor predictors were added to determine if they contributed additional predictive variance. After evaluating contributions of blocks of related predictors, contributions of individual predictors were examined. Yet, it must be noted that using related stressor variables is a strength of block modeling but may also cause an underestimation of individual stressor contributions.

The specific types of hierarchical regressions included Poisson regression for the count of psychiatric morbidities outcome. The two PROMIS outcomes, pain interference, and fatigue, represented a mixed distribution therefore two-part modeling was used. Part 1 included a dichotomous (yes/no) component of experiencing any pain interference or fatigue utilizing logistic regression, followed by part 2 a normal distribution characterizing the magnitude of pain interference or fatigue utilizing OLS linear regression.

Results

Reflective of the conventional US MS research population, including previous studies using the NMSS listserv and other large studies, most participants were female (*n* = 597, 84%), White (*n* = 415, 88%), with relapsing remitting MS (RRMS, *n* = 559, 78%), and a college education (Table 2) [17, 22, 23]. Compared to the normalized *t*-scores of a healthy general population who's mean (SD) is 50 (10) [24], this sample had higher mean fatigue 57 (9) and pain interference 53 (10.5). On average, participants experienced 2.6 (1.96) stressors in childhood with a severity of 9.8 (8.8), and 23.6 (14) stressors during adulthood with a severity of 55.3 (30.8).

Table 2. Sample characteristics

Characteristics	Mean (SD)
Age, mean (SD) (*n* = 713)	49 (12.7) range: 21–85
Length of time since MS onset, mean (SD) (*n* = 713)	18 (12) range: 0–59
Gender, *n* (%) (*n* = 712)	
Female	597 (84%)
Male	100 (14%)
Transgender, non-binary, gender non-conforming, or other	15 (2%)
MS subtype, *n* (%) (*n* = 712)	
Relapsing remitting MS (RRMS)	559 (78%)
Secondary progressive MS (SPMS)	87 (12%)
Primary progressive MS (PPMS)	35 (5%)
Progressive Relapsing MS (PRMS)	9 (1%)
Unsure	23 (3%)
DMT, *n* (%) (*n* = 709)	
None	129 (18%)
First line	272 (38%)
Second line	308 (43%)
Count of medication classes that can impact pain, mean (SD) (*n* = 705)	1.63 (1.29) range: 0–5
Race/ethnicity, *n* (%) (*n* = 471)	
White	415 (88%)

Table 2. Sample characteristics (*continued*)

Characteristics	Mean (SD)
Bi-racial or mixed	24 (5%)
Black	23 (5%)
Asian	4 (< 1%)
Latinx	2 (< 1%)
American Indian or Alaska Native	2 (< 1%)
Native Hawaiian or Pacific Islander	1 (< 1%)
Smoking status, *n* (%) (*n* = 709)	
Never smoker	465 (66%)
Former smoker	198 (28%)
Current or social smoker	46 (6%)
Education, *n* (%) (*n* = 713)	
High school equivalency or below	36 (5%)
Associate degree or some college	167 (23%)
Bachelor's degree	259 (36%)
Master's degree or above	251 (35%)
Stressors, mean (SD) (*n* = 713)	
Childhood count	2.6 (1.96)
Childhood severity	9.8 (8.8)
Adult count	23.6 (14)
Adult severity	55.3 (30.8)
Outcome variables (*n* = 713)	
Fatigue, median (IQR), mean (SD)	58 (52–63), 57 (9)
Pain interference, median (IQR), mean (SD)	54 (41–62), 53 (10.5)
Psychiatric morbidity count, mean (SD)	2.2 (1.7) range: 0–6

Pain interference

Base model predictors contributed to a significant overall two-part model estimating the likelihood and magnitude of pain interference (logistic regression pseudo R^2 = 0.2219, P < 0.0001; OLS regression R^2 = 0.1831, P < 0.0001; model AIC = 3,751) (Table 3). The childhood stressor block of predictors in Model 2 improved predictions significantly over the base model (logistic regression pseudo R^2 = 0.2448, P < 0.0001; OLS regression R^2 = 0.2152, P < 0.0001; model AIC = 3,719, LR P < 0.0001). Similarly, the adult stressor predictors in Model 3 contributed significantly more information over the prior nested modes (logistic regression pseudo R^2 = 0.2578, P < 0.0001; OLS regression R^2 = 0.2667, P < 0.0001; model AIC = 3,685, LR P < 0.0001).

Regarding individual predictors, childhood stress severity was significantly associated with the higher magnitude of pain interference (b = 0.33, P = 0.005) in Model 2 but lost significance when adult stress was added for Model 3, suggesting shared variance among child and adult stressors. In the final model, age impacted both the likelihood (OR = 1.02, P < 0.03) and magnitude (b = –0.10, P < 0.001) of pain.

Fatigue

The base model of predictors contributed to a significant overall two-part model estimating the likelihood and magnitude of having fatigue (logistic regression pseudo R^2 = 0.074, P < 0.04; OLS regression R^2 = 0.086, P < 0.0001; model AIC = 4,192) (Table 4). The childhood stressor predictors in Model 2 contributed a significant amount of variance over and above the base model (logistic regression pseudo R^2 = 0.11, P < 0.01; OLS regression R^2 = 0.14, P < 0.0001; model AIC = 4,160, LR P < 0.0001). While adult stressor severity was independently significant for the magnitude of fatigue (b = 0.073, P = 0.001), overall, the adult stressor predictors in Model 3 did not significantly contribute and reduced model fit (logistic regression pseudo R^2 = 0.136, P = 0.004; OLS regression R^2 = 0.242, P < 0.0001; model AIC = 4,844, LR P = 1.0). Thus, adult stressors were removed from the final analytic model, as only base covariates and childhood stressors correlated with fatigue.

Table 3. Final analytic model of pain interference using two-part regression modeling

Variables within hierarchical models	First part—logistic regression (*n* = 701)					Second part—OLS regression (*n* = 459)				Overall model stats		
	Any pain interference (binary)					Magnitude of pain interference						
	OR	SE	95% CI	*P*	Pseudo R^2	b	SE	95% CI	*P*	R^2	AIC	LR test
Base covariates				< 0.0001	0.222				< 0.0001	0.183	3,751	Base
Age	1.02	0.01	1.00–1.04	0.02		–0.10	0.03	–0.16—0.05	< 0.001			
Gender (ref. female)												
Male	0.65	0.18	0.38–1.11	0.12		1.09	0.93	–0.74–2.92	0.24			
Transgender, non-binary, gender non-conforming, or other	1.21	0.88	0.29–5.06	0.80		–2.12	1.91	–5.86–1.63	0.27			
Education (ref. ≤ HS)												
Associates degree or some college	0.13	0.11	0.03–0.65	0.01		–0.86	1.23	–3.27–1.55	0.47			
Bachelor's degree	0.09	0.07	0.02–0.44	< 0.01		–2.88	1.22	–5.26—0.50	0.02			
Master's degree or above	0.08	0.07	0.02–0.40	< 0.01		–3.43	1.23	–5.83—1.03	< 0.01			
MS subtype (ref. RRMS)												
PPMS	1.44	0.69	0.57–3.67	0.44		0.33	1.37	–2.37–3.02	0.81			
SPMS	1.57	0.54	0.81–3.07	0.18		2.58	0.91	0.80–4.36	< 0.01			
PRMS	1.35	1.29	0.21–8.8	0.75		5.71	2.36	1.08–10.35	< 0.02			
Unsure	1.13	0.63	0.38–3.35	0.82		2.81	1.70	–0.52–6.14	0.10			
DMT (ref. no therapy)												
First line	1.49	0.43	0.85–2.61	0.17		–0.63	0.91	–2.39–1.14	0.49			
Second line	2.22	0.65	1.25–3.95	< 0.01		–1.32	0.86	–3.01–0.38	0.13			
Pain med count	2.31	0.23	1.90–2.80	< 0.001		1.02	0.24	0.56–1.48	< 0.001			
Childhood stressors				< 0.0001	0.245				< 0.0001	0.215	3,719	< 0.0001
Child stressor count	1.19	0.22	0.83–1.71	0.34		–0.58	0.54	–1.63–0.47	0.28			
Child stressor severity	0.99	0.04	0.91–1.07	0.73		0.14	0.12	–0.10–0.38	0.24			
Adult stressors				< 0.0001	0.258				< 0.0001	0.267	3,685	< 0.0001
Adult stressor count	1.04	0.02	1.00–1.08	0.07		0.06	0.05	–0.04–0.16	0.24			
Adult stressor severity	1.00	0.01	0.98–1.02	0.92		0.04	0.02	–0.01–0.08	0.10			

≤ HS: high school equivalency or below; PPMS: primary progressive MS; PRMS: progressive-relapsing MS; ref.: reference; SPMS: secondary progressive MS. Blank cells indicate not applicable to individual variables

Table 4. Final analytic model of fatigue using two-part regression modeling

Variables within hierarchical models	First part—logistic regression (*n* = 600)					Second part—OLS regression (*n* = 576)				Overall model stats		
	Any fatigue (binary)					Magnitude of fatigue						
	OR	SE	95% CI	*P*	Pseudo R^2	b	SE	95% CI	*P*	R^2	AIC	LR test
Base covariates				< 0.04	0.074				< 0.0001	0.086	4,192	Base
Age	1.00	0.02	0.96–1.03	0.83		–0.07	0.03	–0.12–0.01	0.02			
Gender (ref. female)												
Male	0.72	0.39	0.25–2.07	0.54		–0.94	0.92	–2.73–0.86	0.31			
Education (ref. ≤ HS)												
Bachelor's degree	0.14	0.14	0.02–1.07	0.06		–2.48	0.82	–4.09–0.88	0.002			
Master's degree or above	0.16	0.17	0.02–1.25	0.08		–4.51	0.81	–6.10—2.92	< 0.001			
DMT (ref. no therapy)												
First line	0.60	0.41	0.16–2.27	0.45		–1.34	0.97	–3.23–0.56	0.17			
Second line	1.84	1.45	0.39–8.58	0.44		0.25	0.97	–1.65–2.15	0.80			
MS subtype (ref. RRMS)												
SPMS	1.50	1.22	0.31–7.35	0.62		2.55	0.99	0.62–4.48	0.01			
Childhood stressors				0.01	0.105				< 0.0001	0.138	4,160	< 0.0001
Child stressor count	0.51	0.19	0.24–1.07	0.07		–1.23	0.59	–2.38—0.08	< 0.04			
Child stressor severity	1.24	0.12	1.02–1.51	0.03		0.47	0.13	0.21–0.74	< 0.001			

Categories within variables dropped from the model based on collinearity: 1) transgender, non-binary, gender non-conforming, or other, 2) associate degree or some college, 3) PPMS, 4) PRMS, 5) unsure. ≤ HS: high school equivalency or below; PPMS: primary progressive MS; PRMS: progressive-relapsing MS; ref.: reference; SPMS: secondary progressive MS. Blank cells indicate not applicable to individual variables

In the final model, childhood stress severity was significantly associated with 24% higher odds of experiencing any fatigue for each increase 1-unit increase in severity rating (OR = 1.24, $P = 0.03$), and with the magnitude of fatigue (b = 0.47, $P < 0.001$). Interpreting this in context of the average childhood stress severity (9.8), this translates to the average PwMS in this sample being 235% more likely to experience fatigue. Childhood stressor count (b = –1.23, $P < 0.04$) and age (b = –0.07, $P = 0.019$) were both negatively associated with the magnitude of fatigue.

Psychiatric morbidity

The base model contributed significantly to estimating the risk of accumulating psychiatric morbidity ($R^2 = 0.061$, $P < 0.0001$; model AIC = 2,560) (Table 5). The childhood stressor predictors in Model 2 significantly improved over the base model ($R^2 = 0.09$, $P < 0.0001$; AIC = 2,485, LR $P < 0.0001$). Similarly, the adult stressor predictors in Model 3 contributed significantly more information over the prior nested model ($R^2 = 0.116$, $P < 0.0001$, AIC = 2,420, LR $P < 0.0001$). Therefore, childhood and adult stressors both correlate with psychiatric morbidity for PwMS.

Table 5. Final analytic model of psychiatric morbidity using Poisson regression (n = 705)

Variables within hierarchical models	IRR	SE	95% CI	*P*	Overall model statistics		
					Pseudo R^2	AIC	LR test
Base covariates				< 0.0001	0.061	2,560	Base
Age	0.98	0.002	0.98–0.99	< 0.001			
Gender (ref. female)							
Male	0.90	0.08	0.76–1.06	0.20			
Transgender, non-binary, gender non-conforming, or other	0.97	0.15	0.71–1.32	0.86			
Education (ref. ≤ HS)							
Associate degree or some college	0.93	0.11	0.75–1.16	0.54			
Bachelor's degree	0.96	0.11	0.77–1.19	0.70			
Master's degree or above	0.93	0.11	0.75–1.17	0.54			
MS subtype (ref. RRMS)							
PPMS	1.27	0.16	0.99–1.62	0.06			
SPMS	1.10	1.00	0.92–1.30	0.30			
PRMS	1.34	0.27	0.91–1.98	0.14			
Unsure	1.24	0.18	0.94–1.64	0.14			
Pain med count	1.10	0.02	1.06–1.15	< 0.001			
Childhood stressors				< 0.0001	0.090	2,485	< 0.0001
Child stressor count	0.97	0.05	0.88–1.07	0.57			
Child stressor severity	1.02	0.01	1.00–1.04	0.11			
Adult stressors				< 0.0001	0.116	2,420	< 0.0001
Adult stressor count	1.00	0.004	0.99–1.004	0.27			
Adult stressor severity	1.01	0.002	1.006–1.014	< 0.0001			

≤ HS: high school equivalency or below; IRR: incident rate ratio; PPMS: primary progressive MS; PRMS: progressive-relapsing MS; ref.: reference; SPMS: secondary progressive MS. Blank cells indicate not applicable to individual variables

Regarding individual predictors, adult stress severity was significantly associated with psychiatric morbidity (IRR = 1.01, $P < 0.0001$). As adult stressor severity increased by 1-unit, the risk of having an additional psychiatric diagnosis or symptom increased by 1%. Interpreting that within the context of the average adult stressor severity in this sample, 55.3 (30.8) this translates to a 55% increased risk for the average PwMS, with nearly 31% more risk just one standard deviation away. In Model 2, childhood stressor severity carried nearly five times that risk, with a 4.8% increased risk of psychiatric morbidity for each 1-unit increase in severity rating, however lost significance when adding the adult stressors for Model 3, again suggesting shared variance. In the final model, the risk of psychiatric morbidity decreased by 2% for each year since MS onset (IRR = 0.98, $P < 0.001$).

Discussion

Measurement

To our knowledge, this is the first study to use a lifetime approach to comprehensively measure the effect of child and adult stressors on three invisible issues in MS, fatigue, pain interference, and psychiatric morbidity. Use of hierarchical block modeling allowed us to determine the overall contribution of similar stressor variables, count and severity, to better assess the latent concept of stress. Cumulative childhood stressors correlated to all three outcomes, while adult stressors additionally associated with pain interference and psychiatric morbidity (Table 6). This work aligns with the few previous studies which associated only ACE-focused childhood stressors with adult fatigue [6], pain catastrophizing [8], and mental health outcomes [7, 9, 10] in PwMS or immune-mediated inflammatory diseases. Expanding beyond childhood stressor literature, this current study also aligns with evidence suggesting increased adult and lifetime stressors relate to worsening MS outcomes more broadly; although, this literature is largely focused on physical clinical outcomes (e.g., disease onset, relapses, progression) [14, 25, 26]. Specifically, since only childhood stressors related to fatigue in our study, our findings do not align with evidence that adult adversity (i.e., adverse life events in the last 60 days) is associated with MS fatigue [27]. This

divergence may stem from measurement differences (e.g., adult *vs.* lifetime). The current findings suggest that stressor severity may individually carry a more significant impact relative to stressor count for some outcomes; therefore, relying solely on count-based measures (e.g., ACEs) is not ideal. Similarly, evidenced by multiple instances of shared variance or contributions in our analyses, examination of childhood stressors without consideration of adult stressors is not ideal; therefore, a lifetime approach should be used when possible.

Table 6. Summary of stressor correlations to MS outcomes

MS clinical feature outcomes	Predictor blocks included in final model	Additional significant individual stressor contributions to MS outcomes
Pain interference	Child & adult stressors	
Fatigue	Child stressors	Childhood stress severity related to:
		reporting any fatigue & magnitude of fatigue
		Child stress count related to the magnitude of fatigue
Psychiatric morbidity	Child & adult stressors	Adult stress severity

Blank cell indicates model level significance and no additional individual level contributions

Omitting race/ethnicity from analyses is not optimal for discerning unique racial/ethnic experiences or differences across outcomes, yet may be necessary due to included stressors (e.g., discrimination) to avoid statistical issues. Since MS samples are largely White, even when studies do include race/ethnicity in analyses, small individual cell sizes typically lead to collapsing multiple categories into a dichotomous variable to abide by ethical/IRB reporting standards to protect participant identity and to create less statistical error variance. A recent review revealed that race/ethnicity was not accounted for in a third of the studies assessing childhood stressors and MS risk or features [5], leaving much room for improvement. More diverse samples are needed to address health disparities and inequities in MS research and treatment; and race and ethnicity should be included in future analyses when possible [28].

Clinical relevance and future directions

Our finding that each incremental increase in childhood stressor severity increased the odds of experiencing fatigue by 24% is noteworthy. Fatigue is the most common symptom experienced by PwMS yet remains one of the most challenging symptoms to treat, in part because of its personalized nature that can be influenced by stress. Meta-analyses highlight that mindfulness-based stress reduction approaches may be effective for fatigue, with mixed results for pain for PwMS [29], however, symptoms often co-occur thus broader outcomes should be considered. A recent study by Braley and colleagues found that telephone-based version cognitive behavioral therapy (CBT) for fatigue performed similarly to pharmacological treatment with modafinil [30, 31] in terms of fatigue impact reduction; however, combination therapy with both was associated with more global benefits based on the Patient Global Impression of Change (PGIC) score. Although the PGIC was a secondary outcome in this trial, the findings suggest that an interdisciplinary approach may offer the most benefit when considering a person's perception of global function. Further, benefits of interventions for invisible symptoms may be best captured by multifaceted instruments that capture overall activity, symptoms, mood, physical, and social function, which themselves can be influenced by stress, and targeted with psychotherapy. Future work is needed to implement and evaluate the benefits of adjunct therapies, in tandem with standard MS care, on invisible symptoms and broader measures.

Machine learning research has been burgeoning, especially for healthcare applications such as clinical decision making and treatment optimization [32, 33]. Our findings may inform future work such as using stressor history as one of the parameters in supervised machine learning to help determine whether those with high childhood adversity may respond better to cognitive or pharmacological treatment of fatigue. Similarly, integrating stress informed machine learning decision tools may help optimize treatment for other invisible and physical symptoms. Evidence suggests that interventions including stress reduction, coping/resilience skills, and smoking cessation, are useful for symptom management (e.g., pain, fatigue,

depression, disability) [34–37]. However, such research progress and clinician acceptance of these strategies hinge on health system parameters and infrastructure [38]. Additional implementation studies focused on provision of new services (e.g., stress reduction, coping, smoking cessation clinics), and/or protocols that facilitate increased referrals (e.g., screening, therapy, smoking clinics) are sorely needed to demonstrate feasibility and acceptability throughout various neurological settings to promote clinical buy-in and adoption of translational change.

As PwMS aged, the risk of psychiatric morbidity decreased by 2%, suggesting that PwMS may be most vulnerable at diagnosis but may learn to cope or feel more in control of their disease over time. This is somewhat supported by the finding that while the presence of pain increased with age, the magnitude of interference in daily life decreased. Interestingly, as both the count of childhood stressors and age increased, the fatigue magnitude decreased, which may suggest that PwMS who experienced more stressors may have already received mental health support and similarly learned to cope better over time. Alternatively, this may also indicate that PwMS who experienced high childhood stressors and potentially high coping skills, may be faring better and participating in research more than their counterparts. Since fatigue was the only outcome to which adult stressors did not have a significant relationship, yet evidence of this relationship has previously been shown to be mediated by resilience [27], there may be additional factors like coping and resilience that may have different mediating impacts across the three outcomes. Other complex considerations may be differing genetic contributions and intergenerational transmission of trauma. As this emerging area of research grows, more prospective and mechanistic work is needed to determine how resilience, coping, and other complex factors may mediate, moderate, or otherwise impact relationships between stressors and health outcomes in PwMS.

Limitations

Causal inference cannot be determined with cross sectional data. Yet, as the first study to assess many of these lifetime relationships with an MS focused sample, it fills an important gap. Those who responded may have increased ability to take an online survey (e.g., technology access, less disability). A response bias may be present due to the high number of PwMS on the NMSS listserv (approximately 80,000). Self-reported retrospective data has potential for recall bias, therefore, it is recommended to collect self-reported data using measures which have been validated using a test-retest approach and perform well over time (e.g., STRAIN) [12]. Sensitive information such as stressors could have a social desirability bias and be under-reported. However, the online format and anonymity may have facilitated more accurate reporting compared to other formats. Our sample was highly educated and may not represent all groups. However, this sample aligns with traditional US MS research samples including other studies that used the NMSS listserv and captures the widest geographical range and largest sample size in this emerging area and thus bolsters the internal and external validity [17, 22]. Additional strengths include a wide range of covariates compared to other work in this area [5]. While the PROMIS measures allowed us to compare two outcomes against a healthy group, we did not compare stressor experience. Future studies would be more robust by using a design that allows for a true comparison against other populations of interest (e.g., healthy controls, similar chronic diseases).

Conclusions

These findings support an association between childhood stressors and pain interference, fatigue, and psychiatric morbidity; as well as an association between adult stressors and pain interference, and psychiatric morbidity for PwMS. Additional studies are needed to assist clinical efforts of trauma informed precision medicine and intervention efforts to mitigate stressor impact on PwMS. While pediatric MS is far less common, investigating stressor experience across different developmental stages may be helpful in evaluating MS outcomes in this sub-population. Future research should replicate this work with more diverse MS samples and expand to include other positive aspects (e.g., coping, resiliency, social support) with mediation analyses and additional clinical features (e.g., sleep, cognition, substance use).

Abbreviations

ACEs: adverse childhood experiences

AIC: Akaike Information Criterion

DMT: disease modifying therapy

IRR: incident rate ratio

LR: likelihood ratio

MS: multiple sclerosis

NMSS: National Multiple Sclerosis Society

PROMIS: Patient Reported Outcome Information System

PwMS: people with multiple sclerosis

RRMS: relapsing remitting multiple sclerosis

STRAIN: Stress and Adversity Inventory

Declarations

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of Duke CTSI or the VA.

Author contributions

CSP: Conceptualization, Formal analysis, Writing—original draft. TJB: Conceptualization, Resources, Writing—review & editing. RPS: Conceptualization, Formal analysis, Writing—review & editing. CMC: Conceptualization, Writing—review & editing. AW: Writing—review & editing. SAS: Conceptualization, Supervision, Writing—review & editing.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical approval

This study was approved by the University of Michigan IRB (HUM00200716).

Consent to participate

Participants read informed consent materials during the screening process and agreed to an implied consent statement to proceed with the study.

Consent to publication

Not applicable.

Availability of data and materials

Data is available upon request to corresponding author or Harvard Dataverse repository.

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