McMaster University | Health Forum

Rapid Evidence Profile

Examining the potential causal relationship between stress and multiple sclerosis

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[MHF product code: REP 93]

Box 1: Evidence and other types of information

+ Global evidence drawn upon

Evidence syntheses and single studies selected based on relevance, quality, and recency of search

- No forms of domestic evidence used

- No other types of information used

*** Additional notable features**

Prepared in three business days using an 'all hands on deck' approach

Prepared with input from two subject-matter experts

Context

- Multiple sclerosis (MS), an inflammatory and neurogenerative disease affecting an individual's ability to walk and complete daily activities, can be impacted by not only genetic factors but also environmental and behavioural interactions.
- It has been suggested that acute and chronic stress can be a trigger for MS disease onset and progression, but research on the role of stress in MS has produced sometimes conflicting results.(1)
- This rapid evidence profile examines the evidence on the potential causal relationship between stress and MS and the level of stress considered significant if such a causality association exists.

Questions

Is there a causal relationship (association) between stress and multiple sclerosis (MS)? If so, what is the nature and timeline of the relationship and what level of stress is considered significant?

High-level summary of key findings

- We identified one evidence synthesis and eight single studies, all of which we deemed to be highly relevant to the research question.
- Generally, most of the evidence documents focused on determining the potential strength of an association between stress and MS onset or symptoms using quantitative methods, but these documents also provided overlapping evidence of temporal and dose-response relationships between the two variables.
- Several evidence documents found that psychological stressors (e.g., post-traumatic stress disorder (PTSD)) and stressful life events (e.g., childhood abuse, war exposure, and death of a loved one) increased the risk of developing MS or worsening MS activity.
- In terms of more acute or minor stressors, some evidence showed a significant impact on MS onset or reoccurrence, while some evidence found no consistent association between the two variables, consequently limiting the applicability of the results.
- Demographic factors, such as age, gender and level of education were identified in the included evidence as influential considerations in evaluating the extent to which stressful circumstances can impact MS activity.
- Overall, these evidence documents suggest that when life stressors occur, whether acute or historical, they may have some effect on MS onset, MS symptoms, or MS relapse, but the degree of impact may depend on severity of the stressor and subjective variables of individuals with MS.

Framework to organize what we looked for

- Types of MS
  - Clinically isolated syndrome
  - Relapsing-remitting MS
  - Primary progressive MS
  - Secondary progressive MS
  - Other
- Extent/level of MS (using the Expanded Disability Status Scale (EDSS) score)
  - 1.0 no disability, very small sign that one function isn't normal
  - 1.5 no disability, very small signs that more than one function isn't normal
  - 2.0 very small disability in one function
  - 2.5 mild disability in one function or very small disability in two functions,
  - 3.0 moderate disability in one function or mild disability in three or four functions, no problem walking
  - 3.5 moderate disability in one function and mild or moderate disability in several other functions, no problem walking
  - 4.0 significant disability but you can walk without an aid for 500 metres
  - 4.5 significant disability but you're up for much of the day, you can still work but might need some help, you can walk 300 metres without an aid
  - 5.0 disability gets in the way of daily activities but you can walk without an aid for 200 metres
  - 5.5 disability rules out full daily activities, you can walk 100 metres without an aid
  - 6.0 you can walk 100 metres with a stick or crutch, with or without rests
  - 6.5 you can walk 20 metres with the two aids (crutches or sticks) without stopping for rests
  - 7.0 essentially you must use a wheelchair but are active all day, you can't walk more than 5 metres even with an aid
  - 7.5 you can only take a few steps, you use a wheelchair and may need help getting in and out of it, you may need a motorised wheelchair
  - 8.0 basically you need to be in a chair, wheelchair, or bed, you may be out of bed much of the day, you can use your arms
  - 8.5 basically in bed much of the day, you still have some use of your arms
  - 9.0 in bed all the time but you can communicate, eat, or swallow
  - 9.5 in bed but you can't communicate, eat, or swallow
  - 10 death due to MS
- Risk factors of MS
  - Genetic
  - Environmental (e.g., infections, vitamin D deficiency, geographic location)
  - Behavioural (e.g., smoking, obesity)
  - Age
  - Other
- Types of stress
  - Minor life events (e.g., home and work stress)
  - Major life events (e.g., bereavement)
  - Stress disorders (e.g., ASD, PTSD, anxiety, depression)
  - External stressors (e.g., exposure to war activities, COVID-19 pandemic)
  - Emotional stressors (e.g., childhood adversities such as parental divorce)
- Priority populations
  - Active military

    - Veterans
    - Law enforcement officers (e.g., RCMP)
    - Other
- Causality criteria
    - Temporal relationship (e.g., exposure must precede the occurrence of the outcome)
    - Strength of association (e.g., association should meet statistical significance to demonstrate that it was not simply a chance occurrence)
    - Dose-response relationship (e.g., evidence that increasing exposure increases the risk of the outcome)
    - Consistency of evidence (e.g., similar or the same results generated by studies using different methods in different settings)
    - Specificity (e.g., the exposure is the only cause of the outcome that can be shown)
- Outcomes
    - MS onset
    - Disability progression
    - Inflammatory disease activity
        - Relapse
        - New, enlarging, or enhancing MRI lesions

What we found

We identified one evidence synthesis and eight single studies, all of which we deemed to be highly relevant to the research question.

Coverage by and gaps in existing evidence syntheses and domestic evidence

Box 2: Approach and supporting materials

At the beginning of each rapid evidence profile and throughout its development, we engage one or more subject-matter experts who help us to scope the question and ensure relevant context is taken into account in the summary of the evidence.

We searched PubMed on 31 March 2025 and PsychINFO on 8 April 2025 for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses), single studies and protocols for evidence syntheses relevant to the research question. The search strategies used are included in Appendix 1. In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using the first version of the AMSTAR tool. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial, or governance arrangements within health systems or implementation strategies.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) details about each identified evidence synthesis (Appendix 2)
3) details about each identified single study (Appendix 3)
4) documents that were excluded in the final stages of review (Appendix 4).

This rapid evidence profile was prepared in the equivalent of three days of a 'full-court press' by all involved staff.

Most of the evidence documents explored the causality criterion of strength of the association (i.e., association should meet statistical significance to demonstrate that it was not simply a chance occurrence) between life stressors and MS symptoms using quantitative methods to compare the impacts of different stressors. There were also a few evidence documents that explored the causality criteria related to the existence of a temporal relationship (i.e., exposure must precede the occurrence of the outcome) and a dose-response relationship (i.e., evidence that increasing exposure increases the risk of the outcome) between stressors and MS symptoms. Notably, the evidence documents identified often presented insights about multiple causality criteria.

In terms of gaps, the limited number of relevant evidence documents (particularly evidence syntheses) indicates a need for more empirical research exploring causality between stress and MS. While there was some variation in study jurisdictions (e.g., U.S., Sweden, Australia, Saudi Arabia), we did not identify any Canadian studies on the research topic. There were also limitations in the conclusions made from a few studies because of small sample sizes. Future

research should focus on producing high-quality empirical evidence that explores the direct impact of different types of stress on the onset and progression of MS.

Key findings from included evidence documents

We identified one evidence synthesis and eight single studies that explored the potential causal relationship between stress and multiple sclerosis. A summary of the findings from each study and causality implications is provided below, along with potential next steps for this research area based on the identified evidence.

Most of the evidence documents identified focused on determining the potential strength of an association between stress and MS onset or symptoms. The one evidence synthesis identified – a systematic review and meta-analysis that was conducted in 2022 and included 30 longitudinal studies – analyzed the association between psychological stressors (e.g., PTSD, major life events, war exposure) and MS onset, relapse risk, and disability progression.(1) According to the synthesis, diagnosed stress-related disorders (e.g., PTSD) and major stressful life events (e.g., childhood sexual and emotional abuse) were associated with increased risk of developing MS or increasing MS activity. Childhood sexual and emotional abuse were each linked to a higher MS risk among women participants (hazard ratios of 1.65 and 1.40, respectively), and a dose-response effect was found in the MS risk being higher following exposure to several types of abuse. The synthesis also found that exposure to missile attacks during wartime resulted in a threefold increased MS relapse risk (rate ratio 3.0, 95 % CI 1.56–5.81). The meta-analysis of three included studies on diagnosed stress-related disorders showed a 1.87-fold (95% CI 1.061–3.429) increased risk of developing MS. Additionally, PTSD prior to MS onset was linked to faster disability progression and significantly higher annual relapse rates. There was no consistent association found between milder stressors (e.g., divorce or low income) and MS onset, suggesting severity and personal impact of stress may be key factors to MS activity.

Many of the identified single studies also used statistical methods to investigate the strength of the association between stress and MS. The impact of adverse life events and MS symptoms of fatigue, paresthesia, and motor dysfunction were examined is a 2020 cohort study of U.S. adults with MS who were surveyed about their adverse life events and MS symptoms in the previous 60 days.(2) Strong correlations were found between adverse life events and fatigue and paraesthesia, while moderate correlations were found between adverse life events and motor dysfunction. However, small effect sizes were found in this study, suggesting that adverse life events may have a small impact on these MS symptoms. These results are in contrast with those of a 2016 cross-sectional study that found a significantly strong association between stressful life events and central nervous system demyelination among Australian adults who had primary progressive multiple sclerosis and an undiagnosed myelination event.(3) Participants were 1.5 times more likely to have a myelination event if they experienced personal illness or illness of a close friend/family member. In addition to this, a moderate causal relationship demonstrating the strength of the association and a dose-response relationship was identified from a 2020 case-control study examining the risk of developing MS after stressful life events (e.g., conflicts with partners/friends/family, death of a loved one, conflict at work, unemployment).(4) Using extensive questionnaire data from Swedish participants, the study found that stressful life events can increase risk of developing MS symptoms by 14–26%, with women being affected to a greater extent than men under certain stressful circumstances, and most recent events (≤5 years prior to MS onset) having significant effects on MS.

One cross-sectional study based in Saudi Arabia found a temporal relationship between self-reported acute stressors and MS relapses among patients (15–50 years old) diagnosed with an unspecified type of MS.(5) Acute stressors including sleep deprivation, mood swings, social-life stressors, issues at work, family issues, and hot weather were all associated with increased relapse and severity of MS symptoms, with statistically significant associations being found in those with higher education and five to 10 years post-diagnosis. The results highlight the potential of more short-term stressors that can be considered minor to trigger MS attacks and reoccurrence.

Two studies explored correlations between childhood adverse events and MS symptoms. One cross-sectional study explored the relationship between childhood stressors and three prevalent symptoms of MS, psychiatric morbidity,

fatigue, and pain interference among surveyed adults in the U.S. in 2021 who self-reported experiencing MS symptom onset.(6) The study determined that physical and emotional childhood stressors (e.g., hard discipline, physical abuse, sexual abuse) and environmental stressors (e.g., parental mental illness or substance use, domestic conflict, witnessing abuse, separation from a parent, housing instability) were significantly associated with psychiatric morbidity as well as the magnitude of fatigue and pain interference among participating adults with MS. Researchers also found that with age, the risk of experiencing any pain interference increased, whereas psychiatric morbidity and the severity of both fatigue and pain interference declined. These results suggest a potential improvement in MS management skills over time. We also identified a related case report from 2021 that examined the association between childhood adversity, adult stress exposure, and MS symptoms in a Black woman with MS.(7) The 58-year-old who was diagnosed with relapse-remitting MS at age 38 had a history of childhood abuse, as well as adult stressors related to death of a loved one and marital strain. Within four years of an intensive stressful period, her MRI scans revealed four lesions in her periventricular white matter, indicating the onset of MS symptoms. The woman's experiences along the MS diagnosis and disease journey reflect common patterns seen in others with MS, indicating that unresolved stressors might similarly impact their health and well-being. However, it is important to caution against generalizing any findings from a case report.

Finally, a 2023 study exploring the association between perceived stress intensity and functionality in MS among 26 adults diagnosed with relapsing-remitting MS with an EDSS score of ≤ 7 found a bidirectional relationship between the two variables.(8) Higher perceived stress was associated with lower functionality and more frequent stressful events. Psychosocial factors also played a key role in that active coping appeared to be more beneficial under high stress than low stress and individuals with lower anxiety reported better functionality.

Overall, these evidence documents suggest that when life stressors occur, whether acute or historical, they may have some effect on MS onset, symptoms, or relapse, but the degree of impact may depend on severity of the stressor and subjective variables of individuals with MS (e.g., age, gender, mitigation measures).

Next steps based on the identified evidence

- Research efforts should focus on not only expanding the evidence on the causal mechanisms of temporality, dose-response, and strength of associations but also developing new evidence on exploring other causal mechanisms that we did not identify evidence for, including specificity and consistency.
- Additional research should also seek to provide clarity on the direct causal relationship between different types of stress and MS onset, symptoms, or relapse given that the existing evidence may be confounded by reverse causality, especially in studies using self-reported data.

References

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