McMaster University | Health Forum

Rapid Evidence Profile appendices

Examining the potential causal relationship between stress and multiple sclerosis

30 April 2025

[MHF product code: REP 93]

Appendices

Appendix 1: Methodological details

For this rapid evidence profile (REP), we searched PubMed on 31 March 2025 for evidence syntheses, single studies, and protocols, selecting the filter for the publication date range of the last 10 years, using an advanced search strategy: ((("Stress, Psychological"[Mesh]) OR ("Stress, Physiological"[Mesh])) AND (("Multiple Sclerosis"[Mesh] OR "Multiple Sclerosis, Relapsing-Remitting"[Mesh] OR "Multiple Sclerosis, Chronic Progressive"[Mesh]) OR ("Multiple Sclerosis"[Title/Abstract])). We also searched PsychINFO on 8 April 2025 for evidence syntheses and single studies published within the last 10 years using combinations of the mesh terms in the search string above for "stress" and "multiple sclerosis."

One team member screened the results to identify potentially relevant documents. A final inclusion assessment was performed both by the person who did the initial screening and the lead author of the rapid evidence profile, with disagreements resolved by consensus or with the input of a third reviewer on the team. The team uses a dedicated virtual channel to discuss and iteratively refine inclusion/exclusion criteria throughout the process, which provides a running list of considerations that all members can consult during the first stages of assessment. Evidence documents were included if they described any aspect of the organizing framework and explored any potential association between stress and multiple sclerosis onset or progression. We excluded documents that did not directly address the research questions and the relevant organizing framework (e.g., documents that only focused on a causal relationship between stress and other conditions or on the impacts of multiple sclerosis on stress). We also excluded documents where the full text was not accessible.

We did not exclude documents based on the language of a document. However, we were not able to extract key findings from documents that were written in languages other than Chinese, English, French, or Spanish, or were not able to be translated to English via the Google applications. We provided any documents that did not have content available in these languages in an appendix containing documents excluded at the final stages of reviewing.

Assessing relevance and quality of evidence

We assessed the relevance of each included evidence document as being of high or low relevance to the research question. 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.

Preparing the profile

Each included document is cited in the reference list at the end of the REP. For all included evidence documents, we prepared a small number of bullet points that provide a summary of the key findings, which are used to summarize key messages in the report. We then draft a summary that highlights the key findings from all relevant documents as well as a brief summary of coverage by and gaps in the existing evidence on the research question.

Upon completion, the REP is sent to one or more subject-matter experts for their review.

Appendix 2: Details about each identified evidence synthesis

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations

• Types of MS
  ○ Relapsing-remitting MS
• Risk factors of MS
  ○ Environmental (e.g., infections, vitamin D deficiency, geographic location)
  ○ Behavioural (e.g., smoking, obesity)
• 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)
• Causality criteria
  ○ Strength of association (e.g., association should meet statistical significance to demonstrate that it was not simply a chance occurrence)
• Outcomes
  ○ MS onset
  ○ Disability progression
  ○ Inflammatory disease activity
  ▪ Relapse
  ▪ New, enlarging, or enhancing MRI lesions
	Psychological stressors, particularly post-traumatic stress disorder (PTSD) and exposure to severe external stress such as missile attacks, are associated with a minor to modest increase in the risk of multiple sclerosis (MS) onset, relapse, and disability progression (1)
	• This study conducted a systematic review and meta-analysis of 30 longitudinal studies (26 cohorts, 24,781 MS cases) using PubMed searches to assess the association between psychological stressors (e.g., PTSD, major life events, war exposure) and MS onset, relapse risk, and disability progression
	• Small sample sizes were a limiting factor of several included studies (n=19)
	• A meta-analysis of three studies on diagnosed stress-related disorders (e.g., PTSD) showed a 1.87-fold (95% CI 1.061–3.429) increased risk of developing MS
	• Exposure to missile attacks during wartime resulted in a threefold increased relapse risk (rate ratio 3.0, 95% CI 1.56–5.81), based on two independent cohort studies
	• Stressful life events were associated with increased MS activity on MRI, including gadolinium-enhanced lesions (0.29 vs. 0.08)
	• Individuals with PTSD prior to MS onset experienced significantly higher annual relapse rates (0.23 vs. 0.06) and more MRI lesions
	  ○ PTSD before MS onset was also linked to faster disability progression, with patients reaching Expanded Disability Status Scale (EDSS) 6.0 7 years earlier on average (median 23.0 vs. 30.0 years; HR 0.77)
	• Childhood sexual abuse and emotional abuse were each linked to a higher MS risk among women participants, with hazard ratios of 1.65 and 1.40,
		High	No	7/11 (AMSTAR rating by McMaster Health Forum)	July 2022	No	None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
	respectively, and a dose-response effect was found in that the MS risk was higher following exposure to several types of abuse • No consistent association was found between milder stressors (e.g., divorce or low income) and MS onset, suggesting severity and personal impact of stress may be key factors • The evidence for stress impacting MS relapse risk is more heterogeneous and may be confounded by reverse causality, especially in self-reported stress studies • Overall, the findings support the importance of stress appraisal and resilience and suggest that interventions targeting stress may be relevant in MS management						

Appendix 3: Details about each identified single study

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations

• Types of MS
  ○ Relapsing-remitting MS
  ○ Primary progressive MS
  ○ Secondary progressive MS
  ○ Other – Progressive remitting MS
• Types of stress
  ○ Major life events (e.g., bereavement)
• Priority populations
  ○ Other – General population
• 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)
• Outcomes
  ○ Disability progression
	While strong correlations between adverse life events and the multiple sclerosis (MS) symptoms of fatigue, motor dysfunction, and paraesthesia were identified, small effect sizes were found, suggesting that adverse life events may have a small impact on MS symptoms (2)
	• This study evaluated the relationship between adverse life events in the previous 60 days and symptoms of MS, including fatigue, motor dysfunction, and paraesthesia
	• Between March and June 2014, 1,239 individuals with MS, ages 18 to 81 years who were active on MS societies websites or on social media groups completed a questionnaire on their demographic and MS-related characteristics, adverse life events, and MS symptoms
	  ○ Several assessment scales were used to measure adverse life events, fatigue, motor dysfunction, and paraesthesia
	• Most participants (69.3%) reported having the relapse-remitting subtype of MS, were female (84.5%), and were on treatment in the previous 60 days
	• 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, regression coefficients of all scales used to measure these MS symptoms was small, suggesting that the effect of adverse life events on MS symptoms is small
		High	*Publication date:* February 2020
			
			Jurisdiction studied: United States
			
			Methods: Cohort study
				None identified

• Types of MS
  ○ Relapsing-remitting MS
  ○ Primary progressive MS
  ○ Secondary progressive MS
  ○ Other
• Risk factors of MS
  ○ Environmental (e.g., infections, vitamin D deficiency, geographic location)
  ○ Age
  ○ Other
• Types of stress
  ○ Minor life events (e.g., home and work stress)
	In people with multiple sclerosis, childhood emotional and physical stressors showed significant associations with adult psychiatric morbidity as well as the presence and magnitude of fatigue and pain interference, whereas environmental stressors were significantly associated with psychiatric morbidity and the magnitude of fatigue (3)
	• The study investigated how various childhood stressors may be associated with three prevalent symptoms among individuals with MS: fatigue, pain interference, and psychiatric morbidity
	  ○ In terms of childhood stressors, this study clustered them into those that happen to a child (i.e., emotional, physical) and those that happen around a child (i.e., environmental), identifying which types have the most harmful effects, rather than simply tallying adverse experiences or examining them in isolation
	• From September to November 2021, 719 adults (21 to 85 years of age) with a self-reported diagnosis of multiple sclerosis were recruited via email to participate in an online survey; most participants were female (84%), identified as White
		High	Publication date: 2023
			
			Jurisdiction studied: United States
			
			Methods: Quantitative cross-sectional study
				• Features of relationships
				• Time-dependent relationships

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ 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) • 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) • Outcomes ○ Disability progression	(88%), had relapsing-remitting MS (79%), reported symptom onset at an average age of 31, and held at least a bachelor's degree ○ Among the participants, harsh discipline was the most frequently reported childhood stressor (50.9%), followed by emotional abuse (33.4%), physical abuse (16.7%), and sexual abuse (12.8%), with average durations ranging from 60 to 190 months • Childhood stress was assessed using the Stress and Adversity Inventory (STRAIN) ○ Participants first indicated whether they had experienced a given stressor, and for each, follow-up questions gathered details on the age of onset, severity (0 = not at all to 5 = extremely stressful), and duration in years or months ○ Stressors were categorized as childhood-related if they began before age 18, so they could extend into adulthood by definition • Predictors ○ The cluster of childhood emotional stressors encompassed emotional abuse indicators ○ The cluster of childhood physical stressors captured the intensity and length of experiences like physical abuse, recurring sexual abuse, and harsh discipline ○ For the cluster of childhood environmental dysfunction, nine variables were summed into a single count reflecting exposure to the factors of parental mental illness or substance use, domestic conflict, witnessing abuse, separation from a parent, divorce, housing instability, neighbourhood safety concerns, workplace exclusion based on identity (e.g., race, gender), and home break-ins • Outcomes ○ For psychiatric morbidity, 1) anxiety diagnosis, 2) depression diagnosis, 3) post-traumatic stress disorder or other psychiatric diagnosis (e.g., schizophrenia), 4) symptomatic anxiety, 4) symptomatic depression, and 5) emergency hospitalizations were measured ▪ Symptomatic anxiety and depression were measured using the Patient Reported Outcomes Measurement Information System (PROMIS) scales ○ Fatigue and pain interference were also measured with PROMIS scales • Dissecting the clusters of stressors, certain predictors were individually significant across different outcomes (e.g., emotional abuse severity was significantly associated with psychiatric morbidity, while harsh discipline duration was significantly associated with the magnitude of fatigue and pain interference) • With age, the risk of experiencing any pain interference increased, whereas psychiatric morbidity and the severity of both fatigue and pain interference declined, suggesting potentially better disease management skills overtime			

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations

• Types of MS
  ○ Relapsing-remitting MS
• Risk factors of MS
  ○ Other
• Types of 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)
• Causality criteria
  ○ Temporal relationship (e.g., exposure must precede the occurrence of the outcome)
• Outcomes
  ○ Inflammatory disease activity
  ▪ New, enlarging, or enhancing MRI lesions
	Adversity such as pandemic-related socio-political and economic stressors may impact MS and related symptoms, suggesting the value of screening for lifetime stress to enhance case conceptualization, guide mental health referrals, and potentially improve MS progression (4)
	• The case report described a 58-year-old Black woman diagnosed with relapsing-remitting MS at age 38, who began experiencing paresthesias during a period of heightened stress from her mother's declining health and eventual passing
	• Her first MRI scan two years later revealed four lesions in the periventricular white matter; four years later, scans showed two more lesions; and nine years later, scans revealed over 20 ovoid non-enhancing lesions
	• She entered a psychiatric program after months of worsening depression and suicidal thoughts while working from home during the COVID-19 pandemic, triggered by marital strain from her spouse's alcohol use and the subsequent resurfacing of memories of her abusive, alcoholic father
	• A history of severe childhood abuse, neglect, and family dysfunction contributed to her high Adverse Childhood Experiences score of 7 (out of 10)
	• The patient'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
		High	*Publication date:* 2021
			
			Jurisdiction studied: United States
			
			Methods: Case report
				• None identified

• Types of MS
  ○ Relapsing-remitting MS
• Types of stress
  ○ Minor life events (e.g., home and work stress)
  ○ Major life events (e.g., bereavement)
  ○ External stressors (e.g., exposure to war activities, COVID-19 pandemic)
  ○ Emotional stressors (e.g., childhood adversities such as parental divorce)
• Causality criteria
  ○ Temporal relationship (e.g., exposure must precede the occurrence of the outcome)
	A significant association between acute stress and the recurrence of MS attacks was identified among MS patients in Saudi Arabia, but not with the onset of the disease (5)
	• The study involved 370 MS patients who completed a structured, interview-administered Arabic questionnaire assessing emotional, physical, and environmental acute stressors and their perceived effects on MS onset and relapse
	  ○ The study defined acute stressors as emotional/psychological (family problems, bereavement, work and social stress, overthinking, mood swings, sleep deprivation), physical (heavy exercise), and environmental (hot and cold weather)
	  ○ The study included only MS patients aged 15 to 50 years diagnosed from the 2010 McDonald criteria for unspecified type of MS
	  ○ The questionnaire was administered in Saudi Arabia from September 2017 to June 2018, collecting demographic data and MS-related stressor characteristics, with responses measured on a Likert scale
		High	*Publication date:* February 2019
			
			Jurisdiction studied: Saudi Arabia
			
			Methods: Cross-sectional descriptive observational study
				• None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ Strength of association (e.g., association should meet statistical significance to demonstrate that it was not simply a chance occurrence) • Outcomes ○ MS onset	○ Among the participants, 249 were female (67.3%) and 344 (93%) were from Saudi Arabia • Causality in the study was inferred through statistically significant associations between self-reported acute stressors and MS relapse using cross-sectional data analyzed via multinomial and binary logistic regression • Emotional and psychological stressors, such as overthinking social issues (65.4%), mood swings (65.9%), and sleep deprivation (72.7%), were significantly linked to increased relapse frequency and severity • Work and social life stressors were reported by 65.1% of participants to impact relapse, with statistically significant associations in those with higher education and 5–10 years post-diagnosis • Hot weather and physical exertion were both associated with higher relapse risk, while cold weather had no significant effect • Family issues or bereavement influenced relapse in 45.4% of patients, and their link to disease onset was statistically significant • Financial stress was not significantly associated with MS relapse or onset (only 26.5% reported an impact)			
• Types of MS ○ Relapsing-remitting MS • 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	Perceived stress and self-reported functionality may share underlying variance and better capture the day-to-day impact of stress in MS than clinical ratings like the EDSS, which reflect only major disease progression (6) • The study analysed the bidirectional relationship between stress and multiple sclerosis, incorporating measures of stress, impairment, and functionality, while also examining the moderating effects of psychosocial factors such as anxiety, coping, and social support • Twenty-six adult volunteers with clinically definite relapsing-remitting MS with EDSS score of ≤ 7 participated in the study from May 2014 to September 2015 • Over the course of a year, the volunteers participated in a follow-up study involving multi-level assessments: ○ baseline measures captured anxiety and perceived social support, while daily diaries tracked stressful events and coping strategies ○ perceived stress was assessed monthly, and self-reported functionality every three months ○ neurological impairment was evaluated by a clinician at both the beginning and end of the study ○ the data were analyzed using mixed-effects regression models • The bidirectional relationship between stress and multiple sclerosis was supported only by self-reported measures of perceived stress and functionality, showing a negative relationship in both directions; this means that higher perceived stress was associated with lower functionality, and worsening functionality was linked to increased stress	High	*Publication date:* May 2023 *Jurisdiction studied:* Catalonia, Spain *Methods:* Prospective study	• None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ 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 • 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) • Causality criteria ○ Strength of association (e.g., association should meet statistical significance to demonstrate that it was not simply a chance occurrence)	○ Higher perceived stress was associated with worsening functionality and more frequent stressful events, highlighting the subjective nature of how stress and symptoms are experienced ○ Psychosocial factors also played a key role: active coping appeared beneficial under high stress but not low stress, while individuals with lower anxiety reported better functionality ○ However, as stress increased, these differences diminished, and those with high trait anxiety consistently reported lower functionality ○ Additionally, lower social support was linked to more frequent stressful events			
• Types of MS ○ Primary progressive MS	People who experienced a stressful life event were over two times as likely to have a myelination event, particularly primary progressive multiple sclerosis or an	High	*Publication date:* September 2016	None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations

• Risk factors of MS
  ○ Genetic
  ○ Environmental (e.g., infections, vitamin D deficiency, geographic location)
  ○ Behavioural (e.g., smoking, obesity)
• Types of stress
  ○ Minor life events (e.g., home and work stress)
  ○ Major life events (e.g., bereavement)
• Causality criteria
  ○ 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)
• Outcomes
  ○ MS onset
	undiagnosed event, suggesting a relationship between adverse events and MS symptoms (7)
	• This case-control study aimed to examine the association between stressful events and demyelination in 216 individuals aged 18 to 69, recruited from four regions across Australia
	• Cases were defined as individuals who had a first case demyelination and primary progressive multiple sclerosis, as determined by the study neurologist
	• Controls were randomly selected and matched on age, sex, and study region
	• Participants completed several questionnaires and biological data was obtained
	  ○ All participants completed a stressful life event assessment including questions on presence of a serious illness, financial issues, gaining/losing family members, changing relationships, personal achievement/disappointment, problems with law, or relationship issues
	  ○ Participants also reported data on smoking history, alcohol intake, number of children, physical activity, and highest education level completed
	  ○ Questionnaires asked about participants' behaviours within the past 12 months
	  ○ All participants provided blood samples and single-nucleotide polymorphism was used to measure the HLA-DR15 genotype
	  ○ All cases completed the EDSS (scores not reported in text and extent of multiple sclerosis not specified)
	• Participants were primarily female (76.9% cases, 77.6% controls) and 36.8 years old on average
	• There was a strong association between those who had a serious illness, had primary progressive multiple sclerosis, and who had an undiagnosed myelination event (OR=2.43, 95% CI 1.45–4.08)
	  ○ Participants who had a serious illness were more likely to have a myelination event (OR=2.35, 95%CI 1.36–4.06)
	• The most prominent stressful life event was personal illness or illness of close friend/family member, with an increase 1.5-times odds of having a myelination event
	  ○ No significant interactions were seen for age, sex, or presence of an existing disability
	• Total number of stressful events was weakly associated with myelination events, showing mild evidence of a dose-response association; these associations did not remain when people with primary progressive multiple sclerosis were included in the analysis
			Jurisdiction studied: Australia
			
			Methods: Case-control study	

• Types of MS ○ Other • Risk factors of MS	Stressful life events can increase risk of developing multiple sclerosis symptoms by 14–26%, depending on the nature of the event and gender perceptions (8) • This study explored the association between multiple sclerosis and unexpected stressful life events	High	*Publication date:* August 2020	• Gender/sex

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ Behavioural (e.g., smoking, obesity) • Types of stress ○ Minor life events (e.g., home and work stress) ○ Major life events (e.g., bereavement) ○ External stressors (e.g., exposure to war activities, COVID-19 pandemic) • Causality criteria ○ 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) • Outcomes ○ MS onset	• Data was obtained from the Epidemiological Investigation of Multiple Sclerosis in Sweden • Cases (n=2,930) were confirmed by neurologists and disease onset was defined as the timepoint of the presence of the first multiple sclerosis symptom; the type and extent of multiple sclerosis was not specified • Controls (n=6170) were matched based on age, sex, and residential area • Participants completed a questionnaire regarding stressful life events ○ Stressful events were defined as conflicts with partners/friends/family, death of close one, poor economy, conflict at work, or unemployment within the past 10 years or before symptom onset ○ Participants were also asked to state the year the event occurred and rate its overall significance • The risk of developing multiple sclerosis after a stressful life event ranged from 14–26% ○ Sickness/accident of a loved one increased risk 25% (OR=1.25, 95% CI 1.06–1.46) and was only significant for women (OR=1.38, p<0.001) ○ Death of a loved one increased risk by 36% (OR=1.36, 95% CI 0.82–2.28), but was not statistically significant (p=0.24), perhaps because it was a rare event ○ Conflict with partner increased risk by 18% (OR=1.18, 95% CI 1.05–1.34), influencing men and women similarly ○ Divorce increased risk by 28% (OR=1.28, 95% CI 1.12–1.47) ○ Marriage increased risk by 17% (OR=1.17, 95% CI 1.05–1.31), but only in women • Individuals with multiple sclerosis were associated with higher body mass indexes (p=0.03) and smoking (p<0.001) • Women were affected to a greater extent than men under certain stressful circumstances, and most recent events (≤5 years prior to MS onset) had significant effects on MS • The risk of developing multiple sclerosis symptoms after stressful life events showed a moderate dose relationship (p=0.001) ○ A total of 1–2 events: OR=0.88 (95% CI 0.74–1.04) ○ A total of 2–5 events: OR=1.09 (95% CI 0.91–1.31) ○ A total of 6+ events: OR=1.53 (95% CI 1.14–2.05)		*Jurisdiction studied:* Sweden *Methods:* Case-control study	

Appendix 4: Documents excluded at the final stages of reviewing

Document type	Hyperlinked title
Single study	Perceived stress in multiple sclerosis patients: Relationship with mood states and pain experience
	Physical activity and life stress are associated with illness intrusiveness in persons with multiple sclerosis
	Perceived stress and social support in a large population of people with multiple sclerosis recruited online through the COVID-19 pandemic

	Impact of depression and fatigue on relapsing remitting multiple sclerosis in Kingdom of Saudi Arabia
	Effects of psychological stress on multiple sclerosis via HPA axis-mediated modulation of natural killer T cell activity
	Stressful life events and depression and fatigue in people with multiple sclerosis: A cross-sectional analysis of an international cohort

References

1. von Drathen S, Gold SM, Peper J, et al. Stress and multiple sclerosis – Systematic review and meta-analysis of the association with disease onset, relapse risk and disability progression. *Brain, Behavior, and Immunity* 2024; 120: 620-629.
2. Swanepoel I, van Staden W, Fletcher L. Psychological resilience and vulnerability as mediators between adverse life events and fatigue, motor dysfunction, and paresthesia in multiple sclerosis. *Psychosomatic Medicine* 2020; 82(2): 138-146.
3. Polick CS, Ploutz-Snyder R, Braley TJ, Connell CM, Stoddard SA. Fatigue, pain interference, and psychiatric morbidity in multiple sclerosis: The role of childhood stress. *PLoS One* 2023; 18(10): e0292233.
4. Polick CS, Polick SR, Stoddard SA, Braley TJ, Slavich GM. The importance of assessing life stress exposure in multiple sclerosis: A case report. *Multiple Sclerosis and Related Disorders* 2021; 54: 103145.
5. AlZahrani AS, Alshamrani FJ, Al-Khamis FA, et al. Association of acute stress with multiple sclerosis onset and relapse in Saudi Arabia. *Saudi Medical Journal* 2019; 40(4): 372-378.
6. Briones-Buixassa L, Montañés-Masias B, Milà-Villaroel R, et al. The bidirectional effect of stress and functionality in multiple sclerosis and the interaction role of anxiety, coping and social support. *Journal of Psychosomatic Research* 2023; 170: 111375.
7. Saul A, Ponsonby AL, Lucas RM, et al. Stressful life events and the risk of initial central nervous system demyelination. *Multiple Sclerosis* 2017; 23(7): 1000-1007.
8. Jiang X, Olsson T, Hillert J, Kockum I, Alfredsson L. Stressful life events are associated with the risk of multiple sclerosis. *European Journal of Neurology* 2020; 27(12): 2539-2548.

Bain T, Dass R, Wu N, Chen K, Grewal E, Ciurea P, Sivanesanathan T, Ali A, Wilson MG. Rapid evidence profile appendices #93: Examining the potential causal relationship between stress and multiple sclerosis. Hamilton: McMaster Health Forum, 30 April 2025.

This rapid evidence profile was funded by the Chronic Pain Centre of Excellence for Canadian Veterans and the Atlas Institute for Veterans and Families, which in turn are funded by Veterans Affairs Canada. The McMaster Health Forum received both financial and in-kind support from McMaster University. The views expressed in the rapid evidence profile are the views of the authors and should not be taking to represent the views of the Chronic Pain Centre of Excellence for Canadian Veterans and the Atlas Institute for Veterans and Families or McMaster University.