The Impact of Child and Adult Stressors on Multiple Sclerosis Biopsychosocial Disease Features

by

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DEDICATION

This dissertation is dedicated to my husband, Scott. Thank you for making this work possible through your endless patience, love, and support. I am deeply grateful for all the work that you have also put in behind the scenes to give me the gifts of time and focus.

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ABSTRACT

Background: Multiple Sclerosis (MS) is a neuroinflammatory demyelinating autoimmune disease of the central nervous system that disproportionately affects people in North America. Although the etiology and cure remain unknown, interactions among genetic, environmental (e.g., latitude), and behavioral (e.g., smoking) influences are considered contributing factors. The Social Safety Theory offers a pathway from stress to disease through the physiological responses of the inflammation cascade. Through this cascade, childhood stressors have been implicated in the development of many physical health conditions including heart disease, stroke, Alzheimer's disease, obesity, diabetes, and numerous autoimmune diseases. Childhood stressors are also linked with behavioral and mental health outcomes including perceived stress in adulthood and substance use. Adult stress has been associated with MS onset and relapses. Although traumatic stressors have been associated with the development of autoimmune diseases, remarkably few studies (n=5) have investigated the relationship between childhood stressors and MS *disease features*. Of these studies, none accounted for adult stressors, and few accounted for MS specific covariates.

Purpose: The purpose of this cross-sectional study was to evaluate relationships among childhood adversity, adult stressors, and features of MS while accounting for MS specific confounders. Guided by the Social Safety Theory, this work posits that child and adult stressors are social threats which elicit neuroinflammatory responses contributing to MS symptoms.

Methods: An electronic invitation was sent to the National MS Society listserv of 80,000 people with MS, and 924 participants successfully completed the survey. The aims of this dissertation include to examine the associations between: 1) *cumulative child* stressor characteristics (e.g., severity, duration), and *cumulative adult* stressor characteristics with individual MS disease outcome features; 2) child stressor types, grouped by emotional, physical, and environmental, and MS disease features; and 3) individual *lifetime* stressor type characteristics (e.g., physical danger severity) and MS disease features. Hierarchical block modeling was used for aims 1 and 2 to assess the shared contribution of similar stressors, while multiple regression was used for aim 3. **Results:** For aim 1, hierarchical block modeling was used to sequentially assess childhood cumulative and adult cumulative stressors in relation to the six MS outcomes. Both child and adult stressors were associated with three outcomes, pain interference, disability, and mental health comorbidity. Only child stressors were associated with fatigue, while only adult stressors were associated with relapse burden changes since Covid-19. The age at symptom onset was not significantly associated with any stressors. For aim 2, hierarchical block modeling was used to sequentially assess childhood stressors, grouped by emotional, physical, and environmental stressors. At least two types of childhood stressors were significantly associated with all MS feature outcomes, except the relapse burden change since Covid-19 which was unaffected by stressors. For aim 3, multiple regression was used to assess cumulative stressors across the lifespan, grouped into five core social-psychological types, and the same six MS features. Stressors were significantly associated with four features, fatigue, pain

interference, age at symptom onset, and mental health comorbidity. Stressors did not impact disability or relapse burden change.

Conclusions: Findings across all aims fill gaps and advance knowledge in this field. This dissertation supports relationships between stressors experienced across the lifespan and common clinical features of MS.

CHAPTER I

Introduction

Multiple Sclerosis, an autoimmune demyelinating inflammatory disease of the Central Nervous System (CNS) is the most common non-traumatic contributor to young adult disability (Drori & Chapman, 2019; Perricone et al., 2019). The damage to myelin, a protective sheath around the axon of a neuron, disrupts messages between the brain and body (Colasanti et al., 2019; Lunde et al., 2017). The United States (US) has the second highest prevalence rate, with 288 cases per 100,000 people compared to Germany's rate of 303, while the global rate is only 36 per 100,000 people (Multiple Sclerosis International Federation [MSIF], 2020). The US also bears the burden of approximately one third of all global cases (MSIF, 2020), and increasing mortality rates despite decreasing rates elsewhere (Magyari & Sorensen, 2019).

Problem Statement

There are several factors that contribute to an increased risk of developing or altering the disease features of MS. Examples include genetic predisposition, viral exposure, latitude of birth or long-term residence, obesity, and smoking (Drori & Chapman, 2019; Hedstrom et al., 2016; Versini et al., 2019). However, the exact cause of MS remains unknown. Research suggesting stress and the subsequent inflammation cascade as a possible risk factor has started to emerge, but remains preliminary (Handel et al., 2010; Artemiadis et al., 2011). Although traumatic childhood stressors

have been associated with the development of autoimmune diseases, remarkably few studies (n=5) have investigated the relationship between childhood stressors and MS disease features. Of these studies, none accounted for adult stressors, few accounted for additional MS features (e.g., fatigue, pain, comprehensive mental health comorbidity) or other contributing factors (e.g., latitude, birth month, smoking).

Purpose

The purpose of this exploratory cross-sectional study is to examine the relationships between stressors across the lifespan and MS disease features while accounting for other contributing factors in a large sample of people with MS. There is a critical need to better understand how childhood and adult stress may alter mental, behavioral, and physical outcomes to possibly trigger MS at a younger age or modify other disease features such as disability, fatigue, pain, relapses, or mental health comorbidity. Groups of similar stressors and individual stressor types will both be evaluated for their unique contributions to MS features including mental health comorbidity. This approach will determine which stressors are most impactful for each MS feature.

Theoretical and Conceptual Overview

The Social Safety Theory (Slavich, 2020) is the guiding framework for this study. Social Safety Theory posits that real or perceived threats to an individual's safety can elicit the stress response which alters physiological processes (e.g., neurodevelopment, inflammatory response), perception of future threats, and responding behavior (e.g., social, emotional, cognitive) (Slavich, 2020). These theoretical concepts are multi-factorial, and can be interdependent and iterative. To distill the overarching theoretical

framework into one conceptual model to address cumulative MS risk and outcomes, an adaptation of the Adverse Childhood Experiences (ACEs) pyramid will be used (CDC, 2022). As seen in Figure 1, the ACE pyramid represents a lifetime approach starting with accumulating experiences in childhood (e.g., abuse) creating potential for proximal outcomes. Disrupted neurodevelopment, social, emotional, and cognitive impairment, and adoption of risky health behaviors can further accumulate and accelerate negative distal outcomes such as disease, disability, social problems, and early death. The adapted model in Figure 2 builds upon the ACE model by 1) adding two tiers to incorporate environmental risk factors for MS as well as highlighting the adult experience of stress, and 2) detailing in parentheses which variables this study will measure. Synthesis and further development of the theoretical and conceptual model is provided later in this chapter.

Specific Aims

Aim 1 (Paper 1)

Examine the associations of *cumulative child* stressor characteristics and *cumulative adult* stressor characteristics (e.g., count, severity), with individual MS disease outcome features (e.g., disability, mental health comorbidity).

Aim 2 (Paper 2)

Examine the associations between child stressor types, grouped by emotional, physical, and environmental, and MS disease features (e.g., pain, fatigue).

Aim 3 (Paper 3)

Examine the associations between individual *lifetime* stressor type characteristics (e.g., physical danger severity) and MS disease features (e.g., age at onset, pain).

Review of the literature

This review will include the pathophysiology, symptomatology, disease trajectories, and known environmental risks of Multiple Sclerosis. Childhood adversity is introduced as an initial stressor that accumulates over the lifespan with adult stress. Stress (e.g., stressful life events) is proposed as a potential environmental risk, and the mental, physical, and behavioral outcomes are reviewed. The literature is synthesized to integrate health aspects of both childhood adversity and MS, highlighting gaps in the literature and an evaluation of the state of the science. This work is grounded in the Social Safety Theory. Lastly, the gaps this study will address are presented along with the aims that address the gaps.

Introduction to Multiple Sclerosis (MS)

Multiple Sclerosis is an autoimmune neurologic inflammatory demyelinating disease of the central nervous system (CNS) (Drori & Chapman, 2019). It is the leading cause of non-traumatic disability during young adulthood in many countries (Perricone et al., 2019). The global prevalence rate has been increasing over the last decade and has reached 2.8 million cases (Multiple Sclerosis International Federation [MSIF], 2020). A disproportionate number of cases, 1 million, reside within the United States (US) (MSIF, 2020). The US has the second highest prevalence rate at 288 cases per 100,000 people (MSIF, 2020). In comparison, the average global rate is only 36 per 100,000 people (MSIF, 2020). MS also disproportionately impacts women up to 3 times higher than men (National Multiple Sclerosis [MS] Society, 2020b; Roostaei & De Jager, 2020). Although mortality rates have decreased across Europe, mortality rates in the US have increased, especially for non-Hispanic Whites and Blacks (Magyari & Sorensen,

2019). Similarly, MS is diagnosed more frequently in Whites, yet other races typically bear a higher disease burden once diagnosed with MS (NMSS, 2020). On average, people with MS (PwMS) die 7 to 10 years earlier than the general population (Magyari & Sorensen 2019; Oh et al., 2018).

While the specific etiology remains unknown, it is widely accepted that environmental factors interact with varying genetic predispositions to trigger the disease (Drori & Chapman, 2019). Because it is an inflammatory disease, the immunological response is the most understood aspect thus far (Zephir, 2018). This understanding also lends some insight on how certain environmental risks may be explained through the inflammation and immune responses.

Pathophysiology of MS

Multiple sclerosis is characterized by autoreactive T-lymphocytes in the periphery which cross the blood brain barrier (BBB) and engage with resident immune cells including B-lymphocytes, microglia, and other cells to incite an inflammatory cascade in the CNS (Colasanti et al., 2019; Torres-Ruiz & Shoenfeld, 2019; Zephir, 2018). Although the myelin sheath (a fatty protein covering on neurons that facilitates axonal conduction) is the proposed target of the inflammation, axonal damage and degeneration accompanies destruction of the myelin sheath (Drori & Chapman, 2019; Comi et al., 2020). Autoreactive cells have lost the ability to distinguish between “self” or cells that belong, versus “non-self” or foreign cells that need to be destroyed, giving MS the distinction of an autoimmune or immune-mediated disease.

In a healthy neuron, the myelin sheath surrounds and protects the axon and facilitates electrical signal conduction between the brain and body (NMSS, 2020; Sa,

2012). The damage to the myelin slows signal conduction and can eventually inhibit signals all together (Colasanti et al., 2019; Lunde et al., 2017). The body initially tries to remyelinate through other neural cells called oligodendrocytes whose function is to make and support the myelin sheath (Coyle, 2020a). However, since oligodendrocytes have the same material as the myelin sheath that was marked by the B-cells, the oligodendrocytes eventually succumb to the immune system and fail to remyelinate which contributes to disability (Coyle, 2020a). Areas where this tissue damage is visible on Magnetic Resonance Imaging (MRI) is characterized as a lesion. To be diagnosed with MS, lesions must be disseminated throughout space and time (Polman et al., 2011), meaning that a single lesion or single attack of symptoms does not yet meet official diagnostic criteria.

Symptomatology

The amount of immune cells in acute and active chronic lesions corresponds with the amount of injury and damage (Ferguson et al., 1997; Zephir, 2018). Similarly, the location of the lesion may correspond with the symptoms PwMS experiences, but that is not always the case (Kincses et al., 2011; Rosenthal et al., 2020). For example, damage to the myelin and axon of a motor or sensory neuron will present different symptoms than damage to neurons that carry out emotional processes. Symptoms can arise directly from a lesion and through a combination of other symptoms.

Disability Related to Motor Control

Motor symptoms (e.g., weakness, spasticity) are common issues with MS (Rosenthal et al., 2020). Damage to neurons in the spinal cord or brainstem that normally facilitate smooth movements can result in slower signal conduction, slowed,

weak movements, stiffness, spasticity, hypertonia (Caligiore et al., 2017; Rosenthal et al., 2020). Damage to the circuitry that helps move the eye muscles can cause dysconjugate gaze, double vision, impairments in volitional eye movements (Rosenthal et al., 2020). Lesions that affect other cranial nerve pathways can disrupt facial expression, swallowing, and speech (Rosenthal et al., 2020). Eventually, a PwMS can develop complete disability in the corresponding part of the body, such as the legs (Sa, 2012). In a prospective study with a 15 year follow up, 41% of PwMS who did not receive treatment needed walking aids to walk 100 meters, compared to just 13% of PwMS who did receive treatment (Kalincik et al., 2021). Understandably, these symptoms can disrupt quality of life and may inhibit PwMS from engaging with their social networks as their symptoms progress.

Fatigue

Fatigue is one of the most common symptoms, occurring in 80% of PwMS (NMSS, 2022a). The direct cause of fatigue is unknown, but other MS symptoms can also impact sleep, thus contributing to overall fatigue. For example, because of lesions in areas corresponding to their legs, PwMS can have spasms, pain/tingling, or restless leg syndrome which can make it difficult to fall asleep (Rosenthal et al., 2020). People with MS who have urinary issues can have frequent sleep disruptions throughout the night (Rosenthal et al., 2020). MS also impacts sleep by disordered breathing such as obstructive (OSA) or central sleep apnea (CSA) which can arise from lesions or medications PwMS are frequently prescribed (e.g., narcotics, muscle relaxants) (Braley & Chervin, 2015; Braley & Boudreau, 2016). It can be especially difficult to decipher the true origin of fatigue for PwMS that have comorbid depression. When compared to

sleep related fatigue, direct fatigue is typically more severe, more susceptible to heat and humidity, and can occur even after restful sleep (NMSS, 2022a).

Pain

Acute and chronic neuropathic pain throughout the body is a direct result of the damage to somatosensory neurons and higher-level neurons that affect pain processing (NMSS, 2022b). Some common presentations involve feelings of electric shocks down the spine (Lhermette's sign), and severe pain in the cheek or mouth (trigeminal neuralgia) (Drori & Chapman, 2019; Rosenthal et al., 2020). Musculoskeletal pain typically arises from other symptoms that MS has caused, such as pain from spasticity (Kratz et al., 2021; NMSS, 2022b). For example, increasing disability and gait instability can alter the way PwMS walk, causing pain in the back or lower extremities, and injuries from falls (NMSS, 2022b; Rosenthal et al., 2020). Regardless of the pathway, pain from MS can interfere with quality of life, commonly requires medication and sometimes even intrathecal pumps or surgery (Rosenthal et al., 2020).

Phenotypes of MS

Relapsing Remitting (RRMS)

Most (85-90%) people diagnosed with MS present with a relapsing remitting subtype (Drori & Chapman, 2019; Zephir, 2018) This phenotype is characterized by periods of increased symptomatology (relapses) and periods of stability (remissions). Relapses are concurrent to increasing number or size of demyelinating lesions that result from the peripheral immune cells in the CNS (Zephir, 2018). People with RRMS can, but typically do not, regain all the function that was lost during each relapse (NMSS, 2022c).

Secondary Progressive (SPMS)

About half of those with RRMS will maintain this disease course plateauing with remissions and declining with relapses for the rest of their lives (Zephir, 2018). If left untreated, older natural history studies that predate disease modifying therapy (DMT) use suggest that the other 50% will convert to Secondary Progressive MS (SPMS) after about 11 to 18 years (Hanna & Strober, 2020; Zephir, 2018). Although relapses are less frequent with this phenotype, PwMS lose the luxury of relative stability from remissions; instead, neurologic function progressively worsens (Drori & Chapman, 2019; Hanna & Strober, 2020; Zephir, 2018).

Primary Progressive MS (PPMS)

Ten to fifteen percent of people will follow the Primary Progressive (PPMS) disease course (Drori & Chapman, 2019; Zephir, 2018). This phenotype is characterized by progressively worsening neurologic function in the absence of relapses (Lublin et al., 2014). Progression is usually continuous from disease onset (Drori & Chapman, 2019; Lublin et al., 2014).

Progressive Relapsing MS (PRMS)

Prior to 2013 some PwMS may have been diagnosed with a rare disease course called Progressive Relapsing MS. This form was characterized by progressive dysfunction from disease onset in addition to acute relapses (Tullman et al., 2004). In 2013 the PRMS subtype was retired and this form has since been included under the PPMS form with disease activity (Lublin et al., 2014). Research participants who were diagnosed prior to 2013 may still identify themselves as PRMS, therefore, this category is sometimes still used in studies where patients self-report MS phenotype.

Known Environmental and Behavioral Risk Factors

Only 30 to 50% of MS risk can be attributed to genetics (Coyle, 2020a). Non-genetic factors that have been shown to increase the risk of MS are the latitude of birth or long-term residence, birth month, smoking tobacco, obesity, and microbial exposure such as the Epstein-Barr Virus (EBV) (Drori & Chapman, 2019; Tao et al., 2016). These environmental and behavioral risk factors are thought to interact within a genetically predisposed individual to trigger MS through Vitamin D and/or the inflammatory response mechanisms.

Epstein-Barr Virus (EBV)

The most established environmental risk factor for the development of MS is the Epstein-Barr Virus, the pathogen that can induce infectious mononucleosis (IM) (Roostaei & De Jager, 2020). Almost all (99.5%) of PwMS are positive for having EBV antibodies, proving immune system activation (Handel et al., 2010). In fact, when tested with high sensitivity the prevalence of MS without EBV antibodies is essentially zero (Jacobs et al., 2020). If EBV induces infectious mononucleosis after the age of 15, the individual is twice as likely to develop MS, suggesting a critical period during childhood and adolescence (Handel et al., 2010). However, EBV antibodies in the general population are not uncommon, making it unlikely that EBV acts alone to increase the risk of MS. Exposure and immune reaction to EBV appears to be a mandatory prerequisite for later developing MS, yet the actual triggering of the disease seems more dependent on interaction with other environmental risks and underlying genetic factors (Jacobs et al., 2020).

Latitude

The risk of MS is on a gradient starting at the equator where it is the lowest (NMSS, 2022d; Tao et al., 2016). The further away one is born or migrates from the equator, the higher the risk is of developing MS (Handel et al., 2010). If a child migrates before the age of 15 they assume the risk of the new long-term residence (Handel et al., 2010). Yet, after age of 21, the risk of developing MS is less likely to change with migration (Handel et al., 2010), further suggesting a critical time period during childhood and adolescence. In addition to overall risk, latitude can impact the disease course. In a large study of over 22,000 PwMS throughout 21 countries, Tao et al. (2016) found that participants at higher latitudes had an earlier age of disease onset by nearly two years. Both geographic latitude and the seasonality of birth are thought to impact MS through a lack of Vitamin D (Tao et al., 2016). Although food can be a source of Vitamin D, a lack of sunlight has been more strongly implicated in the research.

Seasonality of Birth

Similarly, maternal sunlight exposure during pregnancy is thought to influence the child's risk of later developing MS (Ismailova et al., 2019; Handel et al., 2010). Individuals born in April have the highest risk of developing MS, followed by May (Handel et al., 2010). A spring birth means a winter pregnancy with less sunlight exposure and consequently lower maternal and fetal serum Vitamin D levels (Bradshaw et al., 2020; Handel et al., 2010). For example, from October to March, there is insufficient sunlight above 52 degrees of latitude for the skin to synthesize Ultraviolet (UV) rays into Vitamin D (Ismailova et al., 2019). Inversely, individuals born in the late fall, particularly November, experience a summer pregnancy, and have lower rates of

MS (Ismailova et al., 2019). Further supporting this association is that lower serum levels are also associated with relapse rates, and that supplementing Vitamin D decreases relapses (Bradshaw et al., 2020).

Obesity

Early development through young adulthood is also a critical period when obesity can heighten the risk of MS. There is over a two-fold increased risk of MS for individuals with a body mass index (BMI) greater than or equal to 30kg/m^2 at age 18-20 years old (Gianfrancesco & Barcellos, 2016; Versini et al., 2019). Similarly, for girls aged 7 to 13 years, a higher BMI was associated with a 1.61-1.95-fold risk of developing MS (Versini et al., 2019). Obesity at age 25 has been linked to a five year younger age at onset for adults with MS (Gianfrancesco & Barcellos, 2016). Child and adolescent obesity have also been associated with the development of pediatric onset MS (Gianfrancesco & Barcellos, 2016).

In addition to genetics, both the Vitamin D and inflammatory pathways have been implicated as potential mechanisms for the increased risk of MS from obesity. Individuals with high body fat have decreased levels of serum Vitamin D, which again is known to increase MS risk (Gianfrancesco & Barcellos, 2016; Versini et al., 2019). Further, those living at higher latitudes may not receive enough sunlight to maintain sufficient vitamin D levels. Also, obesity is characterized by chronic inflammation (Gianfrancesco & Barcellos, 2016), and high fat could switch adipose tissue macrophages from anti-inflammatory to pro-inflammatory states (Versini et al., 2019).

Smoking Tobacco

Another route to MS under the inflammation umbrella is through smoking tobacco (Hedstrom et al., 2016), which has direct neurotoxic in addition to inflammatory effects (Rosso & Chitnis, 2020). The proposed mechanism is the heat and smoke from smoking are respiratory irritants that elicit an inflammatory and immune response resulting in the creation of antigens (Perricone et al., 2010; Rosso & Chitnis, 2020). The new antigens are thought to cross reference with myelin antigens and activate the T-cells which would contribute to MS onset and disease trajectory (Rosso & Chitnis, 2020). Smokers convert from CIS to RRMS at twice the rate of non-smokers, and they convert faster from RRMS to SPMS (Ramanujam et al., 2015; Rosso and Chitnis, 2020; van der Vuurst de Vries et al., 2018). Smokers who are genetically susceptible to MS have an increased Odds Ratio (OR) of 7.7-13.5, meaning they are nearly 8 to 14 times more likely to develop MS (Hedstrom et al., 2014; Perricone et al., 2019). The odds are much lower for non-smokers who are also genetically susceptible (OR= 4.5-4.9; Perricone et al., 2019). Smokers have been found to bear a higher lesion load, more brain atrophy, relapses, and disability burden (Perricone et al., 2019; Rosso & Chitnis, 2020). There appears to be a dose response between smoking and adverse MS outcomes, which improve with cessation (Hedstrom et al., 2016; Rosso & Chitnis, 2020), highlighting an opportunity for screening and intervention.

Proposed yet Controversial Environmental and Behavioral Risk Factor: Stress

Stress has been thought to impact MS since the time of Charcot who first described the disease in 1877 (Meyer-Arndt et al., 2020). Stress induces an inflammation cascade that may contribute to triggering MS and relapses (Artemiadis et

al., 2011; Handel et al., 2010). In the short term, the stress response is a necessary adaptation for survival that elicits the fight, flight, or freeze reaction (McEwen et al., 2015; Rosemberg et al., 2017). When a real or perceived threat is detected, the hypothalamic pituitary adrenal (HPA) axis coordinates a multi-system response through the autonomic, neuroendocrine, cardiovascular, and immune systems (Lupien et al., 2009; Slavich, 2020). In case the threat involves an injury, the HPA axis stimulates hormones and neurotransmitters to start a preemptive inflammation cascade to help fight off a possible infection (McEwen & Seeman, 1999; Slavich, 2020). A key part of maintaining balance in this system is the ability to turn it off when the threat is over (McEwen & Seeman, 1999; Slavich, 2020). The system can dysfunction from repeated or prolonged stress responses so feedback loops can no longer downregulate the stress/inflammation cascade properly (McEwen & Seeman, 1999; Slavich, 2020). This results in bodily damage and chronic systemic inflammation that can make individuals susceptible to many adverse outcomes including viral infections, autoimmune, and even neurodegenerative diseases (Furman et al., 2019; Slavich, 2020).

Adult stress has been significantly associated with MS onset and disease trajectory (Artemiadis et al., 2011; Jiang et al., 2021; Sharif et al., 2019). A large majority of the studies (88%) in the review by Artemiadis et al. (2011) supported the relationship that stress impacts MS. Regarding MS onset, studies found significantly more negative stressors and consequently more negative emotions in the few months to years before onset for PwMS compared to healthy controls. For example, parents exposed to the stress of losing a child younger than 18 had nearly twice the risk of developing MS compared to non-exposed parents (Artemiadis et al., 2011; Li et al.,

2004). Regarding MS disease trajectory, in studies of prevalent MS, studies found significant relationships among the number, frequency, and duration of stressors preceding symptom exacerbation and relapses. For example, adult stressors were significantly related to new lesions eight weeks later (OR= 1.62, 95% CI= 1.12- 2.34) (Artemiadis et al., 2011; Mohr et al., 2002). Even the presence of one stressor could increase the exacerbation risk four weeks later (RR= 2.2, 95% CI= 1.2-4.0) (Artemiadis et al., 2011; Buljevac et al., 2003). More recently, prospective research has shown that psychological stress is associated with more grey matter atrophy in the brains of PwMS (Meyer-Arndt et al., 2020). This is especially important, as grey matter atrophy correlates highly with MS disability progression and lacks drug therapy but does seem amenable to cognitive interventions (Meyer-Arndt et al., 2020). Lending further support to the stress-MS relationship, intervention studies focusing on stress reduction or mindfulness have found improvements in symptoms and less lesion development for PwMS (Sharif et al., 2019). However, there is much heterogeneity regarding the measurement of stressor timing and impact, leaving gaps in the literature that a comprehensive lifespan approach could help to fill.

Similar to other risk factors, in utero, childhood, and adolescence is a critical time of development, especially neurologically, when negative stressors could carry lifelong implications for MS. Using mice, Khaw et al., (2021), revealed that early life trauma (i.e., emotional and physical distress) is associated with the susceptibility, severity, and phenotype shifts of Experimental Autoimmune Encephalitis (the mouse equivalent used as a proxy for human MS). A recent review revealed that only 12 studies have assessed traumatic childhood stressors and the prevalence of adult MS and/or disease features

(Polick et al., 2022). Using a large national database of nearly three million people, Neilsen et al. (2014) found that parental divorce alone increased the risk of developing MS by 13% (RR= 1.13, 95% CI=1.04-1.23). Goodwin and Stein (2004) used a list of three neurological disorders, including MS, finding that participants had over twice the odds of developing any of the neurological disorders after experiencing childhood physical abuse (OR= 2.2, CI= 1.1-4.5, p<.05).

Of those 12 studies reviewed by Polick et al. (2022), only five assessed *physical* MS disease features. Shaw et al., (2017) found that a cumulative score of adverse childhood experiences (ACEs) was significantly related to an earlier age at MS onset. Spitzer et al. (2012), found that PwMS who experienced severe childhood abuse had significantly higher relapse rates than PwMS without histories of severe abuse. More recently, studies have linked childhood adversity to adult MS fatigue (Pust et al., 2020), and pain catastrophizing (e,g., exaggerated pain response, ruminating over and/or feeling helpless about pain) (MacDonald et al., 2021). One study initially found significant results for two outcomes, an earlier age at MS onset and walking disability, yet these lost significance when adjusting for multiple testing comparisons (Horton et al., 2022). Regarding mental health features, Eilam-Stock et al., linked ACEs and worse anxiety and adjustment over the first year after an MS diagnosis (2021). Wan et al., correlated childhood trauma and mental health comorbidity (e.g., anxiety disorders, depression) in a sample of people with Immune Mediated Inflammatory Disorders, inclusive of MS. While this emerging area of research appears promising, additional research on stressors, particularly including those during childhood, is needed to elucidate pathways for future interventions.

Introduction to Childhood Adversity

Childhood adversity is a public health crisis, traditionally encompassing emotional, sexual, physical abuse/neglect, parental mental illness, substance abuse, or separation, and other household dysfunctions such as witnessing violence, before the age of 18 (Felitti et al., 1998). Two thirds of the US population have experienced some form of these Adverse Childhood Experiences (ACEs), otherwise known as child maltreatment, traumatic, or toxic stress (Centers for Disease Control and Prevention [CDC], 2022). Traumatic stressors during childhood cause substantial economic and disease burdens from the individual to a systemic level. Ramifications such as acute and chronic health care and criminal justice costs just within the US total about $2 trillion dollars annually (Peterson et al., 2018). Even though a majority of Americans have experienced this adversity and the costs at a national level are staggering, there remains an overall lack of awareness connecting childhood adversity to the myriad of subsequent mental, physical, and behavioral health outcomes. Part of this is due to the insidious pathways by which the adversity accumulates through the stress and inflammation responses. It can sometimes take years for adult clinical symptoms to fully manifest which makes it much easier to misattribute risk and causative factors.

Recent research suggests that the ACE criteria are too narrow and should be widened to include stressors such as discrimination, community violence, living in foster care, social rejection, bullying, and sexual abuse despite the age of the offender (Cronholm et al., 2015; Kang & Burton, 2014; Krienert et al., 2011; Slavich, 2020; Stoddard et al., 2021). For example, the traditional ACE questionnaire asks whether the sexual offender was at least five years older than the research participant (Felitti et al.,

1998). Conversely, Krienert et al. (2011) revealed that over 25% of 12,293 sexual offenders were less than five years older than those whom they abused. Additionally, Kang & Burton (2014) found that discrimination is associated with post-traumatic stress symptoms. The narrow focus on traditional abuse leaves a gap in the literature where additional stressors that can also elicit the stress response are not being measured. This measurement gap can be filled by widening the childhood adversity criteria to include significant stressors disclosed by participants.

Health Consequences of Traumatic Childhood Stressors

Physical Health Consequences of Traumatic Childhood Stressors

After the landmark ACE study was published in 1998, clinicians and researchers slowly started to become aware of and investigate the vast consequences of childhood stressors on health (Felitti et al., 1998). ACEs have a dose response relationship with outcomes, meaning the more adversity a child faces, the higher the consequences (Felitti et al.,1998). Childhood adversity can elicit the stress response; thus, it has been associated with a myriad of diseases and disorders, many of which are among the top causes of mortality (e.g., obesity, heart disease, diabetes) (Dube et al., 2009; Felitti et al.,1998; Furman et al., 2019; Grummitt et al., 2021; Kalmakis & Chandler, 2015; Kochanek et al., 2019).

Autoimmune diseases have gained attention as outcomes of childhood stressors. Dube et al., (2009) used the original ACE study (n=15,375) to examine increased risk of hospitalizations for 21 autoimmune diseases (including MS). Findings revealed that depending on sub-categories, individuals who have two or more ACEs were 70%-100% more likely to be hospitalized for an autoimmune disease than individuals with no ACEs

(Dube et al., 2009). Similarly, Slavich and Shields (2018) found that for every additional stressor across the lifespan, the risk of developing any of the 21 listed autoimmune diseases (including MS) increased by 3.8% (RR=1.038, 95% CI=1.013- 1.055, p<.001).

Childhood stressors influence pertinent health consequences through at least three pathways. First, the stressors themselves, via the HPA axis inflammatory response, may pose a risk for developing adverse outcomes such as MS (Artemiadis et al., 2011; Jiang et al., 2020; Khaw et al., 2021, Sharif et al., 2019). Second, child trauma increases the risk for obesity which in turn doubles the risk of developing MS (Versini et al., 2019). Third, maladaptive social, emotional, and cognitive behaviors can yield serious physical health consequences such as eating disorders (e.g., over-eating) or smoking, increasing the risk for MS, in addition to suicide (Felitti et al., 1998; Kalmakis & Chandler, 2015).

Psychological Consequences of Traumatic Childhood Stressors

Traumatic stress during childhood has been associated with mental health outcomes such as anxiety, depression, suicidality, PTSD, complex-PTSD, emotional reactivity, mood, and personality disorders (CDC, 2022; Felitti et al., 1998; Herman, 2015; Kalmakis & Chandler, 2015). Through the dysregulated feedback loops in the brain, significant stress during child development can change brain structures and make an individual hyper-aroused for threat detection (Herman, 2015; McEwen et al., 2015). This essentially lowers the threshold at which an individual can tolerate stress. For this reason, traumatic childhood stress has been shown to increase the perception of adult stress (Albott et al., 2018). The subsequent emotional reactivity could increase the difficulty of maintaining adult social and emotional functions such as appropriate

relationships, a healthy social network, and quality of life (CDC, 2022; Herman, 2015). However, there are gaps in the literature surrounding these aspects within the MS population. Therefore, this study will be the first to comprehensively assess perceptions of stressors in childhood, unrestrained by the traditional ACE criteria, and adult stressors in PwMS, while accounting for psychological consequences.

Behavioral Health Consequences of Traumatic Childhood Stressors

Similar to physical and mental health, traumatic stress during childhood has long term implications for an individual's social, emotional, and cognitive behavior which can be arduous to change in adulthood. Childhood stressors have been associated with increased smoking, drinking, early and chronic illicit substance use, eating disorders, self-harm, homelessness, teen pregnancy, interpersonal violence, and risky sexual behavior including involvement in sex trafficking (CDC, 2022; Felitti et al.,1998; Jones & Pierce, 2020; Kalmakis & Chandler 2015; Trottier & MacDonald, 2017). Behavioral consequences are somewhat less insidious than the physical outcomes which take time to accumulate physical wear and tear. Social, emotional, and cognitive behavioral issues can emerge as early as childhood or adolescence and can be a crucial shift which impacts the trajectory for adulthood. For example, Jones and Pierce (2020) found significant relationships among individual, cumulative, and clustered ACEs experienced by five years old and adolescent delinquency at 15 years old (e.g., substance use, violence, criminal activity). Children exposed to just two ACEs are expected to have increased delinquency by a factor of 1.436 or 43.6% (Jones & Pierce, 2020). The dose response relationship is demonstrated by an increase of ACEs correlating with an increase in the count of delinquency behaviors, while adjusting for other causes. For

example, children exposed to three different ACEs are expected to have increased delinquency by a factor of 1.659 or 65.9%, while four ACEs increases the expected delinquency to 89% (Jones & Pierce, 2020). The propensity for early initiation of substance use undoubtedly contributes to the higher risk of adult addiction as a result of ACEs (Zarse et al., 2019). If framed as warning signs, the emerging social, emotional, and cognitive impairments that result from childhood stressors can serve as proximal outcomes to be addressed to prevent further stressor accumulation and worse adult health outcomes.

Together the accumulating physical, psychological and behavioral consequences of childhood stressors can increase trauma and stressors across the lifespan. This can impair an individual's ability to be attuned with, nurture, and protect their own children from, or even inflict, childhood stressors (Zarse et al., 2019). This transmission of trauma contributes to psychological and behavioral patterns found in families (Zarse et al., 2019). As previously noted, MS has genetic and familial patterns, as does substance use (Acheson et al., 2018; Drori & Chapman, 2019). There is a gap in the literature requiring more nuanced information surrounding these issues. For example, this study will be the first to assess child and adult stressors while accounting for substance use (i.e., smoking, pain medication) behaviors in PwMS.

Mental Health as it Relates to MS and Trauma

Trauma and significant stress can be antecedents for many mental health diagnoses that commonly co-occur with MS. Rates of anxiety, depression, and suicidality are all higher in PwMS compared to the general population (Tauil et al., 2018). Uncertainty about when MS symptoms (e.g., gastrointestinal, urinary) will strike

can contribute to increased symptoms of anxiety or PTSD (Butler et al., 2016; Carletto et al., 2018). Additionally, the symptoms of these diagnoses can all overlap with those of Post-Traumatic Stress Disorder (PTSD), however the literature relating PTSD and MS is very scarce. Symptom similarities and lack of guidance stemming from gaps in the literature could lead to missed clinical opportunities. For example, primary care or neurology clinicians might misattribute some PTSD stress reactions to anxiety since anxiety is so commonly comorbid with MS, and therefore miss opportunities for treatment referrals to mental health services.

Depression

Childhood trauma increases the odds of developing depression after facing just one adult (Colman et al., 2013). Any additional stressor (2+) further increases the odds, so that survivors of childhood trauma have nearly four times the odds of becoming depressed (Colman et al., 2013). Similarly, there is a high prevalence of comorbid depression in PwMS. About 30%-50% of individuals with MS will be diagnosed with depression at some point throughout their disease (Hanna & Strober., 2020; Sharif et al., 2019; Tauil et al., 2018). Hanna and Strober (2020) found that substance use, social support, and education contributed the most to depression for PwMS, contributing 24% of the variance. The depression etiology has been proposed to be both biological (e.g., lesion activity in emotional areas of the brain), and psychological due to the uncertainty of the disease (Hanna & Strober, 2020). In fact, those with the progressive form of MS have less uncertainty than those who cycle through unpredictable relapses and have been found to have less depression than the RRMS population (Zabad et al., 2005).

This is an important issue because depression also increases the risk of suicidality in PwMS (Tauil et al., 2018; Sharif et a., 2019).

Anxiety

Traumatic childhood stressors increase the odds of developing anxiety by 29% per each 1-unit increase of ACEs experienced (OR=1.29, CI= 1.21-1.29, $p<0.001$) (Choi et al., 2017). Unsurprisingly, over 77% of outpatient anxiety patients reported at least one ACE (van der Feltz-Cornelis et al., 2019). Similarly, there is a high prevalence of anxiety for PwMS, ranging from 15.8% - 57%, compared to a global rate ranging from 0.8%-6.4% (Butler et al., 2016). The etiology of anxiety in MS has also been proposed to be biological (e.g., neuronal circuity in brain structures), and psychosocial (e.g., greater social stress, limited social support, higher substance abuse) (Hanna & Strober, 2020). While anxiety receives less attention in the MS literature, it has shown to be more impactful compared to depression (Hanna & Strober, 2020). For example, PwMS and depression have three times the odds of experiencing fatigue, while PwMS and anxiety have five times the odds (Beiske et al., 2008; Hanna & Strober, 2020). Similarly, PwMS and anxiety are four times more likely to disclose symptoms of pain, while depression had no association (Beiske et al., 2008; Hanna & Strober, 2020). Additionally, the cumulative number of MS symptoms has been strongly correlated with anxiety (Butler et al., 2016; Roy-Bellina et al., 2010). In fact, anxiety has been related to higher pain levels, sleep problems, fatigue, and disability issues, lower social support, lower MS treatment adherence, and forms of coping including emotional preoccupation, avoidance/denial, excessive drinking, and substance use in PwMS (Askari et al., 2014; Butler et al., 2016; Milanlioglu et al., 2013).

Interestingly, factors linked with anxiety in MS are shorter disease duration, younger age at onset, and lower disability (Hanna & Strober, 2020), suggesting the post-diagnosis period could be a critical window of heightened anxiety that may subside somewhat after adjustment Smoking is a predictor of anxiety, which some individuals may use to cope with stress, but it is also a risk factor for MS and worse symptomology (Butler et al., 2016; Perricone et al., 2019). Lastly, compared to having either anxiety or depression, the effects of comorbid anxiety and depression (CAD) on the quality of life of PwMS or other chronic conditions are potentiated, with more thoughts of self-harm, worse symptomatology, and social dysfunction (Brown et al., 2010; Hanna & Strober, 2020).

Post-Traumatic Stress Disorder (PTSD)

The chronological, physiological, and directional relationships between stress and MS remains opaque. As the name suggests, PTSD is traditionally thought of as a stress response after a single or series of traumatic external events. A developing area of research challenges this convention by proposing that being diagnosed with MS could also cause PTSD; that the symptoms of PTSD are related to the uncertainty and stress about the cureless future (Carletto et al., 2018; Chalfant et al., 2004; Ostacoli et al., 2013). This argument hinges on the Diagnostic and Statistical Manual (DSM) criteria for PTSD which has evolved over time, but did specifically include threats to life via chronic illnesses (Carletto et al., 2018; Chalfant et al., 2004; Ostacoli et al., 2013). Symptoms of PTSD for PwMS include intrusive thoughts about their future trajectory such as extreme fear about relapse and disease factors including acute paralysis, being wheelchair bound, or having bowel/bladder incontinence in public (Butler et al., 2016;

Carletto et al., 2018). In 2004, the prevalence rate of PTSD in PwMS was 15.5%, while only 6.8% within the general population at that time (Carletto et al., 2018; Chalfant et al., 2004). More recent research in 2018 using the same DSM IV criteria demonstrated prevalence rates between 5.7 and 8.5% (Carletto et al., 2018). However, there is a gap in the literature regarding the assessment of PTSD in PwMS since the DSM V criteria was updated to no longer include chronic illness as a possible cause. This creates potential for decreased screening or attributing symptoms to other mental health issues such as anxiety.

While MS is a major stressor which can precipitate stress response symptoms, it may not be appropriate to fully attribute these symptoms solely to being diagnosed with a debilitating disease, or that PTSD symptoms emerge for the first time due to an MS diagnosis. Stress symptoms may be closer to the surface or already fully manifested for those with a history of childhood adversity or other adult traumas. The literature in this area is limited and does not adopt a lifespan approach. For example, not accounting for other childhood or adulthood traumas, or excluding participants with a history of substance abuse or suicide attempts, yet both are known to be highly associated with childhood trauma and PTSD (Chalfant, 2004; Felitti et al., 1998; Herman, 2015; Ostacoli et al., 2013).

Theoretical Framework Overview

This work is informed by a theoretical framework and a conceptual model which will be synthesized into a new adaptation of the conceptual model. Social Safety Theory was chosen because it comprehensively covers iterative interactions and adaptations of the body, mind, and environment; while similar frameworks, such as Allostatic Load

(McEwen & Stellar, 1993) or the theory of stress and coping (Lazarus & Folkman, 1987), lack full integration of these three critical pieces. The ACE pyramid (Figure 1) was chosen because it captures the essence of stressor accumulation and subsequent consequences across the lifespan. Yet, the original does not include environmental and adult factors, which have been added to create the new adapted model discussed further below (Figure 2).

Social Safety Theory

The Social Safety Theory is the theoretical framework that guided this study (Slavich, 2020). This theory hypothesizes that positive social bonds are a central pillar to human behavior and that threats to social safety cause psychological stress, leading to systemic inflammation and subsequent disease (Slavich, 2020). This theory encompasses the aforementioned physiological stress response that is elicited due to threat detection. In addition to biological responses, the social safety theory delineates how certain characteristics were vital for survival and therefore likely highly conserved during human evolution (Slavich, 2020). Humans that formed friendly social bonds and collaborated (e.g., hunting, gathering) were more likely to survive than humans who were rejected from the group. From this view, social rejection, isolation, and hostile bonds are threats to survival which elicit the stress response and inflammation cascade (Slavich, 2020). Similarly for survival, even at a young age humans develop the ability to remember past threatening social interactions (e.g., abuse, neglect) to better detect and prepare for possible future threats (Slavich, 2020). Therefore, threats or stressors especially during child development can determine the way an individual navigates their social environment and interacts with the world (e.g., friendly, hostile) (Slavich, 2020).

Reacting to and learning from the stressors can result in the formation of different social safety schemas such as a self-schemas (e.g., belief in coping ability), and social world schemas. Schemas about the social world are a lens that an individual generally views other people as 1) friendly versus hostile, 2) predictable versus unreliable, 3) supportive versus critical, 4) helpful versus harmful, and 5) sincere versus manipulative (Slavich, 2020). Informed by empirical literature in the areas of 1) trauma sequelae, 2) psychoneuroimmunology, and 3) neurology, this study proposes that childhood adversity and adult stressors are threats to social safety which contributes to MS features and exacerbates symptomatology. These threats can elicit an inflammatory response, which is one factor that may contribute to MS features and symptoms.

Multiple Sclerosis is a complex disease that can be difficult to manage psychologically and biologically. People with MS, especially those with histories of traumatic stressors, may self-medicate for relief of their many symptoms. To address nerve and musculoskeletal pains, MS patients are often prescribed opiates. Traumatic childhood stressors can make PwMS more sensitive to pain (Tesarz et al., 2016), which could require higher doses or more potent categories of medications to manage. The motivation for substance use could initially be for physical relief, and yet, PwMS might incidentally find psychological or biological relief from neurodevelopmental, social, emotional, or cognitive impairments. Further, childhood or adult stressors, comorbid mental health struggles, and/or the unpredictability of MS may also motivate PwMS to use substances. For example, some PwMS have used substances as a distraction technique to deal with unpredictability during relapses (Hanna & Strober, 2020). Since tobacco can worsen MS disease features (Perricone et al., 2019), and medications

(e.g., opioid or anticonvulsant analgesics) may confound the responses to questions about pain, it is important to account for these substances while evaluating features of MS and comorbid mental health.

Conceptual Model for the Study

This study will use a conceptual model informed by the Social Safety Theory, and the Adverse Childhood Experience pyramid model (Figure 1). Building upon this ACE pyramid model, the adapted model (Figure 2) helps tease out the impact of stressors across the lifespan by adding an additional tier for adult stressors. A foundational tier was also added to encompass the context of environmental factors such as latitude. All core tier concepts remain the same; some have simply been tailored to accommodate more specific language (e.g., “MS features” instead of “disease”) and the focal variables of this study.

Model Components

Environmental Risk Factors

For this dissertation the concept of environmental risk factors, such as latitude or birth season, are passive risk elements that may react with genetic or other risk factors to contribute to the potential to trigger MS or alter the disease trajectory. While the exact cause of MS is unknown, strong empirical evidence supports that environmental factors contribute to the likelihood of developing MS and altering MS features such as age at onset (Ismailova et al., 2019; Handel et al., 2010; Tao et al., 2016). The Social Safety Theory also notes that the microbial environment (e.g., bacteria, fungi) during childhood drives the opportunities for the immune system to practice upregulating and

downregulating (Slavich, 2020). Since environmental factors will always be present, this concept is shown as the foundation of the model.

Traumatic Childhood Stressors

For this dissertation the concept of childhood stressors is defined as a significant event or situation before the age of 18 which has the potential to negatively impact the participant alone or through the duration, frequency, or severity of the exposure. Empirical evidence has supported the shift to widen the criteria of what qualifies as an adverse childhood experience (Jones & Pierce, 2020), and the importance of examining stressor features beyond a simple binary cumulative score (Slavich & Shields, 2018). Chronologically, childhood occurs first, before adulthood, and is therefore shown as the second tier of the model. Examples of traditional childhood stressors included in this study are abuse, neglect, and household dysfunction (Felitti et al., 1998). This study will also capture dysfunction unrestrained by the household convention, such as neighborhood violence, crime, and discrimination. According to Social Safety Theory, once these threats occur, one's body attempts to better prepare for future threats to increase the likelihood of survival; planting the seeds from which maladaptive processes can grow (e.g., negative social schemas, hypersensitivity for threat perception, eliciting the inflammatory response).

Disrupted neurodevelopment

The concept of disrupted neurodevelopment is based on psychoneuroimmunology literature, which encompasses the psychological, neurological, and immunological connections and interactions of an individual's health. As noted, Social Safety Theory and other literature supports how critical these

psychological and physiological processes are throughout the detection/perception of a threat, the following inflammation cascade, and the crucial ability for the body to shut down cascade after achieving safety (Slavich, 2020). Disruptions to a developing brain, due to traumatic stressors, can be paramount in changing the trajectory of the lifespan through dysregulated feedback loops, alterations in brain structures, chronic systemic inflammation, and especially increased threat perception which can lead to further impairment (Herman, 2015; McEwen & Seeman, 1999; Slavich, 2020). Therefore, even though this study will not utilize variables to measure the concept of disrupted neurodevelopment, it is recognized in the model as the mechanism which links childhood traumatic stressors to more distal stressors and health outcomes.

Social, Emotional, and Cognitive Impairment

Similarly, once a traumatic childhood stressor occurs, the Social Safety Theory supports that a child will learn how to better detect threat to increase the likelihood of survival (Slavich, 2020). Evidence supports that because this threat might come from a previously trusted caregiver, whom the child also still depends on for survival, fluctuating discrepancies between safety, trust, threat, and the need to accommodate to survive can inhibit conventional social and emotional schema development (CDC, 2022; Felitti et al., 1998; Herman, 2015; Kalmakis & Chandler, 2015; Slavich, 2020). The concept of social, emotional, and cognitive impairment is shown in the model as the fourth tier. Although it is not measured in this study, like disrupted neurodevelopment, it is a critical turning point that impacts more distal outcomes as stressors and bodily wear and tear accumulate across the lifespan.

Adult Stressors

For this dissertation, the concept of adult stressors is defined as a threat to social safety, a significant event or situation after the age of 18, which has the potential to negatively impact the participant alone or through the duration, frequency, or severity of the exposure. The Social Safety Theory and other literature support that social rejection, isolation, and hostile bonds are threats to survival which can trigger the HPA axis and inflammation cascade (McEwen & Seeman, 1999; Slavich, 2020). Empirical evidence supports categorizing all adult stressors into five core social-psychological domains 1) physical danger, 2) role change/disruption, 3) humiliation, 4) interpersonal loss, and 5) entrapment (Slavich & Shields, 2018; Cazassa et al., 2020). Empirical evidence also supports that traumatic childhood stressors can lower an individual's stress threshold thereby increasing their perception of stress in adulthood (Albott et al., 2018); and that adult stressors can worsen features of MS (Artemiadis et al., 2011; Sharif et al., 2019). For these reasons, the concept of adult stressors is shown as the fifth tier of the model, measured by a comprehensive variety of stressors categorized into the five core domains.

Adoption of Health Risk Behaviors: Substance Use

For this dissertation, the concept of health risk behaviors: substance use is defined as the degree to which a participant uses prescribed or non-prescribed substances that are traditionally thought to carry risk of abuse (e.g., opiates, cannabis). Empirical evidence supports that traumatic stress survivors have an increased propensity to use substances (Felitti et al., 1998; Khantzian, 1997). Substances may be used to cope with the stress of having a chronic disease, to address MS symptoms such as pain, and for relief from psychological, social, or emotional suffering (Braley et

al., 2020; Khantzian, 1997). Further, evidence supports that smokers have a higher risk of developing MS, and that smoking tobacco contributes to MS symptom severity (Hedstrom et al., 2016; Perricone et al., 2010; Rosso & Chitnis, 2020). For these reasons, the health risk behavior referred to as substance use encompass tobacco smoking and pain medication use and is shown as the sixth tier on the model. These variables along with psychiatric medications were accounted for in appropriate analyses, whether they were prescribed or not, due to their potential to confound results whether they are being taken as prescribed or not.

MS Disease Features and Mental Health Comorbidity

The original model core concept of “Disease, disability, and social problems” (Figure 1) remains constant in Figure 2 but is instead labeled “MS features & mental health comorbidity” to align with the focus of this study. MS disease features are defined as the demographic and clinical features of the disease. Empirical evidence supports differing trajectories based on MS phenotype, symptom severity based on stressors, substance use, and mental health (Askari et al., 2014; Butler et al., 2016; Zabad et al., 2005). For example, the perception of pain can be increased for PwMS who are also survivors of traumatic childhood stressors (Tesarz et al., 2016).

For this study, mental health comorbidity is defined as the degree to which a participant has symptoms of anxiety, depression, and/or PTSD. Empirical evidence supports that both PwMS and survivors of trauma have increased propensity to experience mental health challenges (Felitti et al., 1998; Tauil et al., 2018), and mental health issues impact features of MS (Beiske et al., 2008; Hanna & Strober, 2020). Additionally, anxiety and depression are highly prevalent in PwMS, and the proposed

etiology is partially due to the MS disease processes (Hanna & Strober, 2020). Therefore, mental health comorbidity is considered to fall under the umbrella term as a feature of MS, yet for clarity, it is highlighted as a co-concept in the model. The study evaluated the effect of stressors on both MS disease features (e.g., pain, fatigue, disability) and comorbid mental health severity. For these reasons, and because all other tiers contribute to MS features and/or mental health comorbidity, the concept is shown as the seventh tier of the model. The outcome variables for this concept encompass age at onset, disability, relapse burden since Covid-19, pain, fatigue, and mental health comorbidity (e.g., anxiety, depression, and PTSD). Traditionally the relapse rate is used, however, simply using a rate fails to capture other aspects of relapses. In addition, this study was conducted approximately 1.5 years after Covid-19 onset. Covid-19 has been found to be a unique stressor (Kira et al., 2021) that could confound relapse rates and have caused the overall relapse burden to change, perhaps differently depending on stressor history. Therefore, this study used other aspects such as relapse length and symptoms to measure how the overall relapse burden has changed.

Early Death

Both ACEs and MS result in early death (CDC, 2022; Magyari & Sorensen 2019; Oh et al., 2018). This work and similar future work has to the potential to impact the eighth tier, early death, by addressing issues at any of the lower tiers. However, measuring this concept is beyond the scope of this dissertation project.

Gaps in the Literature

In summary, this review and synthesis of the literature covers the etiology,

disease course of MS, and how stressors across the lifespan could alter the course through the stress response. In addition, common comorbidities and behaviors were parsed out as potential candidates to further alter the disease course. A limited number of studies have been conducted in this emerging field of investigating childhood trauma and trauma across the lifespan as stressors affecting MS, leaving many gaps to be filled (Table 1.1). As noted in the literature review, only 12 studies have assessed any form of traumatic childhood stressor and either the prevalence of MS or physical disease features such as age at onset (Polick et al., 2022). Of these, half did not specifically focus on an MS population. Instead, MS was on a list of neurological, immune mediated, or autoimmune diagnoses. Clearly not the primary focus, most of these studies did not specifically assess MS features and mostly reported risk for MS development. Of the five studies that did assess childhood stressors and physical MS features, two did not control for confounders, two included depression and one included anxiety as covariates beyond basic demographics. Therefore, no studies have assessed traumatic childhood stressors and MS disease features while accounting for known risk factors (e.g., latitude, seasonality, smoking) or confounding factors of pain or mental health medication. Further, only one of these studies each assessed or accounted for additional features of pain catastrophizing, fatigue, anxiety, and none have comprehensively measured mental health comorbidity with a sample of PwMS. Further, none of these studies assessed adult stressors which, as noted in the literature review, can also impact MS disease features such as relapse rates (Artemiadis et al., 2011). Therefore, no studies have taken a lifetime approach to comprehensively measure stressors in PwMS. These studies only

addressed the count and/or severity of the limited number of stressors. Therefore, no studies have assessed stressor duration in relation to disease features of MS. Lastly, the Social Safety Theory and the measurement tool, the Stress and Anxiety Inventory (STRAIN), have never been used in a specific MS population, making this study very innovative. Given the emerging state of the science, this study has a unique opportunity to fill many gaps to advance the field.

Table 1.1 Summary of Gaps in the Literature and how this study addressed them

Gaps in the Literature	Addressing Gaps in the Literature
1. No studies have comprehensively assessed child and adult stressors specifically in an MS population.	Childhood and adult stressors will be examined. Individual stressor characteristics (e.g., severity, duration) will be examined with individual MS disease features (e.g., fatigue, pain), while accounting MS specific confounding factors where appropriate (e.g., latitude, smoking). (Aim 1-3)
2. No studies have assessed traumatic childhood stressors and MS disease features while accounting for known risk factors such as latitude, seasonality of birth, smoking, use of pain or mental health medications.	
3. No studies have assessed stressor duration and severity across the lifespan in relation to MS disease features.	
4. No studies have assessed child stressors and additional MS features, such as pain interference, relapse burden changes, mental health comprehensively (e.g., PTSD, anxiety, depression, schizophrenia, bipolar, diagnoses or symptoms, hospitalization) with a focused MS sample. Only one study has assessed child stressors and fatigue.	MS features will be assessed and accounted for throughout multiple analyses. (Aim 1-3)
5. The Social Safety Theory and measurement tool Stress and Adversity Inventory STRAIN have never been used for a specific MS population.	The STRAIN will be used by PwMS, guided by the Social Safety Theory. (Aim 1-3)

Figure 1. Lifetime Impact from Adverse Childhood Experiences (CDC, 2022)

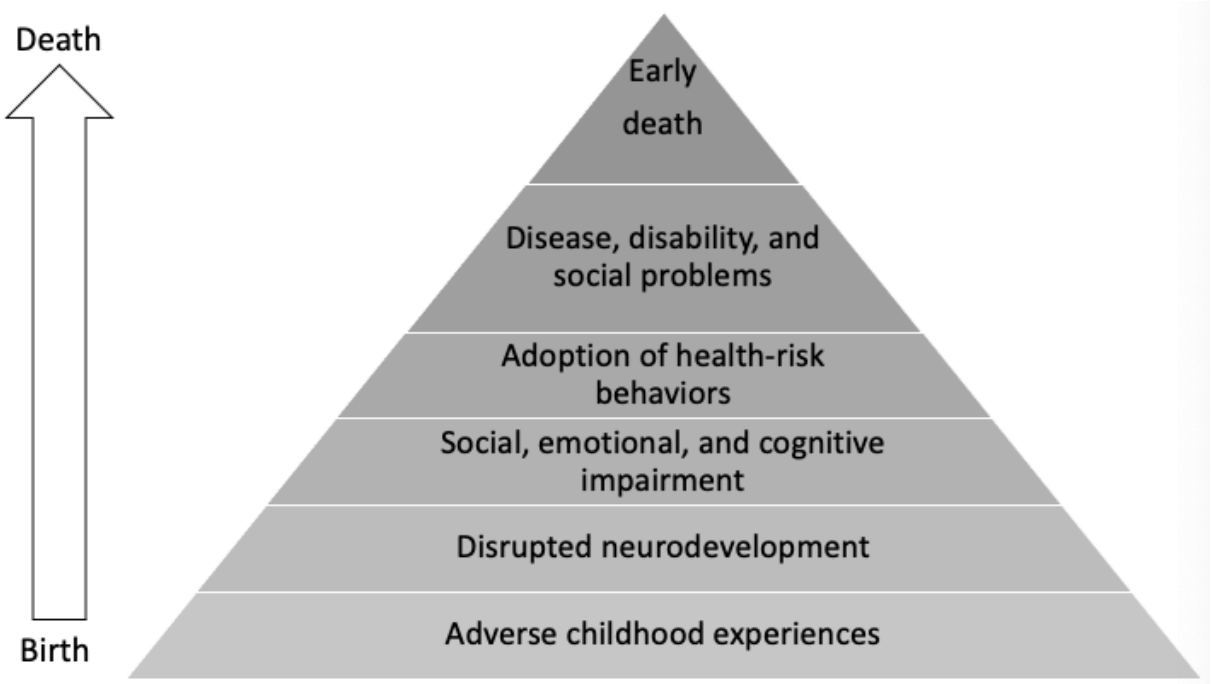
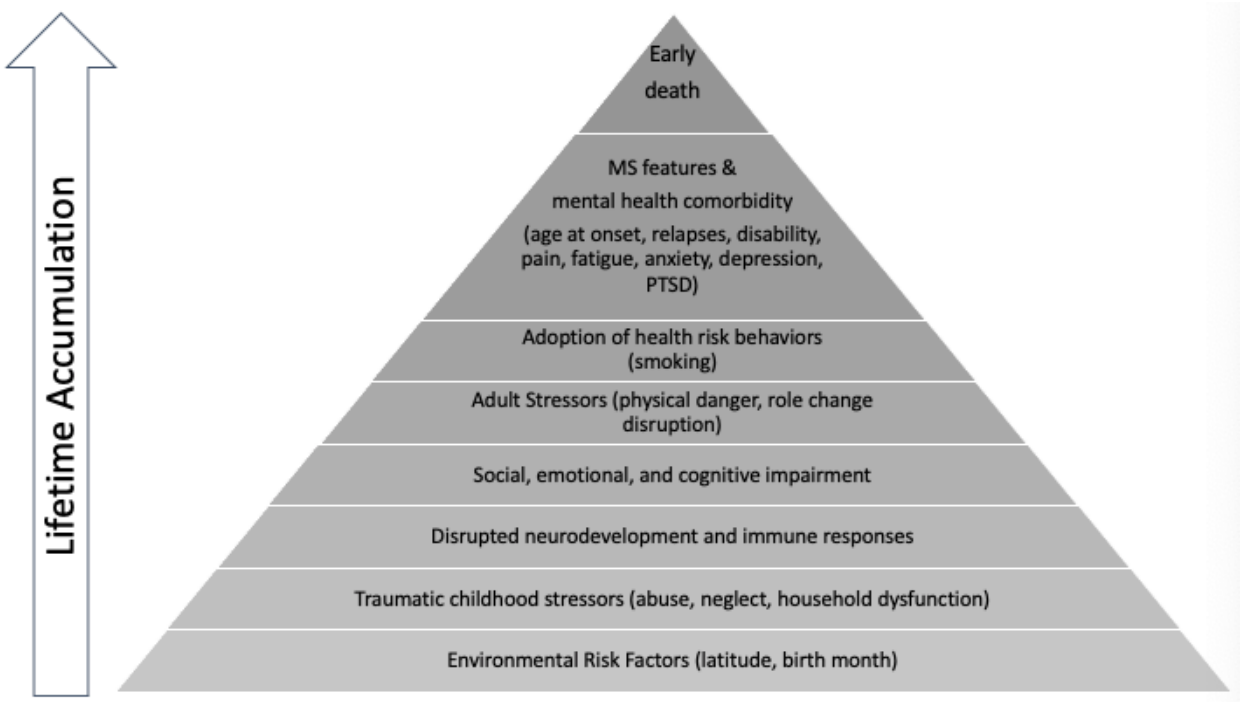


Figure 2. Adapted Model of Lifetime Environmental and Stressor Impact on MS



CHAPTER II

(Aim 1, Paper 1)
Childhood, Adult, and Cumulative Stressor Impact on Multiple Sclerosis Disability, Fatigue, Pain Interference, Relapses, Age at Onset and Mental Health Comorbidity.

Abstract

Background: Traumatic childhood stressors are associated with many negative biopsychosocial health outcomes including autoimmune or immune-mediated diseases and their clinical features. Childhood stressors can increase adult stress perception and may accumulate over the lifespan to impact Multiple Sclerosis (MS) disease features.

Aim: The aim of this cross-sectional study was to examine contributions of childhood and adult stressor characteristics (i.e., count, severity), with six individual MS features: self-reported disability, fatigue, pain interference, relapses, mental health comorbidity, and age at symptom onset.

Methods: People with MS (PwMS) were recruited through the National MS Society to take an online survey. Hierarchical block regression modeling was used to sequentially assess baseline demographic characteristics, childhood stressors, and adult stressors.

Results: Overall, 713 PwMS were included in the six final analytic models. Both childhood and adult stressors significantly contributed to pain interference, disability, and mental health comorbidity. Only childhood stressors significantly contributed to fatigue. Only adult stressors significantly contributed to relapse burden changes since

Covid-19. Age at symptom onset was not associated with any of the blocks of predictors. Childhood stressor severity independently significantly related to both fatigue likelihood and magnitude. Adult stressor severity was significantly correlated to relapse burden change and mental health comorbidity.

Conclusions: This work supports a relationship between stressors across the lifespan and some MS clinical features. Stressor severity may have an important role which may not be captured in count-based trauma measurement tools. This work and future work can help inform clinical decisions to support trauma informed precision medicine, research, and multi-level interventions for PwMS.

Background

Multiple Sclerosis (MS), an immune-mediated demyelinating inflammatory disease of the Central Nervous System (CNS) is the most common non-traumatic reason for young adult disability (Drori & Chapman, 2019; Perricone et al., 2019). Damage to myelin, a protective sheath around the axon of a neuron, disrupts messages between the brain and body (Colasanti et al., 2019; Sa, 2012). The United States (US) has the second highest prevalence rate of MS with 288 cases per 100,000 people, while the global rate is only 36 per 100,000 people (MS International Federation [MSIF], 2020). The US also bears the burden of approximately a third of all global cases (MSIF, 2020), and increasing mortality rates while mortality rates have been decreasing elsewhere (Magyari & Sorensen, 2019). Among other genetic and viral factors, MS risk is impacted by environmental factors such as latitude and birth seasonality (Drori & Chapman, 2019; Tao et al., 2016). There are relapsing and progressive forms of MS. Most people with MS (PwMS), 85-90%, have a Relapsing Remitting (RRMS) form

where their baseline is a remission phase (Drori & Chapman, 2019; Zephir, 2018). During a relapse phase, inflammation and myelin or axonal damage can progress, causing new or worse symptoms which typically improve overall when re-entering a remitting phase, yet some disability may remain.

Common MS symptoms include fatigue, pain, spasticity, vision, gastrointestinal, anxiety, and depression issues (Caligiore et al., 2017; Drori & Chapman, 2019; NMSS 2021). Mental and emotional changes can occur because of changes in the brain due to MS and could be seen as a symptom of MS (Hanna & Strober, 2020). However, mental health issues are also commonly considered comorbidities as mental and emotional symptoms and diagnoses can also simply co-occur with MS, especially since it is a chronic debilitating and uncurable illness (Hanna & Strober., 2020; Sharif et al., 2019; Tauil et al., 2018). For the purpose of this study, we use the term comorbidity, yet acknowledge that some of the mental health comorbidity may also be due to the MS disease process. There are many Disease Modifying Therapies (DMTs) available to help with disease management. Additionally, modifiable lifestyle factors such as smoking and maintaining a healthy weight can also impact symptom and disability burden due to associated inflammation (Stampanoni Bassi et al., 2020; Rosso & Chitnis, 2020).

Another potentially modifiable factor associated with an inflammation response is stress. When a threat is detected by the amygdala in the brain, it initiates a stress response to prepare the body to address the threat (e.g., fight, flight), and also initiates an immune response to address any injuries that may happen during a fight or flight (Lupien et al., 2009; McEwen & Seeman, 1999; Slavich, 2020). These physiological

responses involve immune cells (T-cells, and B-cells), cytokines and chemokines that have roles in MS neuro-inflammation and demyelination (Torres-Ruiz & Shoenfeld, 2019; Slavich, 2020; Zephir, 2018). According to the Social Safety Theory, humans have evolved to increase individual chances of survival by banding together in groups (Slavich, 2020). Real or perceived threats to social safety (e.g., physical/emotional abuse) can elicit the stress response to alter physiological processes, heighten perception of future threats, and responding behavior (e.g., social, emotional, cognitive) (Slavich, 2020).

The overall role that stress plays in MS pathogenesis and disease features is complex and considered somewhat controversial due to preliminary and conflicting evidence. Acute adult stress has been more widely accepted as having an impact on PwMS and their clinical features, as clinical trials and lab-based work can more easily simulate acute stress and measure outcomes. Adult stress has been significantly associated with MS onset and disease trajectory (Artemiadis et al., 2011; Jiang et al., 2020; Sharif et al., 2019). A large majority (88%) of the studies in the review by Artemiadis et al. (2011), and most in the review by Briones-Buixassa et al. (2015) support a relationship among stress and MS. Mohr et al., (2002) found significant relationships between the number, frequency, and duration of stressors preceding symptom exacerbation and relapses. For example, stressors were significantly associated with new MS lesions eight weeks later (OR= 1.62, 95% CI= 1.12- 2.34) (Artemiadis et al., 2011; Mohr et al., 2002). Even the presence of one stressor has been associated with exacerbation risk four weeks later (RR= 2.2, 95% CI= 1.2-4.0) (Artemiadis et al., 2011; Buljevac et al., 2003). More recently, prospective research has

shown that psychological stress is associated with more grey matter atrophy in the brains of PwMS (Meyer-Arndt et al., 2020). This is especially important as grey matter atrophy, a major component of MS disability progression, lacks drug therapy but does seem amenable to cognitive interventions (Meyer-Arndt et al., 2020). For example, stress reduction interventions have been associated with less lesion development for PwMS (Mohr et al., 2012; Sharif et al., 2019). However, acute stress can progress to chronic stress and accumulate, especially as the amygdala and stress response adapts and can become increasingly sensitive to threat detection over the lifespan, starting in childhood. Despite this evidence, few studies have linked childhood stressors and MS or used a lifespan approach to ascertain the cumulative effect of stressors on MS.

The impact that childhood stressors have on MS features remains understudied and more controversial than adult stress. Childhood is the developmental period when a sense of social safety begins, brain structures are malleable, and the foundation of physiological, social, and cognitive responses to stressors are formed (Slavich, 2020). Traumatic childhood stressors, such as abuse, neglect or living with someone with mental health struggles, can change brain structures, increase the perception of adult stress, pain perception, lead to poor or maladaptive coping skills and mental health comorbidity (Albott et al., 2018; Herman, 2015; McEwen et al., 2015; Tesarz et al., 2016). However, unlike acute stress in a lab, measuring traumatic childhood stressors and their impact on physical features of MS in adulthood is more challenging. Few studies have examined the effect of childhood stressors on *physical* MS features; however, most have found significant relationships despite differences in the measurement of trauma and confounders. Yet, heterogeneity in stressor measurement

may be contributing to conflicting results. Spitzer et al. (2012) first associated physical abuse, emotional neglect, and severe trauma all independently with relapse rates using the Childhood Trauma Questionnaire (CTQ). In 2017, Shaw et al. linked cumulative Adverse Childhood Experiences (ACEs) with an earlier age at MS onset in a small sample of US adults. Recently, childhood maltreatment was associated with adult MS fatigue (Pust et al., 2020) and pain catastrophizing (MacDonald et al., 2021). Yet, Horton et al. (2022) did not consistently find a relationship between childhood stressors and age at onset, MS severity, or walking disability. Also recently, research has expanded to the effect of childhood stressors on *mental health* clinical features, finding positive relationships to psychiatric comorbidity (Wan et al., 2022) and anxiety (Eilam-Stock et al., 2021). None of these studies captured the accumulation of stress across the lifespan, and most had a limited sample size. Therefore, a lifetime approach may help elucidate when stressors have the most impact on MS age of onset, severity, and features.

This study fills gaps in the literature regarding the lack of a lifespan approach, consideration for MS specific covariates, and limited sample sizes, also while expanding to unexplored clinical features of MS. The purpose of this study is to examine relationships among comprehensively measured stressors across the lifespan (e.g., child, adult, count, severity, expanded criteria), and six MS disease features of disability, fatigue, pain interference, mental health comorbidity, relapses burden change since Covid-19, and age at onset, in a large national US sample of PwMS. Hierarchical block modeling helps to determine the importance of stressor timing (child vs. adulthood) to better inform preventative and mitigation efforts. We hypothesize that successive

models with a cumulative childhood stressor block and cumulative adult stressor block will contribute significantly more predictive variance over the previous nested models when assessing each clinical feature.

Methods

This study utilized data collected through a self-report online survey of PwMS.

Recruitment

Eligibility screening questions ensured that participants were US based adults officially diagnosed with MS. Individuals with MS symptoms but without a diagnosis were excluded. The vast majority of participants received an invitation and link to a 20-30 minute self-administered online survey through the National MS Society (NMSS) listserv of approximately 80,000 people; although, some may have found the study through the NMSS website or social media engagement. Few participants (n=23) took the survey via these methods before the listserv email. Participants were entered into a raffle for one of seven $25 or $50 electronic gift cards. Institutional Review Board (IRB) approval was obtained from the University of Michigan.

Measures

Stressors

The Stress and Adversity Inventory (STRAIN) measures multi-faceted aspects of stressors across the lifespan encompassing 55 stressors including childhood physical abuse or neglect, sexual abuse, household dysfunction, parental divorce, housing instability and adult stressors such as domestic violence, work, infertility, and financial strain (Slavich & Shields, 2018). If a participant endorsed that a stressor happened, follow up questions captured the age at which it happened and stressor severity.

Stressor severity items are scored on a Likert scale from “Very slightly or not at all” to “Extremely”. Individual stressful event items were summed to create total count. Higher scores for severity or count represent higher stress levels. Stressors were assessed as cumulative childhood count/severity and cumulative adult count/severity. The STRAIN has been validated with autoimmune populations inclusive of MS, and has demonstrated good test-retest reliability (Cazassa et al., 2020; Slavich & Shields, 2018).

Outcomes

Patient Reported Outcome Information System (PROMIS) tools were used to measure Pain interference and fatigue. The PROMIS-Pain Interference (8a) is a validated 8-item questionnaire which measures the impact of pain on the mental, physical, and social aspects of an individual’s life in the past week (Amtmann et al 2010). It has previously been used with a sample of PwMS (Braley et al., 2020). The items are scored on a Likert scale from 1 (not at all) to 5 (very much), with higher scores indicating more pain interference. The scale reliability was very high in this study (Cronbach’s alpha= .98).

The PROMIS-Fatigue MS SF is a validated 8-item questionnaire to measure fatigue in the last week specifically in the MS population (Cook et al., 2012; Senders et al., 2014). Questions include “How often did you have to push yourself to get things done because of your fatigue?” Items are scored on a Likert scale ranging from 1 (never) to 5 (always), with higher scores indicating more fatigue. The scale reliability was very high in this study (Cronbach’s alpha=.95).

Patient Determined Disease Steps (PDDS) is a validated patient reported scale of *MS disability* (Learmonth et al., 2013; Marrie and Goldman, 2007). This is a 1-item

scale with scores ranging from 0-8 representing the progression from normal function (0) to being bedridden (8) (Learmonth et al., 2013). Scores are commonly converted to categorical outcomes for interpretability of mild, moderate, or severe disability (Learmonth et al., 2013), which was implemented in this study.

Participants responded to a single item developed for this study that assesses *change in relapses since the onset of Covid-19*, approximately March 2020. Response options included: they had no relapses, no change, positive changes (e.g., less painful, less fatiguing, less disabling shorter), or negative changes (e.g., more painful, more fatiguing, more disability, longer). Responses were categorized into an ordinal variable representing no relapses (0), lighter relapse burden (1), no change (2), and worse relapse burden (3).

Mental health comorbidity is a composite count score encompassing multiple binary (yes/no) questions about having any current symptoms of anxiety or depression, ever having a psychiatric diagnosis (e.g., bipolar, schizophrenia, Post Traumatic Stress Disorder [PTSD], anxiety, depression), or ever having a hospitalization event due to a psychiatric or substance use issue. This composite count method has been used in previous research (Wan et al., 2022). Scores were summed with a possible range of 0-6 with higher scores representing more mental health comorbidity.

Age at symptom onset was asked as a free text question and converted to a continuous numeric variable.

Covariates

Demographic (e.g., education, gender) and standard MS specific variables such as phenotype, treatment type, and age at diagnosis were collected. MS specific

covariates include smoking status, birth month and the city that participants spend the most time in growing up. *Birth month* was categorized into seasons and adjusted for equivalency depending on the hemisphere where they lived before moving to the US. Google maps was used to convert all cities into a positive *latitude* variable to represent total degrees from the equator, despite hemisphere. A count of different *types of medications* that can impact pain (e.g., opiates, antidepressants) was also collected and used in pertinent analyses such as the pain interference and mental health comorbidity outcomes.

Data screening and pre-processing

Data were collected by self-report online surveys that allowed participants to skip items that they preferred not to answer and involved merging data from two separate survey platforms (i.e., REDCap, STRAIN). The data were reviewed carefully for data entry errors, missing data, out of range items, matching, duplicates, and merge errors. The raw scores from the PROMIS scales were transformed to the t-score metric (healthmeasures.net). We then replaced scores representing “no pain” or “no fatigue” with zeros to evaluate these outcomes appropriately using a two-part statistical model as described below.

We evaluated the extent of missing data and assessed for patterns in missingness to determine the best analytic strategy. The demographic and MS variables were missing very few responses throughout the 924 responders who were matched (0-1.19% of 924), with the notable exception of participants’ self-reported race/ethnicity which was missing 39.7%, and we did not identify specific patterns of missingness among these items. Regarding the missing race data, the primary reason

for this missing data is due to a survey skip pattern error. We identified and fixed this error during data collection and employed a follow-up survey for the participants who had already completed the survey. Most participants (n=697) responded to this follow-up survey, but unfortunately some did not use the same or similar study ID, making matching results impossible. This resulted in a final dataset that could include race/ethnicity of n=205-473 across two-part modeling, versus a much larger sample size of n=459-713 if we exclude race/ethnicity from our modeling. This data collection issue, compounded by an 88% White sample among those who did self-report, as well as the inability to truly disentangle race from other determinants of health while assessing both stressors and MS features, prompted us to omit race from the main analyses and focus on race in subsequent subgroup analyses. These efforts align with our goal to thoughtfully reconsider what race truly contributes for a disease like MS, versus what the social and health systems surrounding race contribute to different outcomes for different races (Amezcua & McCauley 2020). Using race as a predictor in the main analyses could attribute the onus of disease factors on race, while other factors are likely contributing as well. For example, there are many inequities in healthcare access and treatment for minoritized populations with MS (Amezcua & McCauley, 2020; Amezcua et al., 2021; Jefferson, 2021). MS is so widely associated with European descent that healthcare providers, and patients themselves, may not initially pursue MS as a root cause of the symptoms that the patient presents with. Medical insurance issues can also be a barrier due to the high cost of DMTs; this may mean that PwMS who cannot afford the out-of-pocket costs may be left untreated (Langer-Gould et al., 2021). There is also evidence that low-income minorities with MS have experienced

care deficiencies such as not receiving specialty care and not being on a DMT due to poor understanding of the medication and implications, which may be secondary to challenges with trusting White medical providers (Amezcua & McCauley 2020; Okai et al., 2022). These factors and similar structural factors such as inequitable health care access can lead to diagnostic delays (Amezcua et al., 2021), allowing more time for brain lesions to progress, which may then represent a higher disease burden, older age at diagnosis, and poorer outcomes for minoritized PwMS which contrasts from race related genetic differences between groups.

We encountered moderate levels of missing data among stressor variables. All four stressor variables were missing 208 (22.5%) participants. No specific patterns were found, and we believe the missingness is related to the survey platform being overwhelmed with participants all simultaneously engaging immediately after the email delivery. Given that asking about stressors requires disclosure of sensitive information, which could be underreported, it cannot be assumed that the stressor values were missing at random, a necessary assumption of multiple imputation, and therefore we report analyses of complete case data only.

Sample size determination

We conducted a power analysis to inform the target sample size necessary to have 80% power to detect statistically significant improvements in fit between the nested models. These calculations suggested a minimum sample size of 332 was needed to detect at least a 4% change between models, assuming a 2-tailed alpha for significance testing (0.05).

Analytic strategy

Broadly, our analytic approach aimed to assess fit of increasingly complex models that include blocks of related predictors to determine if their contributions provided improved model fit overall, prior to evaluating the contributions of individual predictors in the most parsimonious model. If a block of predictors did not significantly improve the model, it was removed from the final analytic modeling. Table 2.1 shows the predictors included in each of three blocks, with each model nested within the next higher-level model. Assumption testing for all models included assessing for normality, residuals, heteroskedasticity, outliers and collinearity.

Specifically, our approach was to assess if stressors across the lifespan contribute to each of the six outcomes (i.e., pain interference, fatigue, age at onset, disability, relapses, and mental health comorbidity) while accounting for demographics and MS covariates. Per Table 2.1, our base model included only sociodemographic (e.g., gender, education) and MS variables (i.e., phenotype) to determine the baseline contributions to each of the six outcomes. Next, we compared model fit of the base model to our second model which included the base predictors plus a set of childhood stressor predictors (Table 2.1) to determine if these early stressors contribute to MS outcomes over and above the base model. Finally, we added a third set of predictors evaluating the contributions of adult stressors per Table 2.1 to determine if they contributed additional predictive variance overall. Each successive model was compared to the prior model using likelihood ratio testing, and we report Akaike Information Criterion (AIC) as an index of relative model fit, with a lower number indicating better fit. In addition to evaluating contributions of related blocks of

predictors, we then focused our attention to the contributions of individual predictors in the most parsimonious final model (i.e., the model revealing significantly better fit than the prior nested model, without unnecessarily including blocks of predictors that did not contribute significantly to model fit).

Per our evaluation of reasons for missing data described above, and consistent with our goals of comparing successively more complex statistical models, only participants that submitted data for all variables in the full model were included in model comparisons. In this way, we focus our evaluation of increasingly complex models squarely on the addition of predictors, while maintaining the same subjects across models. Participants that informed any model for any aim are characterized in Table 2.2. Outcomes based on the final sample (n=713) were compared to the outcomes for the remaining participants not included due to missing variables (n=211). We found no significant differences across outcomes between samples, except for fatigue magnitude, where we found that the final included sample had a slightly lower median fatigue score (58) than the excluded sample (60). We acknowledge this as a possible limitation to our evaluation of this outcome.

For the normally distributed continuous outcome variable, age at symptom onset, we used ordinary least squares (OLS) linear regression, followed by likelihood ratio tests for model comparisons. For our two ordinally scaled outcome variables, disability and relapses since Covid-19, logistic regression was used. We used Poisson regression with the count of mental health comorbidities outcome variable. The two PROMIS outcomes, pain interference, and fatigue, represented a mixed distribution depending on participants responses. That is, some PwMS reported no

fatigue or pain interference, while others reported the magnitude of their fatigue or pain interference. These outcomes represent a mixed distribution including a dichotomous (yes/no) component of experiencing pain interference or fatigue, followed by a normal distribution characterizing the magnitude of interference or fatigue for participants who answered yes. Therefore, we utilized two-part modeling to evaluate the contributions of our predictors in Table 2.1 on both the presence and magnitude of these outcomes. The first part in these models utilized logistic regression for evaluating the contributions of predictor(s) on the presence/absence of pain or interference, and contingent on having an outcome rating, the second part utilized OLS linear regression to assess the level of pain interference or fatigue.

For the subgroup analysis, outcomes were assessed by median and Interquartile Range (IQR) to allow for evaluation of more categories across racial/ethnic groups.

Results

Participants

Of the 713 participants included in any of the final analytical models, most were female (n = 597, 84%), White (n= 415, 88%), with Relapsing Remitting MS (n= 559, 79%), aligning with the MS population (NMSS, 2022b; Table 2.2). Compared to the normalized T-scores of a healthy general population who's Mean (SD) is 50(10) (Cella et al., 2010), this sample had higher fatigue on average 57 (9) and with median (+/- IQR) 58 (52-63). Pain interference was similarly higher regarding the median 54 (IQR 41-62) and mean 53 (10.5). The average length of time since symptom onset was 18 years (SD 12). Most participants were on a second line Disease Modifying Therapy (n=308, 44%), and had mild disability (n=365, 52%). The average number of stressors

experienced in childhood was 2.6(1.96) with a severity of 9.8(8.8), while the average number of stressors during adulthood was 23.6 (14) with a severity of 55.4 (30.8).

Disability

The base model including demographic and MS history predictors contributed significantly estimating disability (R^2=.256, p<.001; model AIC=1066) (Table 2.3). The childhood stressors in model 2, contributed a significant amount of variance over the base model (R^2=.261, p<.001; AIC=1063, LR p<.05). The adult stressor predictors in model 3 also contributed significantly more information over the prior nested models (R^2=.2725, p<.001, AIC=1051, LR p<.001), resulting in our final disability model which includes all predictors from all models.

In addition to the overall blocks of predictors significantly contributing to disability, individual predictors were also significant in the final model. Participants born in the Spring had 39% higher odds of disability compared to those born in the summer (OR=.61, p<.05) and winter (OR=.61, p<.05). Compared to RRMS, those with PPMS (OR= 23.1), SPMS (OR= 15.6), and PRMS (OR=31) all had significantly increased odds of disability at the p<.001 level.

Pain Interference

The base model of predictors contributed to a significant overall two-part model estimating the likelihood and magnitude of having pain interference (logistic regression pseudo R^2=.2219, p <.001; OLS regression R^2=.1831, p<.001; model AIC=3751) (Table 2.4). The childhood stressor block of predictors in model 2 improved predictions significantly over the base model (logistic regression pseudo R^2=.2448, p <.001; OLS regression R^2=.2152, p<.001; model AIC=3719, LR p<.001). Similarly, the adult stressor

predictors in model 3 contributed significantly more information over the prior nested modes (logistic regression pseudo R^2=.2578, p <.001; OLS regression R^2=.2667, p<.001; model AIC=3685, LR p<.001). Table 2.4 shows the overall block and independent contributions of each predictor in both components in this two-part model. Specifically, each predictors' contributions to the likelihood of reporting any pain interference (the logistic part of the model), as well as the magnitude of interference (OLS regression) when reported using all three blocks of predictors, as they all had significant impact on pain interference.

Regarding individual predictors, childhood stress severity was significantly associated with the magnitude of pain interference (b=.33, p=.005) in model 2 but lost significance when adult stress was added for model 3, suggesting shared covariance with the outcome among child and adult stressors. In the final analytic model, age impacted both the likelihood (OR 1.02, p<.03) and magnitude (b=-.10, p<.001) of pain. Compared to RRMS, participants with SPMS (b=2.58, p<.01) and PRMS (b=5.71, p<.02) reported more pain interference. Participants on a second line DMT, compared to no treatment, had double the odds of experiencing pain interference (OR= 2.22, p<.01). Not surprisingly, multiple levels of college education were significantly associated with lower pain interference and magnitude.

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=.074, p<.04; OLS regression R^2=.086, p<.001; model AIC=4192) (Table 2.5). The childhood stressor predictors in model 2 contributed a significant amount of variance

over and above the base model (logistic regression pseudo R^2=.11, p<.02; OLS regression R^2=.14, p<.001; model AIC=4160, LR p<.001). While adult stressor severity was independently significant for the magnitude of fatigue (b=.073, p=.001), overall, the adult stressor predictors in model 3 did not significantly contribute and reduced model fit (logistic regression pseudo R^2=.136, p=.004; OLS regression R^2=.242, p<.0001; model AIC= 4844) LR p=1.0). Thus, adult stressors were removed from the final analytic model shown in Table 2.5, as only base covariates and childhood stressors impacted fatigue.

In our final most parsimonious 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=.03), and with the magnitude of fatigue (b=.47, p<.001). Interpreting this in context of the average childhood stress severity (9.8) translates to the average PwMS in this sample is 235% more likely to experience fatigue. Childhood stressor count (b= -1.23, p<.04) and age (b= - .07, p=.019) were both negatively associated with the magnitude of fatigue. SPMS was also significantly associated with fatigue magnitude (b=2.34, p<.03).

Mental health comorbidity

The base model of predictors contributed significantly estimating the risk of experiencing mental health symptoms, diagnoses, or event (R^2=.061, p<.0001; model AIC=2560) (Table 2.6). The childhood stressor predictors in model 2 significantly improved over the base model (R^2=.09, p<.0001; AIC=2485, LR p<.0001). Similarly, the adult stressor predictors in model 3 contributed significantly more information over the prior nested modes (R^2=.116, p<.001, AIC=2420, LR p<.0001). Therefore, childhood and adult stressors impact mental health comorbidity for PwMS.

Regarding individual predictors, adult stress severity was significantly associated with mental health comorbidity (IRR=1.01, p=.002). As adult stressor severity increased by 1 unit, the risk of having an additional MH condition, event, 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 mental health comorbidity for each 1-unit increase in severity rating, however lost significance when adding the adult stressors for model 3. In the final model, the risk of mental health comorbidity decreased by 2% for each year since MS onset (IRR=.98, p<.001).

Relapse burden change since Covid-19

The base model of predictors estimated the relapse burden since the onset of Covid-19 (R^2=.0455, p<.001; model AIC=1581) (Table 2.7). The childhood stressors in model 2 increased the variance over the base model (R^2=.048; AIC=1580) and was an overall significant model (p<.001), however, likelihood ratio testing revealed that it was not significant compared to the previous nested base model (LR p=.08). The adult stressors in model 3 contributed significantly more information over the prior nested model (R^2=.0534, p<.001, AIC=1572, LR p<.01), therefore only the base demographics and MS covariates and adult stressor block of predictors remained in the final analytic model shown in Table 2.7.

Regarding individual predictors, childhood stress severity was significantly associated with relapse change (b=.07, p=.03) in model 2, however, this lost

significance when adding the adult stressor block for model 3. With each year age increased, there was a 2% reduction in relapse burden.

Age at onset

Our base model did not contribute significantly to estimating age at symptom onset (R^2=.019, p=.3; model AIC=5221), suggesting that these demographics alone were not sufficient in explaining age of symptom onset. We added the child stressors in model 2 and the adult stressors from model 3. While these additional predictors increased the variance over the nested models (model 2 R^2=.052, p=.18, AIC=5220; Model 3 R^2=.03, p<.143, AIC=5220), these model improvements were not statistically significant (model 2 LR p=.095, model 3 LR p=.19).

Subgroup analysis of race / ethnicity

Due to the low number of responses within some race/ethnic groups, we were unable to include indicators of all racial/ethnic groups in our main analyses. Instead, we needed to collapse the Latinx, Asian, American Indian/Alaska Native, and the Native Hawaiian/Pacific Islander groups into one category named combined. However, we wanted to examine differences in MS outcomes by race/ethnicity. Additionally, we used a missing category to demonstrate how the missing group may differ from the other groups. We report descriptive data, median and Interquartile Range (IQR), so that the largest possible sample could be shown, unrestrained by other potential missingness in other variables.

All groups had a similar median disability of 1 or mild (IQR 1-2), except the combined group which had a slightly smaller IQR, likely impacted by the small number of people in that group (n=12; Appendix A). Black PwMS had the highest median pain of

58, (IQR 41-65) while the combined group had the lowest of 44 (IQR 41-58). Regarding fatigue, all groups were similar again with all medians between 57-60. All groups had a median score of two mental health comorbidities except the Bi-racial or mixed-race group which had 3 (IQR 2-4). Age at onset was earliest for Black PwMS, median age 25.5, (IQR 21-36), followed by the combined group of age 27, (IQR 22-32). White and the bi-racial / mixed race groups both had a median age of 29, while the latest onset was the missing group at age 30, (IQR 23-37). All groups had a median relapse burden change of 2, representing no change, while Black PwMS had a median of 3, representing a worse burden (IQR 2-3).

Discussion

This is the first study to use a lifetime approach to comprehensively measure the effect of child and adult stressors on six physical and mental features of MS. Specifically, we investigated relationships among stressors and MS disability, fatigue, pain interference, age at onset, relapses burden since Covid-19, and mental health comorbidity using hierarchical block modeling. Using block modeling allowed us to determine the overall contribution of similar stressor variables, count and severity, regardless of the individual variable contribution. As seen in summary Table 2.8, child and/or adult stressor blocks significantly contributed, over and above covariates, to all outcomes except for the age at symptom onset. Disability, pain interference, and mental health were significantly impacted by both child and adult stressors. Fatigue was impacted only by childhood stressors, while relapse burden change was impacted by only the adult stressors. The timing of stressors may impact the six outcomes differently based on inflammatory and cognitive response mechanisms. For example, adult stress

may have been more acute, elicited inflammatory markers (e.g., cytokines), and led to relapses or increased pain perception.

In addition to significant stressor blocks, some individual childhood predictors were also significant. In the final models, child stressor severity independently correlated with both the likelihood of having any fatigue and the magnitude of that fatigue, as well as mental health comorbidity in PwMS. Childhood stressor severity was significant for three outcomes, pain interference, relapses, and mental health comorbidity, but lost significance when further accounting for adult stressors. This highlights an important intersection of measurement differences (e.g., child or adult only) throughout the literature and the concept of stressor accumulation across the lifespan. Experiencing traumatic stressors in childhood can alter brain structures and functions, including heightened perception of threat, leading to increased stressful experience as an adult (Albott et al., 2018; McEwen et al., 2015). Through this pathway, childhood adversity may still contribute to findings when only adult stressors are significant, because these individuals may already be primed for increased adult stress based on their childhood trauma.

This work both aligns and conflicts with prior research. It supports findings that traumatic childhood stressors impact fatigue (Pust et al., 2020), pain features (MacDonald et al., 2021), and mental health (Eiliam-Stock et al., 2021; Wan et al., 2022) in PwMS or Immune Mediated Inflammatory Disease (IMID) including PwMS. Revealing that each incremental increase in childhood stressor severity increases the odds of experiencing fatigue by 24% is an important finding because fatigue is the most common symptom of MS. This work conflicts with studies that *did not* find associations

between childhood trauma and disability (Horton et al., 2022; Spitzer et al., 2012). This work also conflicts with studies that *did* find correlations between childhood trauma and an earlier age at MS onset (Shaw et al., 2017), and relapse rates (Spitzer et al., 2021). However, measurement and confounder heterogeneity among the few related studies makes direct comparisons challenging. Measurement inconsistencies regarding demographic and MS specific confounders may also contribute to conflicting results and continued debate over how much stress across the lifespan truly impacts MS. Our findings suggest that childhood stressor severity plays a larger role than stressor count. Studies that use the ACE tool, or other measures that strictly capture stressor count, may be more likely to have null results compared to studies that capture more nuanced stressor information like severity, duration, or frequency (Horton et al., 2022). Similarly, studies that don't include adult stressor experiences may show stronger relationships to childhood stressors.

This work also supports previous work linking adult stressors and MS relapse (Briones-Buixassa et al., 2015; Mitsonis et al., 2008), and symptoms (Brenner et al., 2018; Sorenson et al., 2014). However, the adult stress literature typically focuses on shorter periods of time and does not generally take a lifetime approach. Adult stressor severity independently correlated with relapse burden change since Covid-19. While the overall adult stressor block was not significantly different from the previous model in the fatigue assessment, adult stressor severity was independently significant with the magnitude of fatigue. This suggests that stress management interventions may help alleviate the severity of fatigue in PwMS.

As PwMS age, the risk of mental health comorbidity 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. 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. To confirm this, future studies should incorporate positive experiences that may attenuate the impact of childhood stressors over time, such as therapy and social support with humans and pets. Similarly, we found that higher education was related to better outcomes across most clinical features, and 71% of the sample had at least a bachelor's degree. This may indicate that this sample either had fewer barriers to education or were especially resilient despite their barriers. This may also indicate that stressor relationships could be even stronger in a sample that experienced more adversity, relied on less effective coping strategies, and/or achieved lower levels of education.

Regarding covariates, or other factors that may impact MS disease features, education was generally related to better outcomes across all clinical features. Our study found that birth seasonality impacted disability. Seasonality is more conventionally included in studies assessing MS incidence risk and until now, has not been included in studies assessing childhood or lifetime stressors and MS features. Similarly, a recent review revealed that race/ethnicity was not accounted for in a third of the studies assessing stressors and MS risk or features (Polick et al., 2022). MS samples are largely White so even when studies do include race/ethnicity analyses and interpretation, small individual cell sizes typically lead to collapsing multiple categories

into a dichotomous white/all others variable; to abide by ethical standards to protect participant identity and create less statistical error variance. However, this approach is not optimal to discern unique racial/ethnic experiences and outcomes; especially when inclusive sampled are needed to address health disparities and inequities in research, outreach, and intervention (Okai et al., 2022). This study did not control for race in the main analyses and instead did a larger subgroup analysis, reporting the maximum number of categories containing at least five people, to increase reporting transparency.

Implications

This study highlights the impact of stressors across the lifespan to conceptualize when stressors matter most, which stressors matter, and how nuanced aspects like severity, duration or frequency may also be critical factors. Future research is needed to examine differences in these relationships for different racial/ethnic groups to highlight how the stressors, MS experiences (e.g., disparities in diagnosis time and treatment), and outcomes may differ. Like most health-related research, this study demonstrated a buffering effect that education can have on disease process and outcomes. Education is often connected to income and health insurance which likely increases healthcare access and treatment. This finding lends additional support for policies and programs that can break down barriers to help people overcome adversity so they can stay in school, reconnect to school, and achieve a college education if they desire it (Stoddard et al., 2020).

Clinical implications of the findings from this study include support for stressor screening, referrals to services such as mental health support, and increased potential for trauma informed precision medicine. For example, instead of using stimulant

medication to treat fatigue, perhaps Cognitive Behavioral Therapy (CBT), would be a non-pharmacological solution for PwMS that have a high history of stressors. Future work can help discern whether people with childhood trauma would respond better to CBT and therefore screening could provide information clinicians could use to tailor treatment options. Eilam-Stock et al. found that ACEs measured at MS diagnosis predicted increased anxiety a year later, indicative of decreased coping when faced with the additional stressor of having a chronic disease (2021). Connecting patients with support services earlier in the disease process may help decrease mental health comorbidity. There is evidence to suggest that this, in turn, may also help decrease symptoms of pain, fatigue, relapses, and subsequently some disability, with the potential to increase treatment adherence and quality of life (Koltuniuk et al., 2021; MacDonald et al., 2021; Pust et al., 2021, Xie et al., 2020).

Limitations

Since this study uses cross sectional data, causal inference cannot be determined. Yet, as the first study to assess many of these relationships with an MS focused sample, it fills an important gap. Future longitudinal studies are needed to confirm these relationships. Those who responded may have increased ability to take an online survey (e.g., technology access, less disability). A bias may be present due to the high number of PwMS on the NMSS listserv. Self-reported retrospective data has potential for recall bias and the phenomenon of “effort after meaning” for PwMS who may report more stressors to explain their disease. Sensitive information such as stressors are typically more likely to have a social desirability bias and be under-reported than over-reported. However, the online format and anonymity may have

facilitated more accurate reporting compared to other data collection formats. Recrudescence could not be ruled out with self-report data. Our sample was mostly White college graduates with a bachelor's degree or above (71%) and thus does not represent all groups, especially those who may have faced additional adversity. However, the sample does capture PwMS from all over the US and people born abroad that have moved to the US. Additional strengths are the relatively large sample size, assessing stressors across the lifespan, and including a wide range of covariates. To date, only one published study has included a larger sample of PwMS but included only childhood adversity count (Horton et al., 2022), and much heterogeneity remains throughout the literature.

Conclusion

These finding support an association between childhood stressors and pain interference, fatigue, disability, and mental health comorbidity; as well as adult stressors associating with pain interference, mental health comorbidity, disability, and relapse burden since Covid-19 for PwMS. Additional studies are needed to assist clinical efforts of trauma informed precision medicine and intervention efforts to mitigate stressor impact on PwMS. Future research should replicate this work with more diverse MS samples and expand the focus to include other positive aspects (e.g., coping, resiliency, social support) and clinical features (e.g., sleep, cognition, substance use).

Table 2.1 Predictors per Hierarchical block modeling approach

Sequential modeling	Predictors per each model
Base model 1: demographics and MS covariates	Tailored per outcome
Model 2 adds childhood stressors	Base model + Childhood stressor count, childhood stressor severity
Model 3 adds adult stressors	Model 2 + Adult stressor count, adult stressor severity

Table 2.2. Sample characteristics

Age M(SD) (n=713)	49(12.7) range: 21-85
Gender n(%) (n=713)	
Female	597 (84%)
Male	100 (14%)
Transgender, non-binary, gender non-conforming or other	15 (2%)
Race / Ethnicity n(%) (n=473)	
White	415 (88%)
Black	23 (5%)
Latinx	2 (<1%)
Asian	4 (<1%)
American Indian or Alaska Native	2 (<1%)
Native Hawaiian or Pacific Islander	1 (<1%)
Bi-racial or mixed	24 (5%)
Education n(%) (n=713)	
High school, GED, or below	36 (5%)
Associates degree or some college	167 (23%)
Bachelor's degree	259 (36%)
Master's degree or above	251 (35%)
Smoking status n(%) (n=709)	
Never smoker	465 (66%)
Former smoker	198 (28%)
Current or social smoker	46 (6%)
Latitude M(SD) (n=713) M(SD)	39(6) range: 10-65
Birth Season n(%) (n=710)	
Spring	187 (26%)
Summer	175 (25%)
Fall	178 (25%)
Winter	170 (24%)
MS Phenotype n(%) (n=713)	
RRMS	559 (79%)
PPMS	35 (5%)
SPMS	87 (12%)
PRMS	9 (1%)
Unsure	23 (3%)
Length of time since MS onset M(SD) (n=713)	18 (12) range: 0-59
Disease Modifying Therapy (DMT) n(%) (n=709)	
None	129 (18%)
First line	272 (38%)
Second line	308 (44%)
Count of medication classes that can impact pain M(SD) (n=705)	1.63 (1.29) range: 0-5
Stressors M(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	
Disability (PDDS) n(%) (n=706)	
Mild	365 (52%)
Moderate	236 (33%)
Severe	105 (15%)
Fatigue, median (IQR), M(SD) (n=713)	58 (52-63), 57(9)
Pain interference, median (IQR), M(SD) (n=713)	54 (41-62), 53(10.5)
Age at MS symptom onset M(SD) (n=713)	24 (11)
Relapse change since Covid-19 (n=675)	
No relapse	198 (29%)
Improved	26 (4%)
Stayed the same	242 (36%)
Worsened	209 (31%)
Mental health comorbidity count M(SD) (n=713)	2.2 (1.7) range: 0-6

Table 2.3 Final analytic model of Disability using logistic regression (n=695)

					Overall model statistics		
	OR	**SE**	**95% CI**	**P**	**R^2**	**AIC**	**LR test**
Base covariates				**<.0001**	.2560	1066	base
Age	1.05	.01	1.03 - 1.07	**<.001**			
Gender (ref. female)							
Male	1.10	.27	.67 - 1.78	.72			
Transgender, non-binary, gender non-conforming	.47	.29	.14 - 1.58	.22			
Education (ref. ≤HS)							
Associates degree or some college	.82	.33	.37 - 1.78	.61			
Bachelor's degree	.52	.21	.24 - 1.14	.11			
Master's degree or above	.33	.13	.15 - .72	**<.01**			
Smoking status (ref. neve smoker)							
Former smoker	1.08	.21	.74 - 1.59	.70			
Current or social smoker	1.83	.64	.93 - 3.64	.08			
Birth season (ref. Spring)							
Summer	.61	.14	.39 - .97	**<.04**			
Fall		.16	.43 - 1.06	.09			
Winter	.61	.14	.38 - .97	**<.04**			
Time since MS onset (years)	1.02	.01	1.00 - 1.04	**<.05**			
MS Phenotype (ref. RRMS)							
PPMS	23.07	9.76	10.07 - 52.84	**<0.001**			
SPMS	15.57	4.52	8.82 - 27.50	**<0.001**			
PRMS	31.26	24.41	6.77 - 144.41	**<0.001**			
Unsure	1.47	.73	.55 - 3.91	.44			
DMT (ref. No therapy)							
First line	.70	.18	.43 - 1.14	.15			
Second line	1.55	.38	.96 - 2.52	.08			
Childhood stressors				**<.0001**	.2611	1063	**.03**
Child stressor count	1.27	.20	.93 - 1.73	.13			
Child stressor severity	.95	.04	.88 - 1.02	.14			
Adult stressors				**<.0001**	.2725	1051	**.0004**
Adult stressor count	1.01	.02	.98 - 1.05	.40			
Adult stressor severity	1.01	.01	1.00 - 1.03	.25			

Table 2.4 Final analytic model of Pain interference using two-part regression modeling

	First part - logistic regression (n=701) **Any pain interference (binary)**					**Second part** - OLS regression (n=459) **Magnitude of pain interference**				**Overall model stats**		
	OR	**SE**	**95% CI**	**p**	**Pseudo R^2**	**b**	**SE**	**95% CI**	**p**	**R^2**	**AIC**	**LR test**
Base covariates				**<.0001**	0.2219				**<.0001**	.1831	3751	Base
Age	1.02	.01	1.00 -1.04	**.02**		-.10	.03	-.16 - -.05	**<.001**			
Gender (ref. female)												
Male	.65	.18	.38 - 1.11	.12		1.09	.93	-.74 - 2.92	.24			
Transgender, non-binary, gender non-conforming	1.21	.88	.29 - 5.06	.80		-2.12	1.91	-5.86 - 1.63	.27			
Education (ref. ≤HS)												
Associates degree or some college	.13	.11	.03 - .65	**.01**		-.86	1.23	-3.27 - 1.55	.47			
Bachelor's degree	.09	.07	.02 - .44	**<.01**		-2.88	1.22	-5.26 - -.50	**.02**			
Master's degree or above	.08	.07	.02 - .40	**<.01**		-3.43	1.23	-5.83 - -1.03	**<.01**			
MS Phenotype (ref. RRMS)												
PPMS	1.44	.69	.57 - 3.67	.44		.33	1.37	-2.37 - 3.02	.81			
SPMS	1.57	.54	.81 - 3.07	.18		2.58	.91	.80 - 4.36	**<.01**			
PRMS	1.35	1.29	.21 - 8.8	.75		5.71	2.36	1.08 - 10.35	**<.02**			
Unsure	1.13	.63	.38 - 3.35	.82		2.81	1.70	-.52 - 6.14	.10			
DMT (ref. No therapy)												
First line	1.49	.43	.85 - 2.61	.17		-.63	.91	-2.39 - 1.14	.49			
Second line	2.22	.65	1.25 - 3.95	**<.01**		-1.32	.86	-3.01 - .38	.13			
Pain med count	2.31	.23	1.90 - 2.80	**<.001**		1.02	.24	.56 - 1.48	**<.001**			
Childhood stressors				**<.0001**	.2448				**<.0001**	.2152	3719	**<.0001**
Child stressor count	1.19	.22	.83 - 1.71	.34		-.58	.54	-1.63 - .47	.28			
Child stressor severity	.99	.04	.91 - 1.07	.73		.14	.12	-.10 - .38	.24			
Adult stressors				**<.0001**	.2578				**<.0001**	.2667	3685	**<.0001**
Adult stressor count	1.04	.02	1.00 - 1.08	.07		.06	.05	-.04 - .16	.24			
Adult stressor severity	1.00	.01	.98 - 1.02	.92		.04	.02	-.01 - 08	.10			

Table 2.5 Final analytic model of Fatigue using two-part regression modeling

	First part - logistic regression (n=600) **Any fatigue (binary)**					**Second part** - OLS regression (n=576) **Magnitude of fatigue**				**Overall model stats**		
	OR	**SE**	**95% CI**	**p**	**Pseudo R^2**	**b**	**SE**	**95% CI**	**p**	**R^2**	**AIC**	**LR test**
Base covariates				**<.04**	.0743				**<.0001**	.086	4192	base
Age	1.00	.02	.96 - 1.03	.83		-.07	.03	-.12 - .01	**.02**			
Gender (ref. female)												
Male	.72	.39	.25 - 2.07	.54		-.94	.92	-2.73 - .86	.31			
Education (ref. ≤HS)												
Bachelor's degree	.14	.14	.02 - 1.07	.06		-2.48	.82	-4.09 -.88	**.002**			
Master's degree or above	.16	.17	.02 - 1.25	.08		-4.51	.81	-6.10 - -2.92	**<.001**			
DMT (ref. no therapy)												
First line	.60	.41	.16 - 2.27	.45		-1.34	.97	-3.23 - .56	.17			
Second line	1.84	1.45	.39 - 8.58	.44		.25	.97	-1.65 - 2.15	.80			
MS Phenotype (ref. RRMS)												
SPMS	1.50	1.22	.31 - 7.35	.62		2.55	.99	.62 - 4.48	**.01**			
Childhood stressors				**.01**	.1052				**<.0001**	.1377	4160	**<.0001**
Child stressor count	.51	.19	.24 - 1.07	.07		-1.23	.59	-2.38 - -.08	**<.04**			
Child stressor severity	1.24	.12	1.02 - 1.51	**.03**		.47	.13	.21 - .74	**<.001**			

*****Categories within variables dropped from the model based on collinearity: 1) transgender, non-binary, gender non-confirming, 2) Associates degree or some college, 3) PPMS, 4) PRMS, 5) unsure

Table 2.6 Final analytic model of Mental health comorbidity using Poisson regression (n=705)

					Overall model statistics		
	IRR	**SE**	**95% CI**	**p**	**Pseudo R^2**	**AIC**	**LR test**
Base covariates				**<.0001**	.061	2560	base
Age	.98	.002	.98 - .99	**<.001**			
Gender (ref. female)							
Male	.90	.08	.76 - 1.06	.20			
Transgender, non-binary, gender non-conforming	.97	.15	.71 - 1.32	.86			
Education (ref. ≤HS)							
Associates degree or some college	.93	.11	.75 - 1.16	.54			
Bachelor's degree	.96	.11	.77 - 1.19	.70			
Master's degree or above	.93	.11	.75 - 1.17	.54			
MS Phenotype (ref. RRMS)							
PPMS	1.27	.16	.99 - 1.62	.06			
SPMS	1.10	1.00	.92 - 1.30	.30			
PRMS	1.34	.27	.91 - 1.98	.14			
Unsure	1.24	.18	.94 - 1.64	.14			
Pain med count	1.10	.02	1.06 - 1.15	**<.001**			
Childhood stressors				**<.0001**	.0904	2485	**<.0001**
Child stressor count	.97	.05	.88 - 1.07	.57			
Child stressor severity	1.02	.01	1.00 - 1.04	.11			
Adult stressors				**<.0001**	.116	2420	**<.0001**
Adult stressor count	1.00	.004	.99 - 1.004	.27			
Adult stressor severity	1.01	.002	1.006 - 1.014	**<.0001**			

Table 2.7 Final analytic model of relapse burden change since Covid-19, using logistic regression (n= 668)

					Overall model statistics		
	OR	**SE**	**CI**	**P**	**R^2**	**AIC**	**LR test**
Base covariates				**<.0001**	.0455	1581	base
Age	.98	.01	.97 - .99	**<.001**			
Gender (ref. female)							
Male	.92	.20	.61 - 1.40	.70			
Transgender, non-binary, gender non-conforming	.68	.36	.24 - 1.92	.47			
Education (ref. ≤HS)							
Associates degree or come college	.41	.16	.19 - .87	**.02**			
Bachelor's degree	.51	.19	.24 - 1.07	.08			
Master's degree or above	.43	.17	.20 - .91	**.03**			
Smoking status (ref. neve smoker)							
Former smoker	.96	.17	.68 - 1.35	.80			
Current or social smoker	.86	.27	.46 - 1.59	.63			
MS Phenotype (ref. RRMS)							
PPMS	.14	.06	.06 - .34	**<.001**			
SPMS	.64	.15	.40 - 1.02	.06			
PRMS	.86	.62	.21 - 3.50	.83			
Unsure	1.47	.65	.62 - 3.47	.39			
DMT (ref. no therapy)							
First line	1.21	.27	.79 - 1.87	.38			
Second line	1.23	.27	.80 - 1.89	.36			
Adult stressors				**<.0001**	.0534	1572	**<.002**
Adult stressor count	1.00	.01	.97 - 1.02	.77			
Adult stressor severity	1.01	.01	1.00 - 1.02	.065			

Table 2.8 Summary of stressor impact on MS clinical feature outcomes

MS clinical feature outcomes	Predictor blocks included in final model	Additional significant individual stressor contributions impacting MS outcomes
Disability severity	• Child & adult stressors	
Pain Interference	• Child & adult stressors	

Fatigue	• Child stressors	• Childhood stress severity impacted:
		  ○ reporting any fatigue &
		  ○ magnitude of fatigue
		• Child stress count impacted the magnitude of fatigue

MH comorbidity	• Child & adult stressors	• Adult stress severity
Age at onset	• None	
Relapse burden change since Covid-19	• Adult stressors	

Chapter III

(Aim 2, Paper 2)
Childhood Adversity and Six Features of Multiple Sclerosis (MS): Fatigue, Disability, Pain Interference, Age at Onset, Mental Health Comorbidity, and Relapse Burden Change Since Covid-19 Onset.

Abstract

Background: Traumatic stress elicits an inflammatory response and has been associated with many negative health outcomes including autoimmune diseases. Multiple Sclerosis (MS) is an immune mediated neuroinflammatory demyelinating disease that disproportionately affects the US. However, remarkably few studies have investigated the relationship between childhood stressors and MS disease features, especially while accounting for MS specific confounders.

Methods: 719 participants completed a cross sectional online survey to report their stressors and MS experiences. Hierarchical block regression was used to assess associations of emotional, physical, and environmental traumatic childhood stressors and six MS clinical features.

Results: Childhood emotional, physical, and/or environmental stressors impacted MS disability, fatigue, pain interference, age at onset, and mental health comorbidity. Regarding relapse burden changes since Covid-19, stressors did not contribute

significantly more than the baseline covariate block of predictors (e.g., smoking, phenotype).

Conclusion: This work supports increased formalized screening of past or current stressors for people with MS. Increased awareness of these stressors and the mental, behavioral, and physical implications can help clinicians deliver trauma informed precision health care and facilitate referrals to support services such as psychiatry.

Background

Childhood adversity is a public health crisis, traditionally encompassing emotional and physical abuse/neglect, sexual abuse, parental mental illness, substance abuse, or separation, and other household dysfunctions such as witnessing violence, before the age of 18 (Felitti et al., 1998). Two thirds of the United States (US) population have experienced some form of these traditional Adverse Childhood Experiences (ACEs), otherwise known as child maltreatment, traumatic, or toxic stress (Centers for Disease Control and Prevention [CDC], 2022). A hallmark dose-response relationship exists between accumulating or cumulative ACEs and worse outcomes, with higher levels of ACEs associated with worse long term health outcomes (Felitti et al., 1998; Grummitt et al., 2021). There has been a growing shift to expand the criteria to include adversities such as poverty, discrimination, community dysfunction, living in foster care, social rejection, and harsh discipline including spanking, as these stressors can also produce the same types of responses (Cronholm et al., 2015; Gershoff & Grogan-Kaylor, 2016; Kang & Burton, 2014; Krienert et al., 2011; Slavich, 2020; Stoddard et al., 2021).

Traumatic stressors elicit many physiologic processes, including stress and inflammation cascades, contributing directly and indirectly to numerous acute and chronic health issues (Grummitt et al., 2021; McEwen, 2015; Slavich, 2020). Childhood stressors have recently been implicated in 439,072 US deaths annually because of their contributions to heart and respiratory disease, cancer, suicide, stroke, and diabetes (Grummitt et al., 2021). ACEs also contribute to behavioral and health markers such as inflammation, obesity, tobacco smoking, alcohol and drug use (Grummitt et al., 2021; Gershoff & Grogan-Kaylor, 2016). Due to the immune system involvement, traumatic childhood stressors have been associated with autoimmune and immune-mediated inflammatory diseases (IMID) (Dube et al., 2009; Furman et al., 2019), however, remarkably few studies have investigated relationships between childhood stressors and Multiple Sclerosis and even fewer have focused on MS clinical features (Eilam-Stock, et al., 2021; Horton et al., 2022; Shaw et al., 2017; Spitzer et al., 2012; Pust et al, 2020).

Multiple Sclerosis (MS) is a chronic IMID characterized by neuroinflammation and neurodegeneration (Colasanti et al., 2019; Drori & Chapman, 2019). Immune cells, such as T-lymphocyes and B-lymphocytes, gain access to the central nervous system where they are not naturally found, and lead to damage of the protective sheath around axons, called myelin (Colasanti et al., 2019; Comi et al., 2020; Drori & Chapman, 2019). This damage disrupts signal conduction resulting in disrupted body functions and disability (Colasanti et al., 2019; Lunde et al., 2017; Sa, 2012). The Social Safety Theory proposes that real or perceived threats to an individual's safety can elicit the stress response to alter physiological processes (e.g., inflammatory response),

perception of future threats, and responding behavior (e.g., social, emotional, cognitive) (Slavich, 2020). We propose that traumatic childhood stressors are threats to social safety which alter the lives of PwMS in ways that impact their disease features through inflammatory or cognitive pathways.

There are primary (PPMS) and secondary (SPMS) progressive phenotypes, yet most people with MS (PwMS), 85-90%, have a relapsing-remitting (RRMS) form (Drori & Chapman, 2019; Zephir, 2018). Relapses are exacerbations of symptoms or emergence of new symptoms indicative of increasing neuroinflammation and damage, possibly secondary to the stress response. Fatigue is a very common symptom, as well as nerve and musculoskeletal pain, spasticity, gastrointestinal/genitourinary and mental health issues (NMSS, 2022a; Rosenthal et al., 2020). At least half of PwMS also have depression, which is commonly comorbid with anxiety (Hanna & Strober., 2020; Tauil et al., 2018). While these diagnoses can occur separately, there is evidence to suggest that MS can also contribute through damage to emotional and cognitive areas in the brain (Hanna & Strober., 2020). Therefore, mental health may be a comorbid feature of MS as mental health issues are neither strictly a symptom nor separate diagnoses across all PwMS.

Several factors have been associated with the development of MS and/or altering the disease course. Smoking tobacco and obesity increase the risk for developing MS and the disease burden; altering behaviors surrounding these factors can help improve symptoms (Gianfrancesco & Barcellos, 2016; (Rosso & Chitnis, 2020; Versini et al., 2019). Non-modifiable factors such as the season of birth and latitude of childhood impact the amount of vitamin-D and subsequently the overall risk of developing MS,

however, these factors are usually not included in analyses of MS clinical features or symptoms (Bradshaw et al., 2020; Handel et al., 2010; Ismailova et al., 2019; Tao et al., 2016). In addition, while there is not currently a cure for MS, many Disease Modifying Therapies (DMTs) are now available that slow disease progression.

Previous research, though limited, has linked traumatic child experiences with MS clinical features (Polick et al., 2022). Shaw et al., (2017) found that a higher ACE count was significantly related to an earlier age at MS onset. Spitzer et al. (2012), found that PwMS who experienced severe childhood abuse, physical abuse, or emotional neglect had higher relapse rates. Childhood adversity has most recently been linked to fatigue (Pust et al., 2020), and pain catastrophizing (Macdonald et al., 2021), for PwMS or IMID which included PwMS. Finally, Horton et al., (2022) found that experiencing at least 4 ACEs related to earlier MS onset by two years, and decreased mobility, but these relationships lost significance when accounting for multiple testing comparisons. Additionally, studies have also linked childhood adversity to worse anxiety the year following an MS diagnosis (Eilam-Stock et al., 2021), and mental health comorbidity (e.g., diagnosis or symptoms of anxiety, depression, PTSD) in an IMID sample that included PwMS (Wan et al., 2022). This emerging area of research appears promising, yet measurement differences regarding stressors (e.g., count, severity) and MS confounders (e.g., smoking, birth season) makes comparisons difficult. More studies are needed to substantiate previous findings and build upon them to examine additional clinical features of MS. For example, previous work has used the rate at which relapses happen as an outcome related to ACEs, however, Covid-19 had been an unprecedented stressor that could have changed relapse rates and relapse symptoms.

Therefore, a novel way to measure relapses would include capturing how the overall burden (i.e., rate, pain, length, fatigue, disability) has changed since the onset of Covid-19. Since ACEs can increase the sensitivity and perception to future stressors (McEwen, 2015; Slavich, 2020), they may play a role in how PwMS reacted to additional stress from Covid-19. Similarly, instead of measuring cumulative count or individual ACEs, a novel way to measure stressors would include clustering by a similar impact level. For example, things that happen *to* a child may impact them differently than things that happen *around* them, or in their environment. Stressors that happen directly to a child may also yield a different effect based on whether the child was physically harmed or not. Therefore, assessing stressors grouped by emotional, physical, and environmental levels may help determine which types of stressors are most detrimental.

Purpose

The aim of this study was to examine the associations between child stressors (e.g., physical/emotional abuse) and six MS disease features: disability, fatigue, pain interference, age at onset, mental health comorbidity, and how the burden of relapses had changed since the onset of Covid-19. We hypothesized that successive hierarchical block models with a childhood emotional stressor block, childhood physical stressor block, and childhood environmental dysfunction block will contribute a significant amount of variance over the baseline covariates block and other prior nested models when assessing each MS feature.

Methods

This study collected cross-sectional data of PwMS through an online self-report survey.

Recruitment

After gaining IRB approval, most participants were recruited by email from the National Multiple Sclerosis Society (NMSS) listserv, although the survey link was also posted on the NMSS website and social media. Recruitment lasted from September 15th to November 4th, 2021. Eligible participants were English reading adults officially diagnosed with MS. Since the MS population has a high potential to be fatigued, participants were able to pause to take a break whenever they wanted and could finish the survey later. Participants were compensated by being entered into a raffle for one of seven electronic gift cards for $25-50.

Measures

Standard demographic and MS information such as gender, MS phenotype, and Disease Modifying Treatment (DMT) were collected. Specific MS confounders were also collected such as month of birth, smoking status, and the city participants spent the most time in growing up. A *birth season* variable was created by collapsing the months into four categories and adjusting appropriately if a participant was from an area with different seasonality from the US. Google Maps was used to translate the city information into a numeric *latitude* variable, rounded to the nearest whole degree. The demographic and MS covariates were all used as baseline covariates (Table 3.1).

Predictor variables

Childhood stressors were measured with the Stress and Adversity Inventory (STRAIN) which queries about stressors across the lifespan (Slavich & Shields, 2018). However, the focus of this paper is on childhood stressors that align closest with traditional and expanded ACE items. The STRAIN has been validated with autoimmune

populations inclusive of MS (Cazassa et al., 2020; Slavich & Shields, 2018). Participants were asked about whether a stressor happened and if it had, follow up questions captured their age and the stressor severity and duration (e.g., years, months). Childhood emotional stressors included indicators of emotional abuse. Childhood physical stressors included items on physical abuse, recurring sexual abuse, and harsh discipline. For both the emotional and physical stressors, stressor duration was operationalized into overall months. Stressor severity was scored on a 0-5 Likert scale from “Very slightly or not at all” to “Extremely” with higher scores representing higher levels. Childhood environmental dysfunction was a count variable (0-9) summing the exposure to parental mental illness and/or substance use, fighting, witnessing abuse, child being separated from the parent, parental divorce, housing instability, feeling unsafe in their neighborhood or of being excluded at work based on factors like race or gender, and having their home broken into.

Outcome variables

Disability was measured with the Patient Determined Disease Steps (PDDS), a 1-item scale ranging from normal function (0) to bedridden (8) (Learmonth et al., 2013). The PDDs has been validated and is commonly used in the MS population as a self-report measure that correlates well to the neurologist administered Expanded Disability Status Scale (EDSS) (p= 0.64 - 0.783) (Learmonth et al., 2013; Marrie and Goldman, 2007). This study used the categorical scoring representing mild, moderate, and severe disability (Learmonth et al., 2013).

Age at onset was measured with a 1-item free text area for participants to report their age at which they first started experiencing symptoms. Age at diagnosis is used

similarly in the literature, but symptoms can sometimes be vague and onset years before an official diagnosis. Therefore, symptom onset age is used to capture this more nuanced information.

Relapse burden change since COVID-19 was measured with a 1-item select all that apply question asking participants how their relapses have changed since Covid-19 onset (approximately March 2020). There were negative options (i.e., more fatiguing, more painful, more disabling, more frequent, longer), positive options (i.e., less fatiguing, less painful, less disabling, less frequent, shorter), and options to report that relapses have been the same or have changed in some other way. A categorical variable was used to represent (0) no relapses, (1) a lighter burden, (2) no change, and (3) worse burden.

Mental health comorbidity was measured as a count score encompassing multiple questions about having any current symptoms or lifetime diagnosis of anxiety or depression, ever having another psychiatric diagnosis (e.g., schizophrenia, Post Traumatic Stress Disorder [PTSD], bipolar), or ever having an event such as a hospitalization for a psychiatric or substance use issues. Consistent with previous research, scores were summed with a possible range of 0-6 with higher scores representing more mental health comorbidity (Wan et al., 2022).

Fatigue and pain interference were measured with Patient Reported Outcomes Measurement Information System (PROMIS) scales. The PROMIS system is a publicly available repository of valid self-report measurement instruments funded by the National Institutes of Health (NIH) (Senders et al., 2014). For analyses, raw scores were

converted to standardized T-scores to compare MS sample results to a healthy general population, with a mean of 50 and standard deviation of 10 (Cella et al., 2010).

The PROMIS-Fatigue MS SF is an 8-item scale measuring fatigue over the last week for PwMS (Cook et al., 2012; Senders et al., 2014). Items are scored on a Likert scale ranging from (1) never to (5) always, with higher scores representing higher fatigue. The PROMIS Fatigue-MS is highly correlated to the PROMIS-Fatigue-SF (r=0.92) which has excellent internal consistency reliability (Cronbach's alpha = 0.99) (Cook et al., 2012; Senders et al., 2014). Internal consistency for this study was very high (Cronbach's alpha .95)

The PROMIS-Pain Interference 8a is an 8-item scale measuring the magnitude that pain had interfered with mental, physical, and social aspects of an individual's life over the last week and has previously been used in the MS population (Cronbach's alpha= 0.84 - 0.99; Amtmann et al 2010; Braley et al., 2020; Cella et al., 2010; Senders et al., 2014). The items are scored on a Likert scale from (1) not at all to (5) very much, with higher scores representing more pain interference. Internal consistency for this study was very high (Cronbach's alpha .99)

Data screening & pre-processing

Data were collected on two separate platforms (i.e., REDCap, STRAIN) and were merged using an ID that participants made themselves based on prompts. Data were reviewed and cleaned regarding data entry errors, ID errors that preventing matching, missing data, out of range items, and duplicates.

Most demographic, MS specific, and outcome variables were missing very little data from the 924 people that could be matched (0-1.19%). However, the race/ethnicity

variable 38.7% and the stressors (5-22%) had higher rates of missing information. While we believe the missingness is due to survey error, it is possible that participants underreported sensitive information like stressors; therefore, we cannot assume the data are missing at random which is a prerequisite for multiple imputation. This analysis employs case-wise deletion, so only participants with complete data would be included in the final sample. Since the sample size would be much smaller, impacting power, the sample was 88% White and cell sizes in other categories were small enough to warrant collapsing, we decided to conduct subgroup analyses to compare outcomes by race/ethnicity instead of having it as a covariate in the main analyses.

Sample size determination

We conducted a power analysis to determine the necessary sample size to have 80% power to detect significant changes in model fit between nested models. A minimum sample size of n=332 was needed to detect a 4% improvement, assuming a 2-tailed alpha (0.05).

Analytic strategy

Broadly, our approach uses blocks of similar predictors to build sequentially more complex models upon a base model to assess the contributions and model fit. If a block of predictors was found to not contribute, it was removed from the final model, but not the analyses altogether. This means that the same sample was used in both analyses, with and without that block, and that removal of the block did not allow for more participants to enter the analyses. This allowed for better model fit comparisons. Once a final model was selected, individual predictors were assessed. Table 3.1 displays the hierarchical modeling and what predictors are in each block. Assumption testing (e.g.,

normality, heteroskedasticity) was completed and used to determine more specific analytic strategies.

Specifically, our approach was to determine if stressors grouped by type (e.g., emotional, physical, or environmental) contribute to each of the six outcomes. As seen in Table 3.1, the base model consisted of demographic and MS specific covariates, tailored to be appropriate for each outcome, to assess baseline contributions. We then added the emotional stressor block as seen in model 2 and compared 1) model fit using Akaike Information Criterion (AIC), 2) significant contributions over and above what the base model contributed with likelihood ratio testing, 3) variance contributions of R^2 and pseudo R^2. This process was repeated each time for adding the physical stressor block in model 3 and the environmental stressor block in model 4.

Ordinary least squares (OLS) linear regression was used to assess the normally distributed continuous outcome variable, age at onset. Logistic regression was used to assess two ordinally scaled outcomes, disability and relapse burden change. Poisson regression was used for the count of mental health comorbidity. Two-part modeling was used for the two PROMIS scale outcomes of fatigue and pain interference due to a mixed distribution. T-scores that represented “no pain” and “no fatigue” were replaced with zeros, creating a mixed distribution. Two-part modeling first used logistic regression to analyze yes/no for having *any* fatigue or pain interference. Contingent on having any fatigue or pain interference, the second part used OLS linear regression to analyze the *magnitude* of the fatigue or interference.

Results

Participants

The final sample, encompassing participants who informed any of the six final models, consisted of 719 PwMS. Consistent with the overall MS population (NMSS, 2021), a majority were female (84%), White (88%), with Relapsing Remitting MS (79%) and were on average 31(SD 10) years old at symptom onset (Table 3.2). Most had a bachelor's degree (36%) or above (35%), never smoked (65%), had mild disability (52%), were on a second line DMT, and the average length of time since disease onset was 18.5 years. Compared to a healthy general population with a standardized T-score of 50 (SD 10), this sample had higher mean, 56 (SD 13), and median 58 (IQR 52-63) fatigue. The mean, 53 (SD 10), and median, 54 (IQR 0-62), pain interference scores were higher as well. The most prevalent stressor type was harsh discipline (n=366, 50.9%), followed by emotional abuse (n=240, 33.4%), physical abuse (n=114, 16.7%), and sexual abuse (n=92, 12.8%), with mean duration times spanning 60-190 months overall (Table 3.3). On average, participants had experienced at least two mental health symptoms, diagnoses, or events.

Fatigue

The base model block of predictors contributed to a significant overall two-part model estimating the likelihood and magnitude of having fatigue (logistic regression pseudo R^2=.074, p<.04; OLS regression R^2=.087, p<.001; model AIC=4232) (Table 3.4). The emotional stressors in model 2 contributed a significant amount of variance over and above the base model (logistic regression pseudo R^2=.096, p<.05; OLS regression R^2=.111, p<.001; model AIC=4219, LR p<.001). The physical stressors

model 3 significantly contributed over prior nested models (logistic regression pseudo R^2=.135, p<.03; OLS regression R^2=.142, p<.001; model AIC=4214, LR p<.01). The environmental stressor predictor in model 4 did not significantly contribute as a block over the nested models and greatly reduced model fit (AIC=4982; LR p=1.0), and thus was removed from the final analytic model shown in Table 3.4. However, model 4 was a significant model overall (logistic regression pseudo R^2=.14, p<.03; OLS regression R^2=.149, p<.001), and before being removed, environmental stress count was individually significantly associated with fatigue magnitude (b=.42, p=<.05). Therefore, only childhood emotional and physical stressors were included in the best fitting, final analytic, model, yet environmental stressors do appear to additionally contribute to MS fatigue outside of the best fitting model.

In addition to the blocks or clusters of similar predictors, some stressor variables were independently significant or trending towards significance. Contingent on experiencing any fatigue, harsh discipline duration was significantly associated with the magnitude of fatigue (b=.02, p<.03). Emotional and sexual abuse severity had strong coefficients and trended towards significance (b=.42, p=.06; b=.60, p=.07) regarding the magnitude of fatigue.

Pain Interference

The base model block of predictors contributed to a significant overall two-part model estimating the likelihood and magnitude of having pain interference (logistic regression pseudo R^2=.223, p<.001; OLS regression R^2=.19, p<.001; model AIC=3784) (Table 3.5). The emotional stressors in model 2 contributed a significant amount of variance over and above the base model (logistic regression pseudo R^2=.2379, p<.001;

OLS regression R^2=.204, p<.001; model AIC=3770, LR p<.01). The physical stressor block in model 3 significantly contributed over prior nested models (logistic regression pseudo R^2=.247, p<.001; OLS regression R^2=.237, p<.001; model AIC=3766, LR p<.01). The environmental stressor predictor in model 4 did not significantly contribute as a block over the nested models and reduced model fit (AIC=3768; LR p=.4), and thus was removed from the final analytic model shown in Table 3.5. Therefore, model 3 including emotional and physical childhood stressors, was the best fitting model.

For each 1-unit increase in emotional abuse severity rating there was nearly a 16% increase in the odds of experiencing any pain interference, yet this was slightly over the significance threshold (OR=1.16, p=.057). Harsh discipline was significantly associated with the magnitude of pain interference (b=.014, p=.019), and trended towards significance for predicting any interference (OR=1.004, p=.068). For each 1-unit increase in age (i.e., years), there was a 2.3% increase in the likelihood of experiencing any pain versus no pain (OR=1.023, p=<.01). However, contingent on experiencing any pain, an increase in pain was associated with lower pain interference (b=-.10, p<.0001).

Age at symptom onset

The base model block of predictors did not significantly contribute to the age at symptom onset (R^2=.017, p<.37; model AIC=5267) (Table 3.6). Emotional stressor characteristics in model 2 significantly contributed over the base model (R^2=.026, p=.14; AIC= 5264, LR p<.05). The physical stressors in model 3 did not contribute significantly more information over the prior nested models and reduced model fit (R^2=.03, p<.25, AIC=5272, LR p=.62), and thus was dropped from the final analytic model. Environmental stressors in model 4 did contribute significantly over prior nested models

(R^2=.035, p<.05, AIC=5260, LR p<.02). Therefore, childhood emotional and environmental stressors impacted the age at MS symptom onset.

Regarding key individual predictors, environmental stress count was significantly associated with a lower age at symptom onset (b= -.66, p=.01). Additionally, emotional abuse severity was significantly associated with a younger age at onset in model 2 (b=-.55, p=.029), and model 3 (b=-.72, p=.013), however this lost significance when adding the model 4 predictor of environmental stressor count.

Mental health comorbidity

The base model block of predictors significantly contributed to estimating mental health comorbidity (Pseudo R^2=.062, p<.001; model AIC=2579) (Table 3.7). Emotional stressor characteristics in model 2 contributed a significant amount of variance over the base model (Pseudo R^2=.085, p<.; AIC=2519, LR p<.0001). The physical stressors in model 3 contributed significantly more information over the prior nested models (Pseudo R^2=.092, p<.001, AIC=2513, LR p<.01). Environmental stressors in model 4 also contributed significantly over prior nested models (Pseudo R^2=.094, p<.001, AIC=2508, LR p<.01). Therefore, all stressor blocks of predictors contributed significantly and remained in the final analytic model.

Regarding key individual predictors in the final model, for each additional environmental stressor experienced, participants had 4.8% increased risk of accumulating an additional mental health symptom, diagnosis, or event (IRR=1.05, p<.01). For example, those who experienced eight environmental stressors had 40% more risk of mental health comorbidity compared to those who had no exposure to environmental stressors. Similarly, for each 1-unit increase in emotional abuse severity

rating, the risk of accumulating mental health comorbidity increased by 6% (IRR=1.06, p<.01). For example, those who rated emotional abuse as extremely severe have 30% more risk of accumulating a new mental health symptom, diagnosis, or event, compared to those who were not exposed to emotional abuse.

Disability

The base model with demographic and covariate predictors contributed significantly while estimating disability (R^2=.2519, p<.001; model AIC=1078) (Table 3.8). Emotional stressor characteristics in model 2 did not contribute a significant amount of variance over the base model and slightly worsened model fit (R^2=.2546, p<<.0001; AIC= 1079, LR p=.16) and was dropped from the final modeling. Physical stressors in model 3 did contribute significantly more information over the prior nested model (R^2=.2644, p<.001, AIC=1073, LR p<.01). Environmental stressors in model 4 did not contribute significantly over prior nested models (R^2=.2663, p<.0001, AIC=1072, LR p=.10) and therefore was dropped from the final analytic model shown in Table 3.8. Therefore, childhood physical stressors were the only stressors significantly associated with MS disability.

For each increase in harsh discipline severity rating there was a 21% increase in the odds of having a 1-unit increase in disability, representing moving to the next PDDS category (OR=1.21, p<.01). For example, PwMS exposed to extremely harsh discipline have 105% greater odds of more disability compared to PwMS not exposed, meaning they would belong in the severe PDDS category when compared to moderate. Those born in Summer (p<.05) and Winter (p=.05) both had 37% lower odds of disability compared to those born in the Spring.

Relapse burden change since Covid-19

The base model block of predictors contributed significantly to how relapse burden has changed since Covid-19 (R^2=.0452, p<.001; model AIC=1593). Emotional stressor characteristics in model 2 did not contribute a significant amount of variance over the base model but was an overall significant model (R^2=.0465, p<.001; AIC=1594, LR p=.34). Physical stressor predictors in model 3 did not contribute significantly more information over the prior nested models but was an overall significant model (R^2=.0502, p<.001, AIC=1594, LR p=.42). Environmental stressors in model 4 also did not contribute significantly over prior nested models but was a significant model overall (R^2=.0503, p<.0001, AIC=1602, LR p=.77). Since none of the stressor models added significantly more, only base covariates impacted relapse burden changes.

Regarding individual predictors, age (OR=.98, p<.01, 95% CI .97-.99), any college education, having PPMS (OR=.13, p<.001), or SPMS (OR=.61, p<.05), were all significantly associated with a lower relapse burden since Covid-19.

Subgroup analysis

Even using the full sample (n=924) there were some small cell sizes across the race/ethnicity variable. There were 4 PwMS each who identified as Latinx, or Asian (n=4), two PwMS identified as American Indian/Alaska Native, and one each for Middle Eastern and Native Hawaiian/Pacific Islander groups. Small cell sizes are typically not reported or analyzed individually in order to protect participant identity, have reliable statistics, and such few people are unlikely to be fully representative or generalizable to an entire group of people. Our goal was to be able to compare outcomes between as many race/ethnicity categories as possible. However, we did have to combine the

groups listed above since they had less than five PwMS in each. To achieve the largest subgroup sample size, only descriptive data (e.g., median, Interquartile range [IQR]), are reported so that other potential missingness from other variables did not influence the results. Additionally, we included a missing group to be able to evaluate how those who do have missing data compare to the known groups.

Disability was similar across groups, with all groups having a median of 1, representing mild disability (Appendix A). Median pain interference scores ranged from 44 (IQR 41-58) for the Combined group, to 58 (IQR 41-65) for Black PwMS. Fatigue medians ranged from 57-60, with both the Black (IQR 56-64) and Bi-racial or Mixed (52-63) groups having the highest scores. All groups had a median mental health comorbidity of 2 symptoms, diagnoses, or events, except the Bi-racial or Mixed group which had 3 (IQR 2-4). The youngest median age at symptom onset was 25.5 (IQR 21-36) years old for the Black group, and the oldest was 30 (IQR 23-37) for the Missing group. Four groups indicated no change in relapse burden with a median score of 2, while Black PwMS had a median of 3 (IQR 2-3) indicating a worse relapse burden since the onset of Covid-19 which also coincides with many racially charged events that may have been additionally stressful.

Discussion

This is the first study to assess clusters of similar childhood stressor characteristics including severity and duration, to assess their joint contributions by blocks for estimating six Multiple Sclerosis disease features. As seen in the summary Table 3.9, this study revealed that childhood emotional, physical, and/or environmental stressors impact five features of MS: disability, fatigue, pain interference, age at onset,

and mental health comorbidity. Changes in relapse burden since the onset of the Covid-19 pandemic was not influenced by any blocks of stressors. Stressors during childhood appear to have a greater impact on emotional and cognitive related outcomes (i.e., mental health, fatigue, pain interference). In contrast, childhood stressors have less of an impact on more physically related outcomes (i.e., disability and relapse burden). Mental health comorbidity was significantly affected by all types of stressors. Fatigue and pain interference were both influenced by emotional and physical stressors. Disability was significantly influenced with physical stressors. Age at symptom onset significantly related to emotional and environmental stressors. The differences may be due to different mechanisms such as the inflammatory pathway for more physical outcomes, which might be confounded by DMTs. In contrast, cognitive and emotional responses pathways could lead to higher experience or perception of pain, fatigue, and mental health struggles. It is also possible that mental health comorbidity could be partially mediating a relationship between childhood stress and fatigue (Pust et al., 2021). Fatigue is ambiguous, making it challenging to disentangle what portion is strictly from MS versus symptoms of depression, for example.

In addition to the blocks of predictors having joint significance, some predictors were also individually significant with certain outcomes. Emotional abuse severity significantly impacted age at onset and mental health comorbidity; it also nearly reached significance with fatigue magnitude ($p=.06$) and reporting any pain interference ($p=.057$). Harsh discipline severity significantly impacted disability while the duration impacted fatigue magnitude, pain interference magnitude, and was nearly significant with reporting any pain ($p=.068$). Environmental stressors significantly impacted age at

symptom onset, fatigue magnitude, and mental health comorbidity. Sexual abuse severity was nearing significance with fatigue magnitude, however, lower rates of prevalence and/or reporting may have impacted the ability to determine significance. However, the rates of abuse reported in this study are very consistent with the emotional (33.4% vs. 34.4%), physical (16.7% vs 17.9%), and sexual abuse (12.8% vs. 11.6%) rates found through national surveillance work (CDC, 2022). Additionally, severity and duration contributed differently across outcomes, suggesting the potential for count based analyses to not capture this nuanced information potentially leading to a type II error of underestimated or null results while there may truly be a relationship.

This work supports other findings that childhood adversity influences MS disease features such as age at onset (Shaw et al., 2017), pain characteristics (MacDonald et al., 2021), fatigue (Pust et al., 2020), and mental health (Eiliam-Stock et al., 2021; Wan et al., 2022). It also supports that physical childhood stressors, especially harsh discipline, relate to adult MS disability which was not found in previous studies, however, harsh discipline was not included in the measurement tools in those studies (Horton et al., 2022; Spitzer et al., 2012). This study did not find a correlation between childhood adversity and the change in relapse burden since Covid-19, yet previous work does support a relationship between childhood physical abuse and adult relapse rates overall (Spitzer et al., 2012). These conflicting results are likely due to drug therapy advancement over the last decade, as there very powerful high potency DMTs available now that likely have prevented relapses. There is evidence of this in our sample, as 43% were on second line, or high potency, DMTs, 29% did not have a relapse, and 36%

did not have a change in relapses in the 1.5 years between Covid-19 onset and data collection, suggesting appropriate disease management.

The stressor predictor blocks were ordered to first capture stressors that happen *to* a child (i.e., emotional, physical), then stressors that happen *around* a child (i.e., environmental). However, this ordering could have led to underestimations of the impact of environmental stressors, especially in the two-part models, because it was one additional variable added after many emotional and physical variables. In the two-part models, adding one variable is treated as if two were added because there are two beta coefficients and an additional degree of freedom which the likelihood ratio test is dependent on. There is some evidence of this in the two-part fatigue analysis. The final environmental block did not contribute above and beyond the previous emotional and physical blocks when tested with the likelihood ratio test. However, the individual environmental count variable had a significant p-value (p=.048) in only the second part of the model for estimating fatigue magnitude. This suggests that had the environmental block been added earlier instead, it may have contributed significantly more often and stayed in the most parsimonious models for more outcomes.

Several demographic characteristics also made contributions. Not surprisingly, obtaining higher education was consistently related to better results across all outcomes except age at symptom onset. This study sample was highly educated, with 71% of participants having obtained at least a bachelor's degree, suggesting that the relationships found may be even stronger for other populations who may have experienced additional adversity and barriers to education. This same phenomenon has been well established throughout many other health outcomes and for overall health

(Langsford et al., 2016; Ross & Wu, 1995), again highlighting the need to invest in programs that address barriers and facilitate child, adolescent, and adult educational success to help promote health over the lifespan (Stoddard et al., 2020).

Age was associated with outcomes but not all in the same direction. As PwMS aged the risk for disability and experiencing any pain interference increased. Conversely, mental health comorbidity, relapse burden change, and the magnitude of fatigue and pain interference all slightly decreased with age. This may represent better disease management, better coping skills, perhaps engaging in mental health support, and the shift to progressive forms of MS characterized by less relapses, all happening over time since their diagnosis.

Lastly, birth season significantly related to MS disability. Those born in the spring had about 37% higher odds of disability compared to those born in Summer or Winter, which is consistent with how birth season influences the risk for MS. Traditionally, birth season is used as a covariate in studies assessing the risk for MS development and had not yet been included in studies assessing MS disease features and childhood stressor relationships. It is unclear whether mechanisms of vitamin-D absorption vary over the lifespan of PwMS by birth seasonality and could be explored further. Future investigations between childhood adversity and MS disability should include birth seasonality.

Implications

These study findings expand upon the many known detrimental health outcomes stemming from adverse childhood experiences to include negative impacts on five features of MS. Yet, this area is still understudied and warrants future research, which

should include critical MS confounders and consider how racial and ethnic factors can best be assessed in the context of stressors and MS.

This work supports the movement to integrate trauma informed care and stressor screening into clinical practice, especially for PwMS. Screening will allow neurologists to be more informed about patient backgrounds, risks factors, and possible disease trajectories to better provide precision medicine that could help mitigate the risk of negative outcomes. For example, if screening were integrated into the process while establishing care with a new patient, neurologists could discern that their patient with high childhood stressors was at higher risk of worsening anxiety over the year following an MS diagnosis (Eilam-Stock et al., 2021), and refer them to mental health support to truncate or avoid accumulation of mental health comorbidity. Improved coping skills may also facilitate smoking cessation and other health behaviors which can help improve MS disease burden. In addition, there is also some evidence to suggest that engaging PwMS with mental health support may also help alleviate some symptoms of fatigue, pain, relapses, possibly leading to less disability, increased quality of life and treatment adherence (MacDonald et al., 2021; Pust et al., 2021; Spitzer et al., 2012).

Another clinical implication from this work is supporting the ability to tailor treatment options for PwMS based on stressor exposure. Evidence suggests that some PwMS respond similarly to stimulant drug therapy or a placebo in the treatment of fatigue (Nourbakhsh et al., 2021). Future work should help determine if those with childhood stressors and fatigue respond better to non-pharmacologic options that may even be increasingly beneficial such as Cognitive Behavioral Therapy (CBT). CBT has also shown to be helpful for mental health and DMT adherence when PwMS struggle

with the decision to stop treatment against medical advice (Bruce et al., 2015). Further, because the stress response may have been primed in childhood to be in a higher inflammatory state in adulthood, knowing a patient's stress history could help guide neurologists while determining the DMT treatment plan. While patients often share more current stressors with their neurologists, there is evidence to suggest that formal screening is not a regular part of practice despite the American Academy of Neurology position supporting screening for past and current trauma (Polick et al., 2021; Roque et al., 2013; Schulman & Hohler, 2012). There is also evidence that healthcare providers are uncomfortable screening because they are unsure of what steps to take next (Clark & Jones, 2022) Training and establishing protocols can help guide providers through these conversations with patients. Resources like Aces Aware (acesaware.org) and the Trauma Informed Care Implementation Center (https://www.traumainformedcare.chcs.org) can help healthcare providers learn about, train for, and implement trauma informed care. Lastly, policy changes in some states have facilitated trauma screening by higher billing reimbursement rates of around $30 (California Department of health Care Services, 2020), while some states reimbursement rates are less than $3 (Center for Youth Wellness, 2019). Widespread screening reimbursement could help improve screening practices throughout different healthcare settings and states.

Limitations

There is potential for a bias due to the participant response rate. Thus, this sample may not be representative of those without the technological, physical, or cognitive ability to participate in the survey. As with any self-administered questionnaire

asking about current and past sensitive topics, there is potential for recall and social desirability bias. However, the STRAIN and participant responses have been shown to be reliable over time, not induce negative mood, be impacted by personality, or have social desirability bias (Slavich & Shields, 2018). Additionally, the rates of abuse in this study are very consistent with national rates (CDC, 2022). This study did not include emotional neglect which could lead to underestimated results. The cross-sectional design limits the ability to assess temporal ordering or causation. However, many other studies have found meaningful results using these methods and given the state of the science in this area, this design is appropriate to contribute to a foundation to build on in the future.

Conclusion

These findings support a relationship between childhood adversity and MS clinical features of disability, fatigue, pain interference, age at symptom onset, and mental health comorbidity. Groups of similar stressors, emotional, physical, or environmental, had differing influences across the six outcomes, suggesting multiple pathways from stress to MS features. More studies are needed to add to the scarce literature in this area, replicate results, and expand to other clinical features of MS such as sleep, cognitive function, and response to treatments to support trauma informed precision medicine.

Table 3.1 Hierarchical block modeling approach

	Predictors in each block model
Base model 1: demographic and MS covariates	Tailored per outcome
Model 2 adds emotional block	Base model + emotional abuse severity & duration
Model 3 adds physical block	Model 2 + physical abuse severity & duration, sexual abuse severity & duration, harsh discipline severity & duration
Model 4 adds environmental block	Model 3 + cumulative count of environmental stressors

Table 3.2 Sample Characteristics

Age M(SD) (n=719)	49.3(12.7) range: 21-85
Gender n(%) (n=719)	
Female	602 (84%)
Male	102 (14%)
Transgender, non-binary, gender non-conforming or other	15 (2%)
Race / Ethnicity n(%) (n=477)	
White	421 (88%)
Black	23 (5%)
Latinx	2 (<1%)
Asian	4 (<1%)
American Indian or Alaska Native	2 (<1%)
Native Hawaiian or Pacific Islander	1 (<1%)
Bi-racial or mixed	24 (5%)
Education n(%) (n=719)	
High school, GED, or below	36 (5%)
Associates degree or some college	169 (24%)
Bachelor's degree	260 (36%)
Master's degree or above	254 (35%)
Smoking status n(%) (n=715)	
Never smoker	468 (65%)
Former smoker	200 (28%)
Current or social smoker	47 (7%)
Latitude M(SD) (n=719) M(SD)	39(6) range: 10-65
Birth Season n(%) (n=716)	
Spring	187 (26%)
Summer	178 (25%)
Fall	181 (25%)
Winter	170 (24%)
MS Phenotype n(%) (n=719)	
RRMS	565 (79%)
PPMS	35 (5%)
SPMS	87 (12%)
PRMS	9 (1%)
Unsure	23 (3%)
Length of time since MS onset M(SD) (n=719)	18.5 (12.3) range: 0-59
Disease Modifying Therapy (DMT) n(%) (n=715)	
None	129 (18%)
First line	262 (39%)
Second line	310 (43%)
Count of medication classes that can impact pain M(SD) (n=705)	1.64 (1.3) range: 0-5
Outcome variables	
Disability (PDDS) n(%) (n=712)	
Mild	368 (52%)
Moderate	238 (33%)
Severe	106 (15%)
Fatigue, median (IQR), M(SD) (n=719)	58 (52-63), 56(13)
Pain interference, median (IQR), M(SD) (n=719)	54 (0-62), 53(10)

Age at MS symptom onset M(SD) (n=709)	31 (10)
Relapse change since Covid-19 (n=680)	
No relapse	199 (29%)
Improved	26 (4%)
Stayed the same	244 (36%)
Worsened	211 (31%)
Mental Health comorbidity count M(SD) (n=719)	2.2 (1.7) range: 0-6

Table 3.3 Stressor characteristics

Severity	**Emotional abuse** (n=719)	**Physical abuse** (n=719)	**Sexual abuse** (n=719)	**Harsh discipline** (n=719)
Not exposed	479	599	627	353
Slightly or not at all	1	0	1	38
A little	10	3	9	69
Moderately	18	10	13	85
Quite a bit	75	38	15	94
Extremely	136	69	54	80
Total exposed n(%)	240 (33.4%)	120 (16.7%)	92 (12.8%)	366 (50.9%)
Duration if exposed M(SD)	190 (166) months or 15.8 (13.8) years	114 (90) months or 9.5 (7.5) years	60 (57) months or 5 (4.75) years	108 (69) months or 9 (5.75)
Environmental stressors Range 0-8 (total n=719)	1 stressor	2 stressors	3 stressors	4 or more stressors
PwMS exposed to each count of stressors (n= 255 with no exposure)	165	113	115	101

Table 3.4 Fatigue assessment using two-part regression modeling

	First part - logistic regression (n=606) **Any fatigue** (binary)					**Second part** - OLS regression (n=582) **Magnitude of fatigue**				**Overall model stats**		
	OR	**SE**	**95% CI**	**p**	**Pseudo R^2**	**b**	**SE**	**95% CI**	**p**	**R^2**	**AIC**	**LR tests**
Base covariates				**<.04**	.0739				**<.0001**	.086	4232	base
Age	1.001	.02	.96 - 1.04	.97		-.07	.03	-.12 - -.01	**<.02**			
Gender (ref. female)												
Male	.65	.35	.23 - 1.88	.43		-.75	.92	-2.54 - 1.04	.41			
Education (ref. ≤HS)												
Bachelor's degree	.13	.14	.02 - 1.03	.053		-2.85	.82	-4.45 - -1.25	**<.001**			
Master's degree or above	.15	.16	.02 - 1.22	.08		-4.60	.81	-6.18 - -3.03	**< .001**			
DMT (ref. No therapy)												
First line	.64	.44	.17 - 2.44	.51		-1.40	.97	-3.30 - .50	.15			
Second line	2.09	1.65	.44 - 9.84	.35		.05	.97	-1.86 - 1.95	.96			
MS Phenotype (ref. RRMS)												
SPMS	1.29	1.05	.26 - 6.39	.76		2.52	.99	.59 - 4.46	**.01**			
Emotional stressors				**.02**	.0964				**<.0001**	.1106	4219	**.0004**
Emotional abuse severity	.96	.21	.62 - 1.48	.84		.42	.23	-.02 - .87	.06			
Emotional abuse duration	1.01	.01	1.00 -1.03	.20		-.003	.003	-.01 - .004	.46			
Physical stressors				**<.03**	.1353				**<.0001**	.1420	4214	.004
Physical abuse severity	.71	.17	.45 - 1.13	.15		-.43	.33	-1.08 - .21	.91			
Physical abuse duration	1.004	.01	.99 - 1.02	.71		.01	.01	-.01 - .03	.41			
Sexual abuse severity	1.04	.93	.18 - 5.95	.96		.60	.33	-.06 - 1.24	.07			
Sexual abuse duration	1.17	.42	.57 - 2.38	.67		.002	.02	-.03 - .04	.93			
Harsh discipline severity	1.38	.33	.86 - 2.19	.18		.07	.28	-.48 - .61	.81			
Harsh discipline duration	.99	.005	.98 - 1.00	.07		.02	.01	.002 - .03	**.02**			

*The following categories of variables were dropped due to collinearity: 1) Transgender, non-binary, gender non-conforming, 2) Associates degree or some college, 3) PPMS, 4) PRMS, 5) Unsure

Table 3.5 Pain interference assessment using two-part regression modeling

	First part - logistic regression (n=707) **Any pain interference** (binary)					**Second part -** OLS regression (n= 464) **Magnitude of pain interference**				**Overall model stats**		
	OR	**SE**	**95% CI**	**p**	**Pseudo R^2**	**b**	**SE**	**95% CI**	**p**	**R^2**	**AIC**	**LR test**
Base covariates				**<.0001**	.2231				**<.0001**	.1881	3784	Base
Age	1.02	.01	1.01 - 1.04	**<.01**		-.10	.03	-.16 - -.05	**<.001**			
Gender (ref. female)												
Male	.64	.17	.38 - 1.07	.09		.85	.94	-.99 - 2.69	.37			
Transgender, non-binary, gender non-conforming, other	1.30	.93	.32 - 5.27	.72		-1.40	1.97	-5.26 - 2.45	.48			
Education (ref. ≤HS)												
Associates degree or some college	.16	.13	.03 - .76	**.02**		-1.32	1.26	-3.79 - 1.14	.29			
Bachelor's degree	.09	.07	.02 - .42	**<.01**		-4.40	1.23	-6.80 - -2.00	**<.001**			
Master's degree or above	.09	.07	.02 - .40	**<.01**		-4.78	1.23	-7.19 - -2.37	**<.0001**			
MS Phenotype (ref. RRMS)												
PPMS	1.23	.58	.48 - 3.11	.67		-.24	1.41	-3.01 - 2.52	.86			
SPMS	1.40	.47	.72 - 2.70	.32		2.39	.93	.56 - 4.21	**.01**			
PRMS	1.10	1.02	.18 - 6.81	.92		6.11	2.42	1.36 - 10.86	**.01**			
Unsure	1.04	.57	.36 - 3.03	.94		2.84	1.74	-.57 - 6.26	.10			
DMT (ref. No therapy)												
First line	1.35	.38	.77 - 2.36	.29		-.51	.93	-2.33 - 1.31	.59			
Second line	2.13	.62	1.20 - 3.78	<.01		-1.35	.89	-3.09 - .39	.13			
Pain med count	2.45	.24	2.03 - 2.97	<.001		1.38	.24	.92 - 1.84	**<.001**			
Emotional stressors				**<.0001**	.2379				**<.0001**	.2037	3770	**.0002**
Emotional abuse severity	1.16	.09	1.00 - 1.34	.057		-.06	.20	-.46 - 33	.75			
Emotional abuse duration	1.00	.001	1.00 - 1.002	.52		.003	.003	-.003 - .01	.35			
Physical stressors				**<.0001**	.2468				**<.0001**	.2372	3766	**.006**
Physical abuse severity	1.02	.11	.83 - 1.26	.86		.18	.28	-.36 - .72	.52			
Physical abuse duration	1.00	.003	.99 - 1.01	.76		-.01	.01	-.03 - .01	.25			
Sexual abuse severity	1.05	.11	.85 - 1.29	.66		.33	.28	-.23 - .88	.25			
Sexual abuse duration	1.002	.01	.99 - 1.01	.73		.02	.02	-.02 - .05	.34			
Harsh discipline severity	1.001	.09	.85 - 1.19	.99		.05	.25	-.44 - .54	.85			
Harsh discipline duration	1.004	.002	1.00 - 1.01	.068		.01	.01	.002 - .03	**.019**			

Table 3.6 Assessment of age at symptom onset using standard regression (n= 702)

					Overall model stats		
	b	SE	95% CI	p	R^2	AIC	LR test
Base covariates				.3665	.0171	5267	base
Gender (ref. female)							
Male	2.54	1.11	.36 - 4.72	**.023**			
Transgender, non-binary, gender non-conforming	-2.21	2.70	-7.51 - 3.10	.41			
Education (ref. ≤HS)							
Associates degree or some college	-1.45	1.92	-5.21 - 2.32	.45			
Bachelor's degree	-1.08	1.89	-4.79 - 2.63	.57			
Master's degree or above	-2.95	1.91	-6.69 - .80	.12			
Smoking status (ref. neve smoker)							
Former smoker	-.12	.92	-1.99 - 1.60	.83			
Current or social smoker	.32	1.65	-2.91 - 3.56	.85			
Birth Season (Ref. Spring)							
Summer	.07	1.08	-2.04 - 2.18	.99			
Fall	.02	1.08	-2.10 - 2.14	.99			
Winter	.52	1.10	-1.6 - 2.68	.64			
Latitude (degree from equator)	-.00005	.07	-.13 - .13	.99			
Emotional stressors				.1423	.0262	5264	.0378
Emotional abuse severity	-.32	.26	-.84 -.20	.22			
Emotional abuse duration	.003	.004	-.01 -.01	.53			
Environmental stressors				**.0386**	.0349	5260	.0122
Environmental stress count	-.66	.27	-1.18 - -.14	**.01**			

Table 3.7 Mental health comorbidity assessment using Poisson regression (n=711)

					Overall model statistics		
	IRR	**SE**	**95% CI**	**p**	**Pseudo R^2**	**AIC**	**LR test**
Base covariates				**<.0001**	.0616	2579	base
Age	.988	.002	.98 - .99	**<.001**			
Gender (ref. female)							
Male	.84	.07	.71 - 1.00	**<.05**			
Transgender, non-binary, gender non-conforming	1.04	.16	.76 - 1.41	.82			
Education (ref. ≤HS)							
Associates degree or some college	.88	.10	.70 - 1.09	.24			
Bachelor's degree	.80	.09	.64 - .99	**<.05**			
Master's degree or above	.79	.09	.64 - .98	**<.05**			
MS Phenotype (ref. RRMS)							
PPMS	1.15	.15	.90 - 1.48	.27			
SPMS	1.05	.09	.88 - 1.24	.62			
PRMS	1.23	.25	.83 - 1.82	.31			
Unsure	1.17	.17	.88 - 1.54	.29			
Pain med count	1.15	.02	1.11 - 1.20	**< .001**			
Emotional stressors				**<.0001**	.0853	2519	**<.0001**
Emotional abuse severity	1.06	.02	1.02 - 1.10	**.002**			
Emotional abuse duration	1.00	.0003	1.00 - 1.001	.57			
Physical stressors				**<.0001**	.0916	2513	**.0086**
Physical abuse severity	.97	.02	.92 - 1.01	.17			
Physical abuse duration	1.00	.001	1.00 - 1.002	.80			
Sexual abuse severity	1.03	.02	.99 - 1.08	.17			
Sexual abuse duration	1.00	.001	1.00 - 1.002	.99			
Harsh discipline severity	1.01	.02	.97 - 1.06	.61			
Harsh discipline duration	1.00	.001	1.00 - 1.002	.09			
Environmental stressor				**<.0001**	.0942	2508	**.0075**
Environmental stressor count	1.05	.02	1.01 - 1.09	**.007**			

Table 3.8 Disability assessment using logistic regression (n= 701)

					Overall model statistics		
	OR	**SE**	**CI**	**P**	**R^2**	**AIC**	**LR test**
Base covariates				**<.0001**	.2519	1078	baseline
Age	1.06	.01	1.05 - 1.08	**<.001**			
Gender (ref. female)							
Male	1.02	.25	.63 - 1.63	.95			
Transgender, non-binary, gender non-conforming	.48	.30	.14 - 1.66	.25			
Education (ref. ≤HS)							
Associates degree or some college	.89	.35	.41 - 1.94	.77			
Bachelor's degree	.43	.17	.20 - .93	**.03**			
Master's degree or above	.28	.11	.13 - .61	**<.01**			
Smoking status (ref. neve smoker)							
Former smoker	1.19	.23	.81 - 1.73	.38			
Current or social smoker	2.26	.76	1.18 - 4.35	**.014**			
Birth season (ref. Spring)							
Summer	.63	.15	.40 - .99	**<.05**			
Fall	.73	.17	.46 - 1.14				
Winter	.63	.15	.40 - 1.001	**.05**			
MS Phenotype (ref. RRMS)							
PPMS	16.07	6.64	7.15 - 36.11	**<.001**			
SPMS	14.05	4.02	8.02 - 24.60	**<.001**			
PRMS	30.41	24.16	6.41 - 144.27	**<.001**			
Unsure	1.18	.58	.45 - 3.11	.74			
DMT (ref. No therapy)							
First line	.64	.16	.39 - 1.04	.07			
Second line	1.54	.38	.95 - 2.50	.08			
Physical stressors				**<.0001**	.2644	1073	**<.01**
Physical abuse severity	.91	.07	.78 - 1.06	.21			
Physical abuse duration	1.00	.003	.99 - 1.004	.75			
Sexual abuse severity	.93	.08	.79 - 1.09	.36			
Sexual abuse duration	1.01	.005	1.00 - 1.02	.08			
Harsh discipline severity	1.21	.08	1.06 - 1.39	**.005**			
Harsh discipline duration	1.00	.002	1.00 - 1.003	.82			

Table 3.9 Summary of stressor impact across all six outcomes

	Predictor blocks included in final model	Additional significant individual stressor contributions impacting MS outcomes
Fatigue	• Emotional and physical	• Harsh discipline duration
Pain Interference	• Emotional and physical	• Harsh discipline duration
Age at onset	• Emotional and environmental	• Environmental stress count
MH comorbidity	• Emotional, physical, and environmental	• Emotional abuse severity • Environmental stressor count
Disability severity	• Physical	• Harsh discipline severity
Relapse burden change since Covid-19	• None	

Chapter IV

(Aim 3, Paper 3)
Impacts of Lifetime Stressor Characteristics on Six Multiple Sclerosis Features: Disability, Fatigue, Pain Interference, Age at Onset, Relapse Burden, and Mental Health Comorbidity

Abstract

Background: The relationship between stress and MS clinical features remains understudied and controversial. Most previous work focuses on adult stressors and lacks a lifetime approach to stressor measurement. Additional stressor characteristics have also been lacking.

Aim: The purpose of this cross-sectional study was to examine associations between five lifetime stressor types (e.g., role change, interpersonal loss, humiliation), stressor characteristics (e.g., count, severity) and six MS disease features (e.g., fatigue, age at onset).

Methods: Participants (n=713) were recruited through the National MS Society email listserv to complete an online self-report survey. Multiple regression was used for analyses.

Results: There was variation in the influence of stressor types across the outcomes. Physical danger, entrapment, and role change stressors were associated with fatigue. The count and severity of physical danger and entrapment stressors were associated with pain interference. Interpersonal loss (count/severity) and role change stressor

severity was associated with Age at symptom onset. The count and severity of physical danger, role change, and humiliation stressors was associated with mental health comorbidity.

Conclusion: Physical danger and entrapment (e.g., poverty) stressors appear to be the most impactful across all aims. Stressor screening can help increase both healthcare provider and patient awareness of the impact on MS clinical outcomes. This knowledge can be used to provide referrals to support services, empower those with MS to use coping or stress management skills, and aid in MS disease management through trauma informed precision health care. Further observational and interventional research is needed to expand upon this work to develop best practice health service delivery and treatment options for these and additional features of MS.

Background

Multiple Sclerosis (MS) is a chronic disease that typically onsets at a relatively young age (e.g., 36 years old average globally) and can involve a large loss of independence (MS International Federation, 2021). People with MS (PwMS) deal with progressive and/or intermittent disability, relapses (i.e., exacerbations), fatigue, pain (NMSS, 2022a; NMSS, 2022b, NMSS, 2022;c Zephir, 2018). In addition, MS understandably has high rates of comorbid mental health struggles (Tauil et al., 2018). Only 30-50% of the risk for this immune-mediated neuroinflammatory demyelinating disease can be contributed to genetics (Coyle, 2020). Non-genetic factors that have been shown to increase the risk of MS and/or impact its clinical features are latitude of birth or long-term residence, birth month, smoking tobacco, obesity, and microbial

exposure (Drori & Chapman, 2019; Tao et al., 2016). These environmental and behavioral risk factors contribute through mechanisms related to either Vitamin-D or the inflammatory response (Ismailova et al., 2019; Rosso & Chitnis, 2020). Yet, there is a need to better understand other, perhaps more modifiable, factors that may contribute to MS and its disease features.

The Social Safety Theory also provides a pathway from stress to MS outcomes through the inflammatory system, schemas about the self, and the world (Slavich, 2020). This theory posits that humans have evolved to band in groups and socialize which increases the chances for survival. Threats to social safety elicit the stress and inflammation cascade (e.g., fight or flight) which could impact the MS disease process. The body and mind adapt to become more sensitive to detect future threats which can result in increased perception of stress, and increased somatic experiences like pain (McEwen, 2015; Slavich, 2020; Tesarz et al., 2016). Guided by the Social Safety Theory, we propose that stressors such as physical danger and interpersonal loss are threats to social safety which impact the physical and mental experience of MS.

Stress has been thought to impact MS since the time of Charcot who first described the disease in 1877 (Meyer-Arndt et al., 2020). Stress induces an inflammation cascade that has been proposed to contribute MS and its clinical features (e.g., relapses or exacerbations), however, the stress-MS relationship is still considered somewhat controversial (Artemiadis et al., 2011; Briones-Buixassa et al., 2015; Handel et al., 2010). Most of the literature surrounding the stress-MS relationship, especially studies delving into clinical features, focuses on adult*s* (Artemiadis et al., 2011; Briones-Buixassa et al., 2015). For example, at least three stressful life events increased the risk

of MS exacerbation over five times for adult women (Mitsonis et al., (2008). While there are only five studies specifically assessing childhood stressors and physical MS clinical features, most did find significant results (Horton et al., 2022; MacDonald et al., 2021; Pust et al., 2020; Shaw et al., 2017; Spitzer et al., 2012). However, a lifetime approach is generally lacking, especially one that considers nuances of various stressor characteristics. A recently validated tool, the Stress and Adversity Inventory (STRAIN) groups cumulative lifetime stressors into five core social-psychological types 1) physical danger, 2) interpersonal loss, 3) entrapment, 4) humiliation, 5) role change / disruption (Slavich and Shields, 2018). Certain types have been associated with higher risk of autoimmune diseases inclusive of MS (Slavich and Shields, 2018; Cazassa, 2020), but has not yet been used to assess clinical features of MS. It is important to put stressors in context of the lives of PwMS and how they may be communicating their stress with their healthcare providers. For example, PwMS may share that they were in a serious accident (i.e., physical danger) or that their parent passed away (i.e., interpersonal loss), rather than reporting that their stress count increased by two. Contextualizing stress may help healthcare providers tailor care for PwMS.

The purpose of this cross-sectional study was to examine associations between lifetime stressors, categorized into five core social-psychological types (e.g., physical danger, role change), stressor characteristics (i.e., count, severity) and six common MS disease features (e.g., fatigue). Since Covid-19 was a large worldwide stressor that could be a threat to internal validity if we measured relapse rates over a period of time (before/after) (Kviz, 2020), this study focused on how the relapse burden changed since Covid-19 onset. We hypothesized that lifetime stressors would impact physical and

mental clinical features of MS: 1) fatigue, 2) pain interference, 3) age at symptom onset, 4) relapse burden change since Covid-19, 5) disability, 6) mental health comorbidity).

Methods

This study used a cross-sectional self-report online survey to examine the relationship between the presence of five core social-psychological types across the lifespan and six common MS disease features in a sample of PwMS.

Recruitment

After approval was obtained from the University of Michigan Institutional Review Board, the National MS Society (NMSS) sent recruitment and screening materials to their listserv of about 80,000 PwMS and posted it on their website. Eligible participants were US based English reading adults with an official MS diagnosis. Survey participants were entered into a raffle for $25 or $50 electronic gift cards. Recruitment remained open for nearly seven weeks in the Fall of 2021.

Measures

Demographic and MS specific information such as gender, smoking status, and Disease Modifying Therapy (DMT), were used as covariates tailored to be appropriate for each clinical feature outcome. *Birth month* was collected and then categorized into seasons, accounting for geographical differences. The city that a PwMS spent the most time growing up in was collected and transformed into a positive *latitude* variable by using google maps, adjusting for hemisphere. To control for confounding effects in the pain and mental health comorbidity analyses, a count variable of *types of medications* that can impact pain (e.g., opiates, antidepressants) was used.

Core social-psychological stressor characteristics

The Stress and Adversity Inventory (STRAIN) is a relatively new measurement tool that measures 55 different stressors across the lifespan and has been validated with an autoimmune disease sample (Cazassa et al., 2020; Slavich & Shields, 2018). It is particularly comprehensive, surpassing other tools, because it captures stressor characteristics of count, severity, duration, and frequency, however, the focus of this paper is on cumulative count and severity. A Likert scale measures severity from “Very slightly or not at all” to “Extremely” with a total possible range from 0-167 (Slavich & Shields, 2018). Higher scores represent higher stressor exposure (i.e., count, severity). The total number of lifetime stressors are categorized into five core social-psychological characteristics or types 1) physical danger, 2) entrapment 3) role change/disruption 4) interpersonal loss, and 5) humiliation (Cazassa et al., 2020; Slavich & Shields, 2018). Examples of physical danger include physical abuse, sexual abuse, or life-threatening accidents. Entrapment stressors are ongoing circumstances that are hard to escape (Kendler et al., 2003) such as financial struggles, poverty, living in an impoverished neighborhood, or for a child might represent how they cannot get away from some household stressors. Examples of role change/disruption include needing to provide care to others or requiring help themselves. Interpersonal loss involves a loss of well-being or connectedness spanning all aspects of life such as people, possessions, health (Kendler et al., 2003). Humiliation involves feeling devalued, rejected, or like a failure (Kendler et al., 2003).

MS clinical features as six outcomes

Age at onset was a free text variable that was converted to a continuous numeric variable. If a participant wrote an age range (e.g., 20-22), the middle of the range was used (e.g., 21).

Fatigue and pain interference were both measured with Patient Reported Outcome Information System (PROMIS) measures which are robustly validated publicly available tools (Cella et al., 2010; Healthmeasures.net). The *PROMIS-Pain Interference* (8a), an 8-item questionnaire previously used in an MS sample, was used to measure if pain interfered with any mental, physical, or social aspects of an individual's life over the past week, and the magnitude of the interference (Amtmann et al 2010; Braley et al., 2020). Items on a Likert scale from 1 (not at all) to 5 (very much), are summed, with higher scores indicating more pain interference. Scale reliability for this study was very high (Cronbach's alpha= .98). The *PROMIS-Fatigue MS SF*, an 8-item questionnaire specific to PwMS, was used to measure fatigue over the last week (Cook et al., 2012; Senders et al., 2014). Items on a Likert scale ranging from 1 (never) to 5 (always), are summed, with higher scores indicating more fatigue. Scale reliability for this study was very high (Cronbach's alpha=.95). Raw scores were converted to standardized t-scores that have a mean and standard deviation of 50(10) (Cella et al., 2010). For analysis, the lowest scores representing no fatigue or pain interference were converted to zeros.

Mental health comorbidity was operationalized via a count score, consistent with previous research (Wan et al., 2022). Participants were given 1-point per positive indication of a mental health symptom, diagnoses, or event. Symptoms included those for anxiety or depression. Diagnoses included ever being diagnosed with a psychiatric

disorder such as anxiety, depression, bipolar, schizophrenia, Post Traumatic Stress Disorder [PTSD]. Events included ever having a hospitalization due to a psychiatric or substance use issue. Scores were summed with a possible range of 0-6 with higher scores representing more mental health comorbidity.

Patient Determined Disease Steps (PDDS), a 1-item validated tool, was used to measure *MS disability* (Learmonth et al., 2013; Marrie and Goldman, 2007). Scores represent the decline from normal function (0) to being bedridden (8) (Learmonth et al., 2013). As an option consistent with the literature, scores were converted to categorical outcomes of mild, moderate, and severe disability (Learmonth et al., 2013).

Participants reported how their *relapses have changed since the onset of Covid-19*. Responses included: no relapses, no change, positive changes (e.g., less painful, less fatiguing, less disabling shorter), or negative changes (e.g., more painful, more fatiguing, more disability, longer). This was operationalized into an ordinal variable representing no relapses (0), lighter relapse burden (1), no change (2), and worse relapse burden (3).

Data screening & pre-processing

Prompts were used to guide participants in making their own IDs. These IDs were used to merge the data collected on two separate platforms (i.e., REDCap, STRAIN). Data review and cleaning included assessment for entry errors, ID errors, missing patterns, and duplicates.

The rates of missing data throughout most demographic, MS specific, and outcome variables were very small (<5%). However, the stressor summary scores (22.5%), and the race/ethnicity variables (39.7%) had higher rates. While we believe the

vast majority is due to survey platform, skip pattern errors and unmatched IDs, we did not use multiple imputation because the assumption that data were missing at random was not met. This was because participants may have been hesitant to report sensitive information like stressors.

Regarding race/ethnicity, the sample was consistent with the general MS population at 88% White (NMSS, 2021). Low frequencies in all other race/ethnicity categories would normally lead to collapsing categories to protect participant identities and for statistical viability. However, using a binary, white vs. non-white, approach would not properly support the exploration of unique experiences of PwMS across varying racial/ethnic groups. Additionally, issues regarding social determinants of health such as wealth imbalance, inequitable healthcare access and utilization, lead to diagnostic delays and treatment disparities (Amezcua & McCauley, 2020; Amezcua et al., 2021, Jefferson, 2021). On the surface this may represent a higher disease burden for certain racial/ethnic groups; putting the onus squarely on a racial group, when societal and healthcare systems contribute to disparate outcomes, and it does not properly represent true genetic racial differences. For these reasons, we omitted the race variable from the main analyses to allow for a focused subgroup analysis that could accommodate more than a binary white/all others comparison.

Sample size determination

A power analysis was conducted to determine a target sample size based on a different aim with more variables. Nevertheless, we conducted post hoc power analyses per each of the parameters and sample sizes of the six MS outcomes. From this, we

concluded these six analyses were powered to detect significant variance changes as small as .023-.029 for any single parameter in the models.

Analytic strategy

Two multiple regressions were conducted for each MS clinical feature of 1) age at onset, 2) fatigue, 3) pain interference, 4) mental health comorbidity, 5) disability, 6) relapse burden change since the onset of Covid-19. One analysis focused on the count of stressors throughout the five core social-psychological types and one focused on the severity, totaling to 12 regressions.

Age at onset was a normally distributed continuous variable, therefore ordinary least squares (OLS) linear regression was used. Fatigue and pain interference PROMIS scores both had a mixed distribution; therefore, two-part modeling was used. The first part analyzed *any* fatigue or pain interference versus none in a binary fashion using logistic regression. The second part analyzed the *magnitude* of fatigue or pain if it was reported, using OLS linear regression. Mental health comorbidity was a count variable; thus, Poisson regression was used. Lastly, disability and relapse burden change variables were both ordinal, so logistic regression was used.

Results

Participants

Participants that informed any of the six outcomes were included in the overall sample characteristics displayed in Table 4.1. Most were female (84%), White (88%), with Relapsing Remitting MS (79%) and were on average 31(10) years old when they first experienced symptoms, which is consistent with the general MS population (NMSS, 2021). A majority were never smokers (66%) and had at least a bachelor's degree

(71%). Average disease length was 18 years, most were on a second line DMT (44%) and had mild symptoms (52%). Compared to a healthy general population (50(10); Cella et al., 2010), this sample had higher fatigue (56(13)), and pain interference 52.7(10.5)). Across the five core social-psychological stressor characteristics, the average lifetime count of stressors experienced ranged from 2.2(1.4) for entrapment to 6.6(3.5) for interpersonal loss. Similarly, the average severity ranged from 8.3(6) for entrapment to 16(11) for role change/disruption. Most participants endorsed that their relapse burden had not changed since the onset of Covid-19, and the average count of mental health symptoms, diagnoses, or events was 2.2(1.7).

Age at symptom onset

Interpersonal loss stressor count (b=.45, p=.002) and severity (b=.21, p=.001) were significantly associated with age at symptom onset (Table 4.2). While role change disruption count trended towards significance (b=-.22, p=.06), only the severity had a significant negative relationship, suggesting that as severity increased the age at onset decreased (b=-.11, p<.05). Compared to females, males were nearly three years older at symptom onset throughout count (b=2.93, p<.01), and severity regressions (b=2.9, p=.01).

Pain Interference

With each additional count of physical danger stressors, there was 7% increased odds of reporting any pain interference (OR=1.07, p<.02) (Table 4.3). Interpreting this within context of the range of physical stressors experienced in this sample (0-29), those who reported the highest count were 203% more likely to report experiencing pain interference compared to the PwMS who reported zero. The magnitude of pain

interference was also significantly associated with the count (b=.16, p<.02), and the severity (b=.09, p<.02) of physical danger stressors (Table 4.4). Additionally, physical danger made a significant overall contribution to the count (p<.003) and the severity (p<.04) regressions despite the two-part modeling.

With each additional count of entrapment stressors, there was 42% increased odds of reporting any pain interference (OR=1.42, p<.001). Interpreting this within context of the range of entrapment experienced in this sample (0-6), those who reported the highest count were 252% more likely to report experiencing pain interference compared to the PwMS who reported zero. Similarly, for each 1-unit increase in entrapment stressor severity, there was 8% increased odds of reporting any pain interference (OR=1.08, p<.01). Interpreting this within context of the range of entrapment severity experienced in this sample (0-27), those who reported the highest count were 216% more likely to report experiencing pain interference compared to the PwMS who reported zero. The magnitude of pain interference was also significantly associated with entrapment stressor severity (b=.15, p<.03). Additionally, entrapment stress made a significant overall contribution to the count (p<.001) and the severity (p<.001) regressions despite the two-part modeling.

Regarding covariates, age was associated with slightly higher odds of reporting any pain interference, however contingent upon experiencing any interference, age was also associated with a lower magnitude of interference in both the count and severity regressions. College education was associated with less pain interference throughout both regressions.

Fatigue

Physical danger stressor count (b=.24, p<.001) and severity (b=.07, p=.05) were significantly associated the magnitude of fatigue (Table 4.5). Similarly, role change / disruption stressors count (b=.19, p<.001) and severity (b=.11, p<.01) were significantly associated with magnitude of fatigue (Table 4.6). While the count of these stressors was not significantly associated with reporting any amount of fatigue in the logistic part of the model, physical danger (p<.002) and role change (p<.02) did contribute significantly to the overall model.

With each increase in the severity rating of entrapment stressors there was 15% higher odds of reporting any fatigue (OR=1.15, p<.05). Interpreting this within context of the range of entrapment severity experienced in this sample (0-27), those who reported the highest were 405% more likely to experience fatigue compared to the PwMS who reported zero. The magnitude of fatigue was also very strongly associated with entrapment stressor count (b=.97, p<.001) and stressor severity (b=.21, p<.001). Additionally, for each additional entrapment stressor experienced the odds of reporting any fatigue increased by 54% but this was marginally significant (OR=1.54, p<.08), however, the entrapment count variable contributed significantly overall despite the two-part modeling (p<.001).

Regarding covariates, age was negatively associated with the magnitude of fatigue in both the count and severity regressions (b=-07, p<.01). Having a master's degree or above was associated with less magnitude of fatigue (b=-3.97, p<.01). Progressive forms such as SPMS (b=2.6, p<.01) and PRMS (b=6.35, p<.01) reported higher magnitude of fatigue.

Mental health comorbidity

The count and severity of physical danger, role change/disruption, and humiliation all were significantly associated with mental health comorbidity in PwMS (Table 4.7). For each incremental increase in the count of role change/disruption stressors there is a 3% increase in the risk of an additional mental health symptom, diagnoses, or event (IRR 1.03, p<.001). For example, the range of role change stressors was 0-28 (Table 4.1), so those who experienced 28 stressors had 84% more risk of accumulating an additional mental health comorbidity compared to those who did not experience any role change stressors. Likewise, with each incremental increase in the severity rating, there was a 2% increased risk of additional mental health comorbidity (IRR 1.02, p<.001). In context of the role change severity rating range in this sample (0-58), those with a rating of 58 would be at 116% increased risk of additional mental health comorbidity. Similarly, 1-unit increases in physical danger count (IRR 1.02, p<.01) and severity (IRR 1.01, p<.02) interpreted within context of the variable ranges (0-29, 0-57) translate to 58% and 57% increased risk of mental health comorbidity for those reporting the highest count and severity over those who reported zero count or severity. The count (IRR 1.02, p<.05) and severity (IRR 1.01, p<.05) of humiliation stressors also increased the risk of mental health comorbidity by 2% and 1%. Interpreting these again within context of the ranges translates to 38% and 33% increased risk for the PwMS who reported the highest count and severity compared to PwMS who reported zero humiliation stressors.

In addition to stressors, some covariates were also significant. For each year a participant aged, the risk of mental health comorbidity decreased by 1% (IRR .99,

p<.001). Lastly, males experienced 16% less risk of mental health comorbidity compared to females in only the count (IRR=.84, p=.005) regression.

Disability

None of the five social-psychological stressor types were significantly associated with disability (Table 4.8). Those born in the Winter (38%) and Summer (39%) had lower odds of disability when compared to those born in the spring (p<.05). Each year aged was associated with 6% increased odds of disability in both the count and stressor regressions (OR=1.06, p<.001). Those with at least a master's degree had 65% and 67% lower odds of disability in the count (OR=.36, p<.01) and severity regressions (OR=.33, p<.01). Unsurprisingly, participants with progressive forms had 15-30 times greater odds of disability when compared to RRMS.

Relapse burden change since Covid-19

None of the five stressor types were significantly associated with relapse burden since March 2020, the approximate widespread onset of Covid-19 and many socio-political stressors (Table 4.9). For each year aged, the odds of worsening relapse burden decreased by 2%. Having any college education was associated with a lighter relapse burden when compared to a high school education throughout the count and severity regressions. Unsurprisingly, those with RRMS had about 86% higher odds of a worsening relapse burden compared to PPMS.

Subgroup analysis of race / ethnicity

Using small cell sizes in any categorical demographic variable creates potential for 1) the sample to not truly represent the population, 2) unreliable statistics, and 3) the participant to be identified. Our full sample (n=924) had small cell sizes across the

Latinx (n=4), Asian (n=4), Middle Eastern (n=1, American Indian/Alaska Native (n=2), Native Hawaiian/Pacific Islander (n=1) groups. Therefore, we did have to collapse these five groups into one combined category.

To demonstrate how the missing participants (n<=366) may have different outcomes from the other groups, we included a missing category. For the ability to assess a higher number of racial/ethnic variable categories across the six outcomes, the median and Interquartile Range (IQR) was used for the subgroup analyses. Descriptive data, median and Interquartile Range (IQR), is reported across outcomes so that the largest possible sample could be shown, unaffected by other potential missingness in other variables.

All groups had a median of mild disability (1) and an IQR of mild to moderate (1-2), except the combined group (1-1.5) (Appendix A). The group with the highest median pain was Black 58 (IQR 41-65), while the combined group had the lowest 44 (IQR 41-58). All groups were relatively similar regarding median fatigue, with scores ranging from 58-60. Most groups had a median of two mental health symptoms, diagnoses, or events, except for the Bi-racial or mixed-race group which had 3 (IQR 2-4). Age at onset was between 25.5-30 across all groups, with Black PwMS having the earliest (IQR 21-36). Most groups had a relapse burden change of two, representing no change, while Black PwMS had a median of 3, representing a worse burden since the onset of Covid-19.

Discussion

This is the first study to assess the impact of five core social-psychological types of stressors across the lifespan on Multiple Sclerosis clinical features. As seen in the

summary Table 4.10 this study revealed that four MS clinical features are correlated with stressors across the lifespan. Physical danger and entrapment were the most impactful social-psychological stressor types, followed closely by role changes. In contrast. humiliation was only associated with one outcome, mental health comorbidity. Similarly, interpersonal loss was only associated with the age at symptom onset. The characteristics of our sample may contribute to these findings. For example, it is possible that humiliation could be viewed as less threatening to social safety compared to physical danger or threats to survival such as a lack of food or stable housing due to poverty (e.g., entrapment stress). Additionally, this sample was highly educated and may be less susceptible to humiliation stress, or perhaps even stress in general, due to enhanced self-schemas, confidence, or resilience skills gained from their accomplishments (Slavich, 2020). Similarly, the average age of our sample was 49(12). Unlike an older sample, this sandwich generation age range may suggest that most of our sample might not have undergone losing their parents yet or their adult children as they also age, contributing to the association between interpersonal loss the age at symptom onset. Further, marital or divorce status was not included in our descriptive analyses but would help give context to what portion of the sample had undergone that specific interpersonal loss stressor. Future research could benefit by including this information to also see if perhaps being in a committed relationship is a positive social safety aspect that buffers the impact of negative stressors.

This work both aligns and contrasts with prior research. While no other studies have used the STRAIN in a sample of only PwMS, a few researchers have assessed similar stressors or outcomes in other populations. Childhood, adult, and cumulative

lifespan stressors, measured by the STRAIN, were all significantly higher in a group of cancer survivors with persistent fatigue when compared to non-fatigued survivors, supporting the literature that there are overall cognitive aspects to fatigue despite specific physical diagnoses (Bower et al., 2014; Pust et al., 2020). Of the five core social-psychological types, physical danger and interpersonal loss were the most significant ($p<.001$), however role change disruption ($p<.01$) and entrapment ($p<.05$) also significantly increased risk for having any of 21 autoimmune diseases inclusive of MS (Slavich & Shields, 2018). Physical and sexual abuse, which both fall under physical danger stressors in our study, have been significantly related to higher relapse rates in PwMS, however only childhood stressors were assessed (Spitzer et al., 2012). In contrast, although also using a lifespan approach, Spitzer and colleagues did not find significant results for relapses, however, DMTs treatment has greatly improved over the last decade which might have prevented relapses and thus led to our null results. We also only measured a *change* in relapses since Covid-19 and not overall relapse rates as previous work typically does. Major negative stressors (e.g., physical threats, infidelity) have been associated with new or larger brain lesions in PwMS (Burns et al., 2014), which represents relapse activity and possible increased disability. However, that study also lacked a lifetime approach by only measuring stressors during adulthood. Future research should explore the five core social-psychological types of stressors over the lifetime and additional features of MS, with careful consideration for the measurement of relapses.

Other stressor measurement inconsistencies increase the difficulty for comparisons with prior literature. For example, half of the studies in the review by Polick

et al., (2022) only measure a count or binary (yes/no) exposure to certain childhood or lifetime stressors of PwMS and not nuanced information like severity or duration. This current study revealed that the stressor severity was significant, or closer to significant, for many of our MS outcomes (e.g., age at onset), when compared to stressor count. These nuanced differences in measurement of stressors are likely contributing to conflicting results in the literature, especially if only count or binary exposure is evaluated. Including characteristics such as stressor severity and duration likely aligns closer to the true effect of the stressor when compared to count or binary exposure to any certain categories of stressors (e.g., abuse, neglect).

Our findings related to other known MS risk factors and are also worth to noting. The effect of age varied across outcomes. For example, age was associated with a lighter relapse burden since Covid-19. This may represent the transition to progressive MS forms that have less relapses, and/or better disease management over time. While an increase in age did increase the risk for experiencing *any* fatigue and pain interference, the actual *magnitude* experienced was lower with age. Similarly, there were slightly lower odds of mental health comorbidity with increased age. Together, this may represent improved coping (e.g., stressors, acceptance of chronic disease), perhaps through professional help like therapy, and building resiliency. This aligns with evidence that psychological resilience mediates stressors and MS symptoms, but this finding was measured in adults over the past 60 days (Swanepoel et al., 2020). Future work should expand to include positive factors that may buffer the impact of stressors across the lifespan such as mental health support (e.g., therapy, MS support groups), social relationships (e.g., loved ones, pets), and resiliency.

Birth season is also conventionally included in analyses assessing MS risk and not its clinical features. However, we found that it impacted MS disability. People born in the Spring had approximately 38% more risk of disability compared to those born in the Winter. A Spring birth means that a developing fetus may not have as much serum vitamin D; the mothers are likely not getting as much sunshine exposure compared to those who are pregnant over the Summer and birth in the Winter (Ismailova et al., 2019; Handel et al., 2010). Programming of vitamin D absorption and its effects on immunomodulation during fetal immune system development in utero could help explain the relationship between birth season and adult MS disability (Erlebacher, 2013; Palaniswamy et al., 2016; Salamon & Paro-Panjan 2018). Future research should consider the use of MS specific covariates such as birth seasonality while investigating explanatory factors of disability. Further, tailored treatment for vitamin D supplementation dosing may be informed by future research that accounted for, and could be tailored to, birth seasonality.

Implications

This work highlights the effects of cumulative stressors across the lifespan on MS clinical features to help elucidate which types of stressors and stressor characteristics impact different outcomes. Yet this area is still understudied. Future research should examine additional clinical features of MS such as spasticity, cognition, sleep, and positive experiences that may attenuate stressor impact. The findings from this study related to stressor severity also highlight that using only count based stressor measures may not capture the full association. Additional stressor characteristics such as duration and frequency may also play critical roles.

This work supports the clinical integration of trauma informed care (TIC) and stressor screening practices for PwMS, although it is highly likely that most patients and clinical care settings would benefit from these practices as well. This study found that physical danger stressors are one of the most impactful types. Some physical danger stressors may be unavoidable (e.g., accidents), yet others like physical abuse could be screened for and addressed. The American Medical Association (AMA) and the American Academy of Neurology (AAN) supports screening for past and current abuse or violence, yet evidence suggests formal screening has not been widely implemented (Polick et al., 2021; Roque et al., 2013; Shulman & Hohler, 2012). Patients may informally share insight into their stressors with their neurologist over the course of MS treatment, such as an inability to pay their treatment co-pay or needing more assistance from caretakers which could represent entrapment and role change stressors. Categorizing stressors into a framework such as the five types used in this study can help healthcare providers recognize their accumulation and risk for certain outcomes found in this study.

Stressor screening is only part of a larger framework of providing trauma TIC. A trauma informed approach to providing healthcare includes an awareness of the effects of trauma, its signs and symptoms, having a system to respond, and avoiding re-traumatization (Substance Abuse and Mental Health Services Administration [SAMHSA], 2014). A recent study revealed that barriers to screening are discomfort of healthcare providers to have potentially difficult conversations with patients and the uncertainty of how to respond should a patient need additional resources (Clark & Jones, 2022). Implementing a screening and referral protocol for all patients within a

neurology setting would help tailor the care of PwMS and support TIC for all other patients as well.

Healthcare providers who gain this additional information are better poised for risk assessment, disease management, and facilitating referrals to services that may complement disease management such as mental health support. Evidence supports that improving mental health, coping and stress management skills, and can in turn improve some other MS clinical features such as fatigue, pain, relapses, and quality of life (Koltuniuk et al., 2021, MacDonald et al., 2021; Pust et al., 2020). Policies that incentivize widespread stressor screening for both children and adults, such as creating specific billing codes, promoting healthcare provider training, and increasing reimbursement rates, could increase provider screening practices. For example, California was the first state to implement these changes in January 2020 to promote health and decrease future healthcare costs, and as of September 2021, nearly 11,000 Medi-Cal providers have taken the training and over 640,700 screenings had been completed (California Department of Health Care Services [DHCS], 2022). These changes are a phenomenal start to shift healthcare towards disease mitigation and prevention, yet California's screening focuses on adverse childhood experiences while a cumulative lifetime approach could be more helpful to inform MS treatment.

The results from this study can help guide MS treatment decisions. For example, current treatments for fatigue involve using stimulants in an off label manner, and may create potential for more harm than benefit. Nourbakhsh et al., recently raised ethical considerations after finding that medication did not treat fatigue better than a placebo (2021). Stimulants carry risk of side effects, misuse, and drug interactions and may not

be ethical to prescribe to everyone given the new robust evidence and alternative methods such as Cognitive Behavioral Therapy (CBT) (Nourbakhsh et al., 2021). CBT could be an ideal non-pharmacological solution for PwMS who have a high stressor history. Stressor screening and referrals to CBT may also help improve other factors such as mental health comorbidity, pain perception and quality of life.

Limitations

The cross-sectional nature of this study limits causal inference. The self-administered survey which asked about stressful situations creates potential for social desirability and recall bias. A response bias may be present so that the sample is representative of PwMS who engage with technology and have the ability (e.g., physically, mentally) to participate in an online survey. Similarly, PwMS may experience "effort after meaning" which may impact stressor reporting to help them make sense of their disease. However, the STRAIN has demonstrated good test-retest validity and to not be impacted by social desirability, personality, or induce a negative mood (Slavich & Shields, 2018). Missing data contributing to the race/ethnicity variable being omitted in the main analyses is a limitation, however, for varying reasons this information is not consistently used throughout the literature and would also be lacking nuance if it were included. Future studies should expand upon this study to explore interactions between race and stressors and race and MS clinical features to help the field move forward.

Conclusion

These findings support an association between stress and MS clinical features of age at symptom onset, fatigue, pain interference, and mental health comorbidity. Future research, clinical practice, and policy work should expand upon this study to support

nuanced stressor screening and trauma informed precision health care including the most ethical treatments for PwMS and high stressor exposure.

Table 4.1 Characteristics of final analytic sample

Age M(SD) (n= 713)	49 (12)	
Gender n(%) (n=713)		
Female	597 (84%)	
Male	101 (14%)	
Transgender, non-binary, gender non-conforming or other	15 (2%)	
Race / Ethnicity n(%) (n= 473)		
White	417 (88%)	
Black	23 (5%)	
Latinx	2 (<1%)	
Asian	4 (<1%)	
American Indian / Alaska Native	2 (<1%)	
Native Hawaiian / Pacific Islander	1 (<1%)	
Bi-racial or mixed race	24 (5%)	
Education n(%) (n= 713)		
High school, GED, or below	36 (5%)	
Associates degree or some college	167 (23%)	
Bachelor's degree	259 (36%)	
Master's degree or above	251 (35%)	
Smoking status n(%) (n=709)		
Never smoker	465 (66%)	
Former smoker	198 (28%)	
Current or social smoker	46 (6%)	
Latitude M(SD) (n=713)	39(5.9) range: 10-65	
Birth Season n(%) (n=710)		
Spring	187 (26%)	
Summer	175 (25%)	
Fall	178 (25%)	
Winter	170 (24%)	
MS Phenotype n(%) (n=713)		
RRMS	559 (79%)	
PPMS	35 (5%)	
SPMS	87 (12%)	
PRMS	9 (1%)	
Unsure	23 (3%)	
Length of time since MS onset M(SD) (n=713)	18 (12)	
Disease Modifying Therapy (DMT) n(%) (n=709)		
None	129 (18%)	
First line	272 (38%)	
Second line	308 (44%)	
Count of medication classes that can impact pain M(SD) (n=705)	1.63 (1.29) range: 0-5	
Stressor count & severity M(SD) range (n=713)		
Physical danger	Count: 6(5) 0-29	Severity: 14(11) 0-57
Entrapment	Count: 2.2(1.4) 0-6	Severity: 8.3(6) 0-27
Role change / disruption	Count: 6(4.8) 0-28	Severity: 16(11) 0-58
Interpersonal loss	Count: 6.6(3.5) 0-19	Severity: 15.8(8) 0-43
Humiliation	Count: 4(3.5) 0-19	Severity: 10(7) 0-33
Outcome variables		
Disability (PDDS) n(%) (n=706)		
None to Mild	365 (52%)	
Moderate	236 (33%)	
Severe	105 (15%)	
Fatigue raw t-score median (IQR), M(SD) (n=713)	58 (52-63), 56(13)	

Pain interference raw t-score median (IQR), M(SD) (ref. 50(10)) (n=713)	54 (41-62), 52.8(10.5)
Age at MS onset M(SD) (n=713)	31 (10)
Relapse change since Covid-19 (n=675)	
No relapse	198 (29%)
Improved	26 (4%)
Stayed the same	242 (36%)
Worsened	209 (31%)
Mental Health comorbidity count M(SD) (n=709)	2.2 (1.7) range: 0-6

*Percentages rounded to nearest whole percent and may not always equal 100%

Table 4.2 Stressor count & severity impact on age at symptom onset using two linear regressions (n=696)

	Count regression Model stats: R^2 =.0373 p=.053				Severity regression Model stats: R^2 =.0408 p=.027			
	b	**SE**	**p**	**95% CI**	**b**	**SE**	**p**	**95% CI**
Five core domains								
Physical danger	.01	.10	.96	-.19 - .19	.06	.05	.23	-.04 - .16
Entrapment	-.27	.37	.47	-.98 - .45	-.07	.09	.43	-.25 - .11
Role change / disruption	-.22	.12	.06	-.44 - .01	-.11	.05	**<.05**	-.21 - -.002
Interpersonal loss	.45	.14	**.002**	.17 - .72	.21	.06	**.001**	.09 - .33
Humiliation	-.12	.15	.41	-.41 - .17	-.11	.07	.13	-.26 - .03
Gender (ref. female)								
Male	2.93	1.12	**<.01**	.73 - 5.13	2.90	1.12	**.01**	.70 - 5.11
Transgender, non-binary, gender non-conforming, or other	-2.69	2.72	.53	-7.03 - 3.64	-1.91	2.71	.48	-7.23 - 3.42
Education (ref. ≤HS)								
Associates degree or some college	-1.48	1.92	.44	-5.25 - 2.30	-1.10	1.91	.57	-4.85 - 2.66
Bachelor's degree	-.98	1.90	.61	-4.71 - 2.74	-.53	1.90	.78	-4.25 - 3.19
Master's degree or above	-2.90	1.91	.13	-6.66 - .86	-2.58	1.90	.18	-6.33 - 1.16
Smoking Status (ref. non-smoker)								
Former smoker	-.79	.94	.38	-2.63 - 1.05	-.78	.93	.40	-2.61 - 1.04
Current or social smoker	.53	1.70	.75	-2.80 - 3.87	.46	1.68	.79	-2.84 - 3.76
Birth Season (ref. Spring)								
Summer	.29	1.08	.79	-1.84 - 2.42	.37	1.08	.74	-1.76 - 2.49
Fall	.01	1.08	.10	-2.12 - 2.13	.20	1.08	.86	-1.93 - 2.32
Winter	.60	1.10	.59	-1.57 - 2.76	.78	1.10	.48	-1.38 - 2.94
Latitude (degree)	.003	.07	.96	-.13 - .14	.02	.07	.79	-.11 - .15

Table 4.3 Stressor *count* impact on pain interference using two-part modeling

First part - logistic regression (n=701) **Any pain interference (binary)** Model stats: Pseudo R^2 =.2702 p<.0001					**Overall stressor p**	**Second part** - OLS regression (n=459) **Magnitude of pain interference** Model stats: R^2 .2610 p<.0001			
	OR	**SE**	**p**	**95% CI**		**b**	**SE**	**p**	**95% CI**
Five core domains									
Physical danger count	1.07	.03	**<.02**	1.01 - 1.13	**.003**	.16	.07	**<.02**	.03 - .29
Entrapment count	1.42	.14	**<.001**	1.18 - 1.71	**<.001**	.45	.27	.10	-.08 - .98
Role change / disruption count	.98	.03	.53	.92 - 1.04		.12	.08	.15	-.04 - .28
Interpersonal loss count	.99	.04	.85	.92 - 1.07		.04	.11	.71	-.17 - .25
Humiliation count	1.06	.04	.13	.98 - 1.14		.12	.10	.24	-.08 - .33
Age	1.022	.01	**<.02**	1.00 - 1.04		-.09	.03	**.001**	-.15 - .04
Gender (ref. female)									
Male	.66	.18	.13	.39 - 1.13		.70	.93	.45	-1.11 - 2.52
Transgender, non-binary, gender non-conforming, or other	.92	.70	.91	.21 - 4.05		-2.42	1.93	.21	-6.21 - 1.36
Education (ref. ≤HS)									
Associates degree or some college	.12	.10	**<.01**	.02 - .59		-1.13	1.24	.36	-3.56 - 1.29
Bachelor's degree	.09	.07	**<.01**	.02 - .44		-3.16	1.21	**<.01**	-5.54 - .79
Master's degree or above	.084	.07	**<.01**	.02 - .41		-3.70	1.22	**<.01**	-6.08 - 1.31
MS Phenotype (ref. RRMS)									
PPMS	1.74	.85	.25	.67 - 4.52		.51	1.39	.71	-2.20 - 3.23
SPMS	1.63	.55	.15	.83 - 3.17		2.62	.92	**<.01**	.82 - 4.41
PRMS	1.41	1.34	.72	.21 - 9.11		5.99	2.38	**.01**	1.32 - 10.6
Unsure	1.22	.68	.73	.41 - 3.65		3.02	1.70	.08	-.31 - 6.35
DMT (ref. No therapy)									
First line	1.45	.42	.20	.82 - 2.57		-.56	.90	.54	-2.33 - 1.22
Second line	2.14	.63	**.01**	1.20 - 3.82		-1.27	.87	.14	-2.97 - .431
Pain med count	2.36	.24	**<.001**	1.94 - 2.87		1.09	.24	**<.001**	.62 - 1.55

Table 4.4 Stressor *severity* impact on pain interference using two-part modeling

	First part - logistic regression (n=701) **Any pain interference (binary)** Model stats: Pseudo R^2 =.2619 p<.0001				**Overall stressor p**	**Second part** - OLS regression (n=459) **Magnitude of pain interference** Model stats: R^2 =.0.2675 p<.0001			
	OR	**SE**	**p**	**95% CI**		**b**	**SE**	**p**	**95% CI**
Five core domains									
Physical danger severity	1.01	.01	.47	.95 - 1.04	**.03**	.09	.04	**.012**	.02 - .16
Entrapment severity	1.08	.03	**.002**	1.03 - 1.13	**<.001**	.15	.07	**.026**	.02 - .27
Role change / disruption severity	1.01	.01	.44	.98 - 1.04		.02	.04	.60	-.05 - .09
Interpersonal loss severity	.98	.02	.27	.95 - 1.01		.04	.05	.41	-.05 - .13
Humiliation severity	1.03	.02	.14	.99 - 1.07		.03	.05	.53	-.07 - .14
Age	1.024	.01	**<.01**	1.01 - 1.04		-.10	.03	**<.001**	-.15 - .04
Gender (ref. female)									
Male	.68	.18	.15	.40 - 1.15		1.07	.92	.25	-.74 - 2.9
Transgender, non-binary, gender non-conforming	1.01	.74	.99	.24 - 4.24		-2.15	1.92	.26	-5.90 - 1.61
Education (ref. ≤HS)									
Associates degree or some college	.14	.11	**.02**	.03 - .68		-1.34	1.22	.27	-3.73 - 1.05
Bachelor's degree	.10	.08	**.03**	.02 - .47		-3.30	1.20	**<.001**	-5.65 - .95
Master's degree or above	.09	.07	**.02**	.02 - .41		-3.90	1.20	**.001**	-6.26 - 1.54
MS Phenotype (ref. RRMS)									
PPMS	1.71	.82	.26	.67 - 4.36		.37	1.38	.79	-2.34 - 3.07
SPMS	1.58	.54	.17	.82 - 3.08		2.60	.91	**<.01**	.82 - 4.39
PRMS	1.24	1.20	.83	.19 - 8.25		5.98	2.37	**.01**	1.33 - 10.6
Unsure	1.27	.71	.66	.43 - 3.80		2.86	1.70	.09	-.46 - 6.18
DMT (ref. No therapy)									
First line	1.40	.40	.24	.80 - 2.46		-.58	.91	.52	-2.35 - 1.20
Second line	2.17	.64	**<.01**	1.22 - 3.85		-1.20	.87	.12	-2.90 - .50
Pain med count	2.33	.23	**<.001**	.07 - 2.82		1.03	.24	**<.001**	.57 - 1.49

Table 4.5 Stressor *count* impact on fatigue using two-part modeling

	First part - logistic regression (n=600) **Any fatigue (binary)** Model stats: Pseudo R^2 =.1479 p<.003				**Overall stressor p**	**Second part** - OLS regression (n=685) **Magnitude of fatigue** Model stats: R^2 =.2382 p<.0001			
	OR	**SE**	**p**	**95% CI**		**b**	**SE**	**p**	**95% CI**
Five core domains									
Physical danger count	.98	.07	.72	.86 - 1.12	**<.002**	.24	.07	**<.001**	.11 - .38
Entrapment count	1.54	.38	.08	.95 - 2.49	**<.001**	.97	.26	**<.001**	.46 - 1.49
Role change / disruption count	1.17	.11	.10	.97 - 1.42	**.015**	.19	.08	**.017**	.04 - .35
Interpersonal loss count	1.11	.10	.23	.94 - 1.33		.06	.10	.55	-.14 - .27
Humiliation count	.91	.08	.26	.76 - 1.08		.05	.10	.61	-.15 - .25
Age	.99	.02	.59	.95 - 1.03		-.07	.03	**<.01**	-.12 - -.02
Gender (ref. female)									
Male	.62	.34	.38	.21 - 1.80		-.66	.81	.42	-2.23 - .92
Transgender, non-binary, gender non-conforming	n/a	n/a	n/a	n/a		-3.09	1.90	.10	-6.81 - .63
Education (ref. ≤HS)									
Associates degree or some college	4.98	5.35	.12	.61 - 40.84		-1.13	1.36	.41	-3.78 - 1.53
Bachelor's degree	.88	.40	.78	.37 - 2.12		-2.31	-2.31	.08	-4.89 - .27
Master's degree or above	n/a	n/a	n/a	n/a		-3.87	-.387	**<.01**	-6.46 - -1.27
MS Phenotype (ref. RRMS)									
PPMS	n/a	n/a	n/a	n/a		1.27	1.35	.34	-1.37 - 3.91
SPMS	2.19	1.82	.35	.43 - 11.14		2.66	.92	**<.01**	.87 - 4.46
PRMS	n/a	n/a	n/a	n/a		6.77	2.41	**<.01**	2.04 - 11.50
Unsure	n/a	n/a	n/a	n/a		2.17	1.60	.17	-.95 - 5.29
DMT (ref. No therapy)									
First line	.69	.48	.59	.18 - 2.67		-.85	.84	.31	-2.49 - .79
Second line	1.82	1.48	.46	.37 - 8.96		.26	.82	.75	-1.34 - 1.87

*n/a shown where participants were dropped from the first part modeling due to collinearity

Table 4.6 Stressor *severity* impact on fatigue using two-part modeling

First part - logistic regression (n=600) **Any fatigue (binary)** Model stats: Pseudo R^2 =.1486 p<.0029					**Overall stressor p**	**Second part** - OLS regression (n=685) **Magnitude of fatigue** Model stats: R^2 =.2442 p<.0001			
	OR	**SE**	**p**	**95% CI**		**b**	**SE**	**p**	**95% CI**
Five core domains									
Physical danger severity	.98	.03	.45	.92 - 1.04	.11	.07	.04	**.05**	.00 - .14
Entrapment severity	1.15	.08	**.04**	1.00 - 1.31	**<.001**	.21	.07	**.001**	.08 - .33
Role change / disruption severity	1.04	.04	.38	.96 - 1.12	**.01**	.11	.04	**<.01**	.04 - .18
Interpersonal loss severity	1.04	.04	.39	.96 - 1.12		.02	.05	.71	-.07 - .11
Humiliation severity	1.00	.05	.97	.91 - 1.10		.07	.05	.18	-.03 - .17
Age	.99	.02	.63	.95 - 1.03		-.07	.03	**<.01**	-.12 - -.02
Gender (ref. female)									
Male	.64	.36	.42	.22 - 1.90		-.29	.81	.72	-1.87 - 1.29
Transgender, non-binary, gender non-conforming	n/a	n/a	n/a	n/a		-2.51	1.89	.18	-6.20 - 1.19
Education (ref. ≤HS)									
Associates degree or some college	4.61	4.93	.15	.57 - 37.55		-1.24	1.34	.36	-3.87 - -1.40
Bachelor's degree	.91	.41	.84	.38 - 2.20		-2.41	1.31	.07	-4.98 - .16
Master's degree or above	n/a	n/a	n/a	n/a		-3.97	1.31	**<.01**	-6.53 - 1.40
MS Phenotype (ref. RRMS)									
PPMS	n/a	n/a	n/a	n/a		1.19	1.34	.38	-1.44 - 3.81
SPMS	2.11	1.76	.37	.41 - 10.8		2.6	.91	**<.01**	.82 - 4.38
PRMS	n/a	n/a	n/a	n/a		6.35	2.4	**<.01**	1.64 - 11.06
Unsure	n/a	n/a	n/a	n/a		2.04	1.58	.20	-1.06 - 5.14
DMT (ref. No therapy)									
First line	.61	.42	.47	.16 - 2.35		-1.08	.83	.20	-2.71 - .56
Second line	1.67	1.34	.53	.34 - 8.11		.16	.82	.87	-1.44 - 1.76

*n/a shown where participants were dropped from the first part modeling due to collinearity

Table 4.7 Stressor *count & severity* impact on mental health using Poisson regression (n=705)

	Count regression				Severity regression			
	Model stats: Pseudo R^2 =.1051 p<.0001				Model stats: Pseudo R^2 =. p<.0001			
	IRR	**SE**	**p**	**95% CI**	**IRR**	**SE**	**p**	**95% CI**
Five core domains								
Physical danger	1.02	.01	**.004**	1.01 - 1.03	1.01	.003	**.018**	1.00 - 1.01
Entrapment	1.02	.03	.48	.97 - 1.07	1.00	.01	.77	.99 - 1.01
Role change / disruption	1.03	.01	**<.001**	1.02 - 1.04	1.02	.003	**<.001**	1.01 - 1.02
Interpersonal loss	1.00	.01	.90	.98 - 1.02	1.003	.004	.52	1.00 - 1.01
Humiliation	1.02	.01	**<.05**	1.00 - 1.04	1.01	.01	**.032**	1.00 - 1.02
Age	.986	.002	**<.001**	.98 - .99	.99	.002	**<.001**	.98 - .99
Gender (ref. female)								
Male	.84	.07	**<.05**	.71 - .99	.89	.08	.16	.75 - 1.05
Transgender, non-binary, gender non-conforming	.90	.14	.49	.66 - 1.22	.98	.15	.90	.72 - 1.34
Education (ref. ≤HS)								
Associates degree or some college	.999	.11	.99	.80 - 1.25	.94	.10	.60	.76 - 1.17
Bachelor's degree	.98	.11	.87	.79 - 1.22	.96	.11	.70	.77 - 1.19
Master's degree or above	.97	.11	.75	.78 - 1.20	.94	.10	.59	.76 - 1.17
MS Phenotype (ref. RRMS)								
PPMS	1.23	.16	.11	.96 - 1.58	1.26	.16	.07	.98 - 1.62
SPMS	1.09	.10	.36	.91 - 1.29	1.09	.10	.33	.92 - 1.30
PRMS	1.35	.27	.14	.91 - 1.99	1.32	.26	.17	.89 - 1.95
Unsure	1.21	.18	.18	.91 - 1.61	1.24	.18	.13	.94 - 1.64
Pain med count	1.12	.02	**<.001**	1.07 - 1.16	1.10	.02	**<.001**	1.05 - 1.14

Table 4.8 Stressor count & severity impact on disability using logistic regression (n=695)

	Count regression Model stats: R^2 =.2683 p<.0001				Severity regression Model stats: R^2 =.2676 p<.0001			
	OR	**SE**	**p**	**95% CI**	**OR**	**SE**	**p**	**95% CI**
Five core domains								
Physical danger	1.03	.02	.12	.99 - 1.07	1.01	.01	.56	.99 - 1.03
Entrapment	1.05	.08	.52	.90 - 1.23	1.01	.02	.65	.97 - 1.05
Role change / disruption	1.03	.03	.30	.98 - 1.08	1.02	.01	.13	1.00 - 1.04
Interpersonal loss	1.01	.03	.89	.94 - 1.07	1.00	.01	.91	.97 - 1.03
Humiliation	1.04	.03	.21	.98 - 1.11	1.02	.02	.18	.99 - 1.05
Age	1.06	.01	**<.001**	1.05 - 1.08	1.06	.01	**<.001**	1.05 - 1.08
Gender (ref. female)								
Male	1.06	.26	.81	.65 - 1.72	1.09	.27	.74	.67 - 1.76
Transgender, non-binary, gender non-conforming	.43	.27	.18	.13 - 1.46	.49	.30	.25	.15 - 1.64
Education (ref. ≤HS)								
Associates degree or some college	.91	.36	.80	.42 - 1.97	.85	.34	.68	.39 - 1.85
Bachelor's degree	.55	.21	.12	.25 - 1.18	.51	.20	.09	.24 - 1.10
Master's degree or above	.36	.14	**<.01**	.16 - .78	.33	.13	**<.01**	.15 - .73
Birth Season (ref. Spring)								
Summer	.61	.14	**<.05**	.39 - .97	.62	.15	**<.05**	.39 - .98
Fall	.69	.16	.11	.44 - 1.09	.68	.16	.09	.43 - 1.06
Winter	.62	.15	**<.05**	.39 - .98	.61	.15	**<.05**	.39 - .98
Smoking Status (ref. non-smoker)								
Former smoker	1.10	.22	.64	.75 - 1.61	1.13	.22	.54	.77 - 1.66
Current or social smoker	1.68	.58	.14	.85 - 3.31	1.85	.63	.07	.95 - 3.61
MS Phenotype (ref. RRMS)								
PPMS	20.1	8.42	**<.001**	8.85 - 45.67	20.17	8.43	**<.001**	8.89 - 45.76
SPMS	15.3	4.41	**<.001**	8.68 - 26.91	15.33	4.43	**<.001**	8.71 - 27.00
PRMS	30.9	24.27	**<.001**	6.61 - 144.18	29.14	22.91	**<.001**	6.24 - 136.07
Unsure	1.28	.64	.62	.48 - 3.40	1.34	.67	.56	.51 - 3.55
DMT (ref. No therapy)								
First line	.70	.18	.15	.43 - 1.14	.68	.17	.12	.41 - 1.10
Second line	1.56	.38	.07	.97 - 2.52	1.51	.37	.09	.94 - 2.45

Table 4.9 Stressor count & severity impact on relapse burden change since Covid-19 using logistic regression (n=668)

	Count regression Model stats: R^2 =.0541 p<.0001				Severity regression Model stats: R^2 =.0558 p<.0001			
	OR	**SE**	**p**	**95% CI**	**OR**	**SE**	**p**	**95% CI**
Five core domains								
Physical danger	1.03	.02	.10	.99 - 1.07	1.004	.01	.64	.99 - 1.02
Entrapment	1.04	.07	.56	.91 - 1.19	1.01	.02	.51	.98 - 1.05
Role change / disruption	1.02	.02	.34	.98 - 1.07	1.02	.01	.13	1.00 - 1.04
Interpersonal loss	.96	.03	.11	.91 - 1.01	.98	.01	.11	.96 - 1.00
Humiliation	1.04	.03	.19	.98 - 1.09	1.03	.02	.09	1.00 - 1.05
Age	.98	.01	**.01**	.97 - 1.00	.98	.01	**<.01**	.97 - .99
Gender (ref. female)								
Male	.85	.18	.45	.56 - 1.29	.89	.19	.57	.58 - 1.35
Transgender, non-binary, gender non-conforming	.62	.33	.37	.22 - 1.74	.65	.34	.41	.23 - 1.82
Education (ref. ≤HS)								
Associates degree or some college	.41	.16	**<.03**	.19 - .88	.38	.15	**<.02**	.18 - .82
Bachelor's degree	.48	.19	.06	.23 - 1.03	.46	.18	**<.05**	.21 - .98
Master's degree or above	.41	.16	**<.03**	.19 - .88	.39	.15	**<.02**	.18 - .84
Smoking status (ref. non-smoker)								
Former smoker	.97	.17	.84	.68 - 1.37	.96	.17	.83	.68 - 1.37
Current or social smoker	.84	.26	.57	.45 - 1.55	.86	.27	.63	.47 - 1.57
MS Phenotype (ref. RRMS)								
PPMS	.14	.06	**<.001**	.06 - .33	.15	.06	**<.001**	.06 - .34
SPMS	.61	.15	**<.05**	.38 - .98	.61	.15	**<.05**	.38 - .98
PRMS	.90	.64	.88	.22 - 3.65	.82	.59	.78	.20 - 3.29
Unsure	1.33	.59	.52	.56 - 3.17	1.40	.62	.45	.59 - 3.34
DMT (ref. No therapy)								
First line	1.21	.27	.39	.79 - 1.86	1.19	.26	.43	.77 - 1.84
Second line	1.22	.27	.37	.79 - 1.88	1.20	.27	.41	.77 - 1.86

Table 4.10 Summary of key findings

Outcomes	Lifetime stressor types and characteristics that significantly impact outcomes
Any fatigue	• Entrapment count & severity
Magnitude of fatigue	• Physical danger count & severity • Entrapment count & severity • Role change count & severity
Any pain interference	• Physical danger count • Entrapment count & severity
Magnitude of pain interference	• Physical danger count & severity • Entrapment severity
Age at onset	• Interpersonal loss count & severity • Role change /disruption severity
Mental health comorbidity	• Physical danger count & severity • Role change / disruption count & severity • Humiliation count & severity
Disability	• None
Relapse burden change since Covid-19	• None

Chapter V

Synthesis and Conclusion

Traumatic stressors experienced in childhood and adulthood have both independently been linked to numerous adverse health outcomes, including worsened symptoms or clinical features for PwMS (Brenner et al., 2018; Grummitt et al., 2021; Shaw et al., 2017; Pust et al., 2020). However, the literature is extremely scarce regarding childhood stressors and contains conflicting findings, likely due to heterogeneity in the measurement of stressors and improvements in drug therapy, which contributes to controversy over the stress-MS relationship (Spitzer et al., 2012; Horton et al., 2022). This three-paper dissertation aimed to address gaps in our understanding of the effect of stressors across the lifespan on six common features of MS: fatigue, disability, pain interference, age at symptom onset, mental health comorbidity, and relapse burden chance since Covid-19.

Summary of major research findings

The first aim investigated whether stressors across the lifespan relate to six features of MS. A lifetime approach was taken by sequentially adding childhood stressor count and severity, and then cumulative adult stressor count and severity into the statistical models. As seen in summary Table 5.1, stressors were associated with most outcomes (n=4). Specifically, childhood stressors were significantly related to four MS features (i.e., fatigue, pain interference, mental health, disability). Likewise, adult

stressors significantly related to four outcomes, (i.e., pain interference, mental health, disability, and relapse burden changes). One outcome, age at onset, was not related to stressors in this aim.

Since cumulative childhood stressors did relate to MS outcomes in aim 1, the second aim narrowed to focus on determining which types of childhood stressors, grouped by emotional, physical, and environmental types, related to the same six outcomes. Most outcomes (n=5) were again affected by the stressors. Emotional and physical stressors each significantly influenced four MS features, while environmental stressors related to two, age at symptom onset and mental health comorbidity. Both emotional and physical stressors were associated with fatigue, pain interference, and mental health comorbidity, while emotional stressors also influenced age at onset and physical stressors influenced disability. Childhood stressors were not related to relapse burden change. This aligns with the findings in aim 1 that only adult stressors associated with relapse burden. Although cumulative childhood stressor count and severity were not related to age at onset in aim 1, child stressors when measured by type, severity, and duration in aim 2 did influence age of onset. This suggests that the stressor types aligned with expanded ACEs are critical types of stressors that a cumulative score may not appropriately assess. For example, an individual who experienced four ACE types of emotional, physical, or environmental stressors would have the same cumulative score as an individual who had other types of stressors such as bullying or being in a car accident. Additionally, having stressor duration in aim 2 likely helped with detecting additional significant relationships.

The third aim returned to the lifetime approach but focused on five different types of stressors to determine what core social-psychological characteristics impact the same six MS clinical features. Stressors influenced four outcomes, fatigue, pain interference, age at symptom onset, and mental health comorbidity (Table 5.1). Physical danger and role change/disruption were each associated with three MS features. Both influenced fatigue and mental health comorbidity, while physical danger was also associated with pain interference and role change was associated with age at symptom onset. Entrapment correlated to two (i.e., fatigue, pain interference), while interpersonal loss (i.e., age at onset) and humiliation (i.e., mental health comorbidity) each associated with one outcome. While stressors influenced participant reported disability in the previous two aims, cumulative stressors, operationalized as five stressor types in aim 3, were not related to disability. Similarly, these social-psychological stressors did not relate to relapse burden even though adult stressors were significant with relapses in aim 1. This may be due to the analytic approach switching from hierarchical block modeling in the first two aims, to multiple regression in the last aim. A large benefit of the block modeling is that similar variables, such as stressors, are assumed to have collinearity and can be assessed by their shared contribution. The multiple regression approach assessed similar stressors individually which might not have allowed true stressor relationships to the outcome to show given potential collinearity with each other. Examined together, the three papers highlight how stressor conceptualization and measurement may be contributing to the conflicting findings and subsequent controversy over the stress-MS relationship.

The overall results across all aims support a relationship between stress and MS features (Table 5.1). This was the first study to take a lifetime approach and report both childhood and adult stressor relationships, helping to fill significant gaps in knowledge regarding what stressor timing, types, and characteristics matter for different MS features. Stressors, measured multiple ways, appear to have the largest effect on outcomes that are more cognitively or emotionally related such as mental health comorbidity, fatigue, and pain interference.

The first two aims, which specifically evaluated childhood stressors, largely support the few studies that have analyzed childhood adversity and MS features. For example, we substantiated previous findings that ACEs were related to age at onset (Shaw et al., 2017), mental health (Eilam-Stock et al., 2021), pain catastrophizing (MacDonald et al., 2021), and that emotional abuse/neglect influence fatigue (Pust et al., 2020). Yet, this is the first study to assess childhood stressors and pain interference, mental health comorbidity, and relapse burden change since Covid-19 with an MS focused sample. Additionally, the rates of traditional ACEs in this study were very similar to nationally reported rates of emotional abuse (33.4% vs. 34.4%), physical abuse (16.7% vs 17.9%), and sexual abuse (12.8% vs. 11.6%) (CDC, 2022). However, when compared to healthy controls, PwMS typically report higher abuse and neglect (Spitzer et al., 2012; Wan et al., 2022), suggesting that our sample could have experienced less childhood adversity than typical MS samples. This also aligns with how highly educated the sample was in this study. Together this suggests that our findings may be underestimated, or rather, even stronger in most MS samples that have experiences higher adversity.

This study also supports the adult stressor literature which typically focuses on MS risk, disability, and relapses for PwMS. For example, we substantiated research linking adult stress and relapses (Artemiadis et al., 2011; Mitsonis et al., 2008), as well as symptoms such as disability, fatigue, depression, mental, and emotional concerns (Brenner et al., 2018; Briones-Buixassa et al., 2015; Sorenson et al., 2014).

This study was the first to report nuanced stressor characteristics such as type, count, severity, and duration across the lifespan. Throughout the aim 1 analyses, the individual stressors that were significant were all stressor severity opposed to count. Similarly, in aim 2, stressor severity or duration were more frequently individually associated with MS features. Together, this suggests that it may not be purely the presence of a stressor that matters most, but that the severity and duration may be more influential. Measurement tools using only stressor count or binary operationalization of yes/no exposure may not be sensitive enough to capture these nuanced relationships between stress and MS features.

Further, measuring stress only in childhood or adulthood does not capture the more holistic frame of stress accumulating across the lifespan. For example, there were individual predictors in the childhood stressor blocks throughout aim 1 that were significantly associated with MS features, yet lost significance when adult stressors were included in the model. This suggests shared variance likely because stressors in childhood can increase the perception of stressors in adulthood, so measuring just one of these aspects may not always be appropriate. Therefore, a lifespan approach which captures nuanced stressor characteristics such as severity and duration may be the best approach to elucidate the complexities between stress and MS features.

Lastly, some covariates were consistently contributing to many features throughout all aims. Generally, there was a negative dose response relationship between education and outcomes, such that the higher the education level the lower the detrimental outcome. Age generally related to slight improvements in outcomes such as mental health comorbidity, relapse burden changes, fatigue, or pain interference magnitudes over time. This may represent the natural progression from relapsing forms of MS to progressive forms, in addition to improved self-efficacy regarding disease management, or acceptance of living with a chronic disease. Further, as someone ages they may have had more opportunity to engage with therapy and coping or stress management techniques. Programs that address barriers to graduating high school and receiving higher education, as well as facilitating resiliency and coping, are particularly important upstream interventional points to be addressed.

Implications for future research, practice, and policy

This is the first study to use a lifetime approach to comprehensively measure stressors, stressor type, characteristics, and MS clinical features. By using a lifespan approach, capturing nuances of severity/duration, accounting for MS specific covariates, and including pain interference and relapse burden changes for the first time, it made a substantial contribution to the literature in this area. Yet, additional research is needed to fully understand these complex relationships. For example, this study as well as most others in this area, did not account for race/ethnicity in the main analyses (Polick et al., 2022). Future research that disentangles the genetic contributions of race/ethnicity on MS features from the contributions made by systemic and social determinants of health, stands to greatly improve risk assessment and treatment of PwMS.

Future research should further examine other aspect of social relationships. This study was guided by the Social Safety Theory (Slavich, 2020) yet only assessed threats to social safety. Positive social relationships that foster social safety should also be explored as possible mediators between stressors and MS features. Having at least one positive relationship with a caring adult during childhood has been shown to buffer the effects of adverse childhood experiences (Bronfenbrenner, 2007; Sciaraffa et al., 2018). Positive adult social networks such as friends, marital status, pets or service animals, and religious or MS focused groups may similarly buffer MS outcomes for PwMS who have a history of traumatic stressors throughout their lifespan.

Findings support the need for and importance of ACE screening for people with MS. The ACE tool is the most widely recognized and used for stressor screening, yet only captures a count of stressors. Given our findings regarding stressor type, severity, and duration, other tools may need to be developed, adapted, and/or validated in multiple languages for use in clinical settings. The STRAIN may be an option if patients have the chance to take it online before their healthcare appointment, however, would not be compatible with paper forms in a clinic setting given heavy reliance on skip patterns. Short, reliable screening tools would likely increase the success rates of adopting screening practices. Feasibility and acceptability research is needed regarding implementation of stressor screening and appropriate referral and/or treatment protocols within neurology settings. Screening practices additionally create further research opportunities to evaluate longitudinal outcomes in PwMS who received a referral to services like mental health or substance use support. An updated conceptual model (Figure 3) shows potential areas for intervention for adults with MS. In addition to

screening, treatment options should be explored to determine whether PwMS and traumatic stressor exposure respond better to certain treatments. Our findings that childhood trauma impacts adult fatigue supports the possibility that interventions aimed at social, emotional, and cognitive improvements such as Cognitive Behavioral Therapy (CBT) would be more effective in treating fatigue compared to a stimulant medication. Using stressor screening to make such decisions would put neurology providers on the forefront of providing trauma informed precision health care.

This work and future work, that is well designed to yield robust evidence, may make the stress-MS relationship less controversial so that a growing number of clinicians support the importance of stressor screening, especially for PwMS. However, there are still factors like time demands, non-specific billing codes, and low reimbursement rates that are barriers to widespread screening in the healthcare setting. For example, providers in Michigan can use general billing codes to be reimbursed for screening children for Adverse Childhood Experiences (ACEs), yet they will only be reimbursed $2.97 which is unlikely to be an incentive (Center for Youth Wellness, 2019). Conversely, Medi-Cal in California has recently implemented ACE specific codes and will reimburse around $29 per screening (California Department of Health Care Services [DHCS}, 2020). In just over a year since implementing the changes, about 640,700 screenings were conducted for children and adult Medi-Cal beneficiaries (California DHCS, 2022). Similar state and federal policy changes are needed to support incentivizing widespread screening and referral programs.

Strengths and limitations

This study had notable strengths. First, this study was informed by stakeholder feedback which likely contributed to recruiting one of the largest samples of PwMS throughout the childhood stress literature. Further, the sample was comprised of PwMS from all over the US. Second, robust measures were used, including the PROMIS scales which produced very high reliability (Cronbach's alpha .95-.98). This was the first study to use the STRAIN with a sample of PwMS, which is more comprehensive than other stressor measurement tools. Finally, a more comprehensive approach was also taken regarding confounders and MS specific covariates such as birth season and latitude which has been inconsistent or lacking throughout the literature.

Yet, limitations should also be noted. A small proportion of the very large listserv completed the survey, creating potential for a bias towards those with the means (e.g., internet device, physically/mentally able) and desire to take the survey. Thus, the sample may represent individuals with higher income, less disability, and who have a trauma history. The cross-sectional nature of this study limits causal inference. The self-administered survey which asked about stressful situations creates potential for social desirability, yet the survey was completed anonymously and at online at home likely minimizing social desirability. Similarly, PwMS may experience "effort after meaning" which may impact stressor reporting to help them make sense of their disease. However, the STRAIN has demonstrated good test-retest validity and to not be impacted by social desirability, personality, or induce a negative mood (Slavich & Shields, 2018). Missing data relating to survey platform and skip pattern errors does perhaps limit some power and creates potential for the data to be missing not at

random; however, the analyses were powered, and no patterns of missing data were found. The final model samples were not very diverse (e.g., 88% White). While this does reflect the overall MS population, future efforts should be taken to oversample minoritized PwMS to properly represent different racial/ethnic groups in research. Despite these limitations, this work adds to the field by being the first study to use a lifetime approach to comprehensively measure stressors, stressor type, characteristics, and MS clinical features.

Conclusion

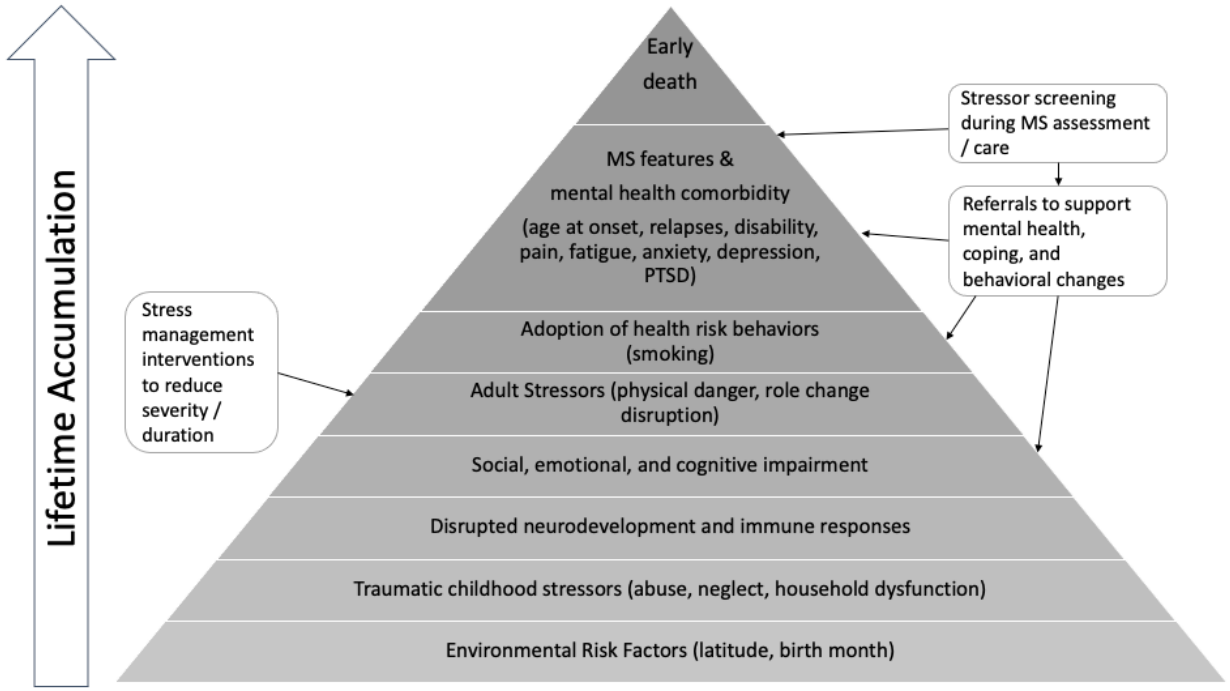
In conclusion, this dissertation revealed significant relationships between stressors, measured multiple ways including nuanced characteristics, and six clinical features of Multiple Sclerosis. Stressors appeared to have the most impact on MS features that are emotionally or cognitively related such as fatigue, pain interference, and mental health comorbidity, as there were significant relationships between stressors and those outcomes (or features) in all three aims. However, there were also significant relationships between stressors and disability and age at symptom onset in two aims each, and between adult stressors and relapse burden change since Covid-19 in one aim. Future research can build upon these findings to enhance the growing yet scarce body of knowledge in this area. These results can also help inform healthcare providers and support having trauma informed practices, screenings, and discussions as standards of care. In turn, trauma informed care can improve the therapeutic alliance. The knowledge gained from screening and discussing how a patient's stressors may impact their behavioral responses (e.g., smoking, medical adherence), and MS clinical feature outcomes can also improve healthcare provider's case conceptualizations and

tailor the treatment plan to provide precision medical care. Together these changes have the potential to reduce MS burden and improve the lives of PwMS.

Table 5.1 Summary of stressor characteristics that impact MS clinical features across all aims

MS clinical feature outcomes	**Aim 1** - Hierarchical regressions with **cumulative childhood and adulthood** blocks of stressors as predictors	**Aim 2** Hierarchical regressions with **childhood emotional, physical, and environmental** blocks of stressors as predictors	**Aim 3** - Multiple regressions with five **core social-psychological types** of stressors and their **count/severity** as predictors
Any fatigue	• Child stressors • Childhood stress severity (individually)	• Emotional stressors • Physical stressors	• Entrapment count & severity
Magnitude of fatigue	• Child stressors (block) • Childhood stress severity (individually)	• Emotional stressors • Physical stressors • Harsh discipline duration (individually)	• Physical danger count & severity • Entrapment count & severity • Role change count & severity
Pain Interference	• Child stressors • Adult stressors	• Emotional stressors • Physical stressors	• Physical danger count • Entrapment count & severity
Magnitude of pain Interference	• Child stressors • Adult stressors	• Emotional stressors • Physical stressors • Harsh discipline duration (individually)	• Physical danger count & severity • Entrapment severity
Age at symptom onset	• None	• Emotional stressors • Environmental stressors • Environmental stressor count (individually)	• Interpersonal loss count & severity • Role change /disruption severity
Mental health comorbidity	• Child stressors • Adult stressors • Adult stress severity (individually)	• Emotional stressors • Physical stressors • Environmental stressors • Emotional abuse severity (individually) • Environmental stress count (individually)	• Physical danger count & severity • Role change / disruption count & severity • Humiliation count & severity
Disability	• Child stressors • Adult stressors	• Physical stressors • Harsh discipline severity (individually)	• None
Relapse burden change since Covid-19	• Adult stressors	• None	• None

Figure 3. ***Adapted Model with proposed areas for interventions***



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APPENDICES

APPENDIX A

Subgroup analysis included in Aims 1-3

Table A.1 Subgroup analyses of MS clinical feature outcomes by race

Outcome median and IQR	**White** (total n=494)*	**Black** (total n=26)*	**Bi-racial or mixed race** (total n=25)*	**Combined: Latinx, Asian, American Indian / Alaska Native, Native Hawaiian / Pacific Islander (** (total n=12)*	**Missing** (total n=366)*
Disability severity (range 1-3)	1 (1-2) (n=484)	1 (1-2)	1 (1-2)	1 (1-1.5)	1 (1-2)
Pain Interference raw t-score (range 40.7-77)	53 (41-60)	58 (41-65)	55 (41-66)	44 (41-58)	56 (41-62)
Fatigue raw t-score (range 34.1-80.7)	58 (52-63)	60 (56-64)	60 (52-63)	57 (50 - 68)	59 (53 - 64)
Mental health comorbidity count (range 0-6)	2 (1-3)	2 (1-3)	3 (2-4)	2 (1-4.5)	2 (1-4)
Age at onset (years) (range 4-62)	29 (23.5-38) (n=488)	25.5 (21-36)	29 (21.5-34) (n=24)	27 (22-32)	30 (23-37) (n=359)
Relapses burden since Covid-19 (range 0-3)	2 (0-3) (n=469)	3 (2-3) (n=24)	2 (2-3) (n=24)	2 (2-3) (n=11)	2 (0-3) (n=352)

*except where alternate n= is provided