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Stress and Multiple Sclerosis – Systematic review and meta-analysis of the association with disease onset, relapse risk and disability progression

Dissertation

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Research question

The main research question focusses on the association of psychological stress and multiple sclerosis. In this process the impact of stress on the three different aspects of multiple sclerosis, namely 1. disease onset, 2. relapse risk and 3. disability progression is investigated. Therefore, different kinds of stressful life events were examined concerning their influence on multiple sclerosis. Based on the existing research literature it was expected, that beyond the backed-up risk factors for multiple sclerosis psychological stressors are also associated with disease onset, relapses and disability progression. Against the background of the wide range of psychological stress different types of stress exposure need to be investigated related to the question how they affect the MS. Further, it seems interesting, if the objective severity of the stressor (e.g., loss of child) is predominantly crucial or if the subjective stress perception of also minor stressful life events can have the same impact on the disease. Aware of the complex (bidirectional) relation between multiple sclerosis this systematic review with meta-analysis addresses to the question, if clearly circumscribed stress events can induce a MS onset, a MS relapse and MS progression with increased disability. Since, there has been conducted studies for many decades, a systematic review with meta-analysis should clarify the research question best.

Abstract

Background: This systematic review and meta-analysis (SR/MA) addresses the evidence on the association of psychological stressors with onset of multiple sclerosis, inflammatory disease activity (i.e., relapses and lesions on MR imaging) and disability progression.

Methods: A systematic literature search was performed including studies with longitudinal assessment of stressors antecedent to MS (onset studies), prospective longitudinal studies with perceived stressors or retrospective studies with pure external stressors (relapse and MRI activity). Longitudinal studies with stressors antecedent to MS or psychiatric comorbidity were selected to assess MS progression measured by Expanded Disability Status Scale scores. It was searched PubMed from 1946 to 15 July 2022. Risk of bias was assessed by the CASP Case Control Study Checklist and the CASP Cohort Study Checklist.

Results: 31 studies reporting data from 27 cohorts reporting on 34.613 cases could be identified. Ten studies addressed stressors and MS disease onset showing a weak to modest effect of psychological stressors. A meta-analysis of three studies investigating diagnosed stress disorders and MS risk showed a 1.87-fold (CI 1.061 to 3.429) increased MS risk. Stress and MS relapse risk were addressed in 19 heterogeneous studies. A meta-analysis could be performed from two independent cohorts investigating the same military threat of a population. Here a threefold increased risk for relapses in association with war (relapse rate: 3.0, CI 1.56 to 5.81) was found. In addition, two studies confirmed an association of stressful life events and MRI activity. Four studies of stressors and disease progression were included indicating an effect on disease progression.

Discussion: Taken together studies indicate a minor to modest impact of psychological stressors on disease onset, inflammatory activity and progression of MS. A possible case-selection bias and lack of confounder analysis were present in many studies. Very few data evaluated progression. The evidence underlines the relevance of psychological interventions as stress management, relaxation, psychotherapy in the management of MS.

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Registration: The study protocol was prospectively registered at PROSPERO (CRD42020222936).

1. Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease with a highly heterogenous disease course mostly affecting young people[1]. While MS prevalence has generally increased over the last decades, the overall prognosis has improved due to an expanded therapeutic armamentarium and potentially other factors[2]. Autoimmune processes are likely at the center of MS etiology, but the immunopathological networks involved are highly complex and extend beyond T-cell driven autoimmunity[3]. Moreover, while MS has a relevant genetic component[4], research has clearly demonstrated that a number of known environmental and behavioral factors or gene x environment interactions can substantially modify MS risk[5]. For example, a large study recently confirmed Epstein-Barr virus infection as possibly the most relevant environmental factor[6]. Psychological stress has been suggested to be associated with the disease onset and evolution of MS since the 19th century[7] and patients often consider stress as a potential trigger for exacerbations[8]. However, epidemiological research on the role of stress in MS has yielded conflicting results.

Stress can be defined as a state in which homeodynamic balance is threatened by a wide range of intrinsic or extrinsic, real or perceived challenges or stimuli, defined as stressors[9]. In a broader sense, stressors are all internal and externa stimuli which require adaptation of an individual. Acute and chronic dysregulation of a stress response has been implicated in a wide range of mental (e.g. anxiety, depression, eating disorders, post-traumatic stress disorder, etc. [10]) and somatic disorders (e.g., chronic pain and fatigue syndromes, obesity, metabolic syndrome[11]). In fact, chronic stress is suggested as a common risk factor in 75–90% of chronic, noncommunicable diseases[12]. Furthermore, there is evidence that chronic stress induces dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to a mild systemic inflammatory state[12].

First case-control studies from the end of the 20th century led to conflicting results[13–15] and in 1999, a task force from the American College of Neurologists concluded that the evidence for a role of stress in MS remained inconclusive[16]. However, 5 years later, Mohr et al. [17] provided the first systematic review and meta-analysis on the association of stress and MS relapses supporting an overall negative impact. In subsequent years, several systematic reviews have addressed selected aspects of

the interaction between stress and MS, most recently by Jiang et al. (2021)[18] aggregating methodological highly heterogenous studies. However, no rigorous systematic review and meta-analysis has been attempted since 2004. Our current systematic review and meta-analysis aimed to synthetize the current evidence on the association of psychological stressors with all possible aspects, i.e. MS onset, MS relapse risk and disease progression.

2. Material and Methods

2.1 Identification of studies

It was searched PubMed from 1946 to 15 July 2022 using a search strategy, which combined terms concerning MS and stress (see supplement S1 for detailed search strategy). According to the manual for systematic research for evidence syntheses and guidelines[19] the author used the filter that balances sensitivity and specificity and concentrated on English and German language studies. Additionally, reference lists of identified studies were screened regarding further suitable studies. The study protocol was prospectively registered at PROSPERO[20] (CRD42020222936: "Stress and Multiple Sclerosis: A meta-analysis of the relationship between stress and disease onset, relapses and progression"). No amendments to information provided at registration were made. The reporting follows PRISMA guidelines[21] (see supplement S2).

2.2 Inclusion criteria

Studies investigating the association between stress and a) MS onset risk, b) MS relapse risk and c) risk of MS disability progression were included. The author included longitudinal studies with a prospective design.

a) MS onset studies

Of the papers examining disease onset, studies were included with a longitudinal between-subject design and verified documentation of stress exposure prior to MS diagnosis. MS diagnosis had to be made according to valid diagnosis criteria at time of publication which means Poser (1983)[22] and McDonald (2005, 2010 and 2017)[23]. Retrospective design was accepted if the stress exposure was clearly based on

memory-independent events in the past, such as proven by registry data or other objective data sources. MS onset was defined as time of MS diagnosis.

b) MS relapse studies

For studies investigating stress and relapse risk, longitudinal studies with stress assessments comparing relapse rates in times with and times without stressors or with matched control MS cohorts were included. For analysis of stressors and triggering of relapses prospective cohorts with predefined stress assessments and following relapse assessments were considered eligible being aware that subclinical relapses might alter stress sensitivity. Therefore, pure external stressors (e.g., missile attack, pandemic threat) were considered as most robust possible triggers for relapses.

c) MS disability progression studies

Regarding MS disability progression an evaluation of diagnosed depression as a possible predictor for progression was included although depression cannot be classified primarily as a stress disorder. In addition, studies which analyzed the association between stress and risk of disability progression compared with control patients with a similar baseline EDSS score were included. Disability progression was defined as worsening of EDSS at best confirmed with a subsequent EDSS being assessed at least three months later. The highest methodological quality was reached when confirmation of progression was assessed 12 months after the first observation of a decline.

d) Overall inclusion criteria

A variety of stress factors with range from minor life events or daily hassles to major life events was included. The author also included studies which focused on diagnosed stress disorders, based on the idea that an individual´s reaction to a stressor might be more representative of personal threat, than the severity of the stressor. Here, major life stressors before MS diagnosis provide unbiased information for the risk of disability progression. Studies with clearly measured, external stress factors, but also self-reported stress factors and longitudinal design were selected. It was postulated that compared to pure external events self-reported stress factors show an association with minor validity.

In addition, retrospective design was accepted if the stress exposure was clearly based on memory-independent events in the past, such as proven by registry data or other objective data sources. No minimum sample size was used as a predefined selection criterium. However, for the quality assessment sample sizes were also taken into account.

Finally, also solely memory-based stressors were accepted, when not influenced by a known diagnosis of MS disease at the time of the survey (for onset aspect). Socioeconomic status reflected in household income as a stressor was included but not education or household crowding, the latter rather being protective in one study[24] as stressors which can be debated. Notably, only single studies addressed these aspects.

To evaluate the overall impact of stress on MS, criteria which refer to both quality of the study methodology and clarity of the results and provided a simple rating were defined (for details see section 2.6). Through this integrative rating scheme, the evidence of each study was assessed, and this kind of simple evidence synthesis was inserted in the tables of quality assessment (Table 1-3).

2.3 Exclusion criteria

Studies with a retrospective design and solely memory-based (self-reported) stressors when MS had already been diagnosed were excluded. Studies with incomplete data for stress exposure and outcomes were excluded.

2.4 Data extraction

By a dual control principle all studies found by the search strategy were checked for suitability on title-abstract level by at least two reviewers (SvD/CH/SMG/HCH) being blinded for each other´s choice by the use of the online software rayyan[25]. Disagreements were resolved by personal discussion. Subsequently, full text studies were screened by two independent reviewers (SvD/CH) for eligibility. Disagreements were again resolved by discussion between the mentioned reviewers. All included studies were assigned to the categories of disease onset, relapse and/or disability progression. From the included studies it was extracted cohort characteristics, study design, type of stressors, follow-up duration and main results. As effect measures, risk estimates were extracted as odd ratios, hazard

ratios and relative risks. In some publications, it was focused on one or more stress factors which was rated as the most severe or relevant. One reviewer extracted data, which was subsequently checked by another. Disagreements were handled by discussion to reach consensus. In case of persisting disagreement, a third reviewer decided. As due to heterogeneity the conduct of meta-analyses was substantially limited. Results of all included studies are displayed in tables 4-6, broken down by the aspects MS onset, relapse and disability progression.

2.5 Risk of bias (quality) assessment

Study quality was assessed independently by two reviewer persons (SvD/CH) for each study based on the Critical Appraisal Skills Program (CASP) tool. For studies on disease onset the CASP Case Control Study Checklist[26] was used. Studies with focus on relapse and disability progression were assessed by a merged model of Case Control Study Checklist[26] and CASP Cohort Study Checklist[27]. By focus on the quality assessment concerning the studies´ design and the conduct of the studies the items of Section B and C of the CASP Case Control Study Checklist[26] and the items of Section B and C of the merged model of CASP Case Control Study Checklist[26] and CASP Cohort Study Checklist[27] were left out as they rather address interpretation of data. The exact definitions of the items are provided in the supplement (S3-S4).

2.6 Rating scheme for evidence level

For the overall evaluation of the evidence levels, an integrated rating scheme was added to assess the studies quality and the clarity of the results. The highest rating (+++) was given, when a clear association of stress (effect size 0.5 and higher) and the specific MS risk (onset, relapse, disability progression) shown in connection with a convincing study methodology. A high rating (++) was carried out, when a clear association (effect size 0.5 and higher) was found, but study methodology had some limitations or if a study of high methodological quality has shown a modest association (effect size 0.3-0.49). A positive rating (+) was given, when the study indicated a minor association (effect size 0.2-0.3) of stress at sufficient study methodology. A neutral rating level (0) was provided, when no association was found with a sufficient study methodology or a minor association with limited study

methodology. Finally, a negative rating (-) was given, when the study showed a negative association of stress and MS at sufficient methodology.

2.7 Statistical analysis

Effect estimates (e.g., logarithms of the odds ratio or rate ratio) were extracted with standard errors from the publications. If standard errors were not reported, these were derived from confidence intervals or p-values. For the meta-analysis in the relapse section hazard ratios of risks were calculated based on original study data. The Normal-Normal Hierarchical Model (NNHM) for random-effects meta-analysis was used in the Bayesian framework[28]. Since the meta-analyses were based on few studies only and between-study heterogeneity was suspected due to variations in study design, a weakly informative prior for the between-study heterogeneity (tau), specifically a half-normal prior with scale 0.5, was used[28]. Uninformative priors (specifically, uniform on the interval from minus infinity to infinity) were used for the treatment effects. The results are summarized by marginal posterior means of the treatment effects (on the logarithmic scale), and by marginal posterior medians for the between-study heterogeneity tau. Shortest 95% credible intervals (CI) are provided. Between-study heterogeneity was visually explored in forest plots; 95% prediction intervals are included to indicate the range of expected true study effects[29]. In the result section usually confidence intervals are not reported for better readability, while they are given in the tables. Only our own meta-analyses are presented with CI. For all meta-analyzed studies hazard ratios and shrinkage estimates (grey diamonds) are displayed with 95% confidence intervals. The “mean” gives the combined hazard ratio with 95% credible interval; “prediction” refers to the 95% prediction interval.

The R package bayesmeta was used to carry out the Bayesian random-effects meta-analyses[30].

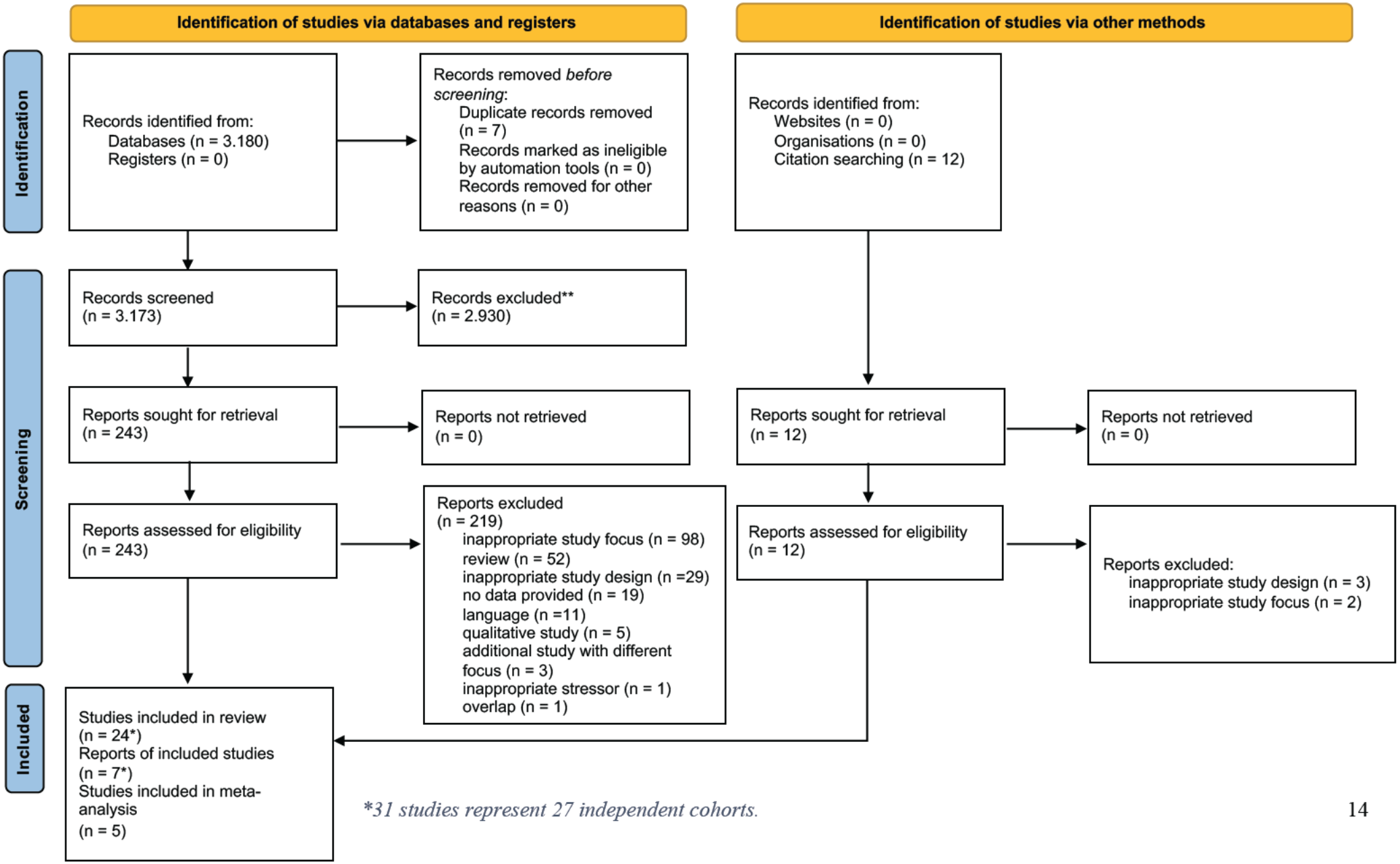
2.8 Patient and Public Involvement statement

Patients and the public were not involved in the study.

3. Results

A total of 3.180 records were screened for inclusion (figure 1). The display corresponds to the specifications of the PRISMA guideline for reporting systematic reviews[21]. After removing duplicates, 3.173 results remained. 2.930 studies were excluded on title-abstract level. 243 studies which potentially met the inclusion criteria were assessed in full text. Of those, only 24 fulfilled the eligibility criteria. Two independent meta-analyses were calculated including five studies in total. Major reasons for study exclusion were inappropriate study focus and design. The detailed listing of the reasons for exclusion is found in the supplement (Supplement 5). In addition, seven further studies were included from other sources (such as reference lists). Considering the cohort overlaps of several studies, the final 31 studies represented 27 cohorts, which were included in the synthesis.

Figure 1: *PRISMA flow diagram*



**31 studies represent 27 independent cohorts.*

Most of the studies focused on the relapses (19), followed by the aspect of MS onset (10) and finally by the studies which investigated disability progression (4). Two of the included studies contributed data for both relapse risk and disability progression. Geographically, most of the studies were conducted in Europe (13), followed by North America (12), Asia (5) and Australia (1).

In summary, the included studies frequently showed limitations by restricted consideration of potential confounders. Further, predominantly studies which focused on relapses had quality restrictions in case recruitment and controls selection. Overall, highest study quality was found in in those investigating MS onset (for details of quality assessment see tables 1-3).

***Table 1**:Studies on stress and MS onset - quality assessment and evidence synthesis*

		Quality criteria								
		Clear focus	Appropriate method	Acceptable case recruitment	Acceptable controls selection	Accurate exposure measure	Accurate outcome measure	Confounders mentioned	Confounders analyzed	Evidence synthesis
Studies	Li 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	+
	Riise 2011	Yes	n.d.	n.d.	n.d.	n.d.	Yes	Yes	Yes	0
	Nielsen 2011	n.d.	Yes	Yes	Yes	Yes	Yes	No	No	0
	Nielsen 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	0
	Nielsen 2014a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	0
	Nielsen 2014b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	+
	O'Donovan 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	++
	Song 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	++
	Bookwalter 2020	Yes	Yes	Yes	Yes	n.d.	Yes	No	No	++
	Eid 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	+

n.d.: no data; stands for the assessment category "can´t tell" due to lack of data according to CASP Case Control Study Checklist[26]

(++): A clear association (effect size 0.5 and higher) was found, but study methodology had some limitations or a study of high methodological quality has shown a modest association (effect size 0.3-0.49).

(+): Study indicated a minor association (effect size 0.2-0.3) of stress at sufficient study methodology.

(0): No association was found with a sufficient study methodology or a minor association with limited study methodology.

(-): Study showed a negative association of stress and MS at sufficient methodology.

Table 2: *Studies on stress and MS relapse risk - quality assessment and evidence synthesis*

Studies	Quality criteria										
	Clear focus	Appropriate method	Acceptable case recruitment	Acceptable controls selection	Accurate exposure measure	Accurate outcome measure	Confounders mentioned	Confounders analyzed	Follow-up complete	Follow-up duration long enough	Evidence synthesis
Rabins 1986	Yes	Yes	Yes	Yes	Yes	n.d.	No	No	Yes	Yes	0
Sibley 1987	Yes	Yes	n.d.	Yes	Yes	Yes	No	No	n.d.	Yes	0
Franklin 1988	Yes	Yes	Yes	n.d.	Yes	Yes	Yes	Yes	Yes	Yes	+
Nisipeanu 1993	Yes	Yes	n.d.	Yes	Yes	n.d.	No	No	n.d.	Yes	-
Morrison 1994	Yes	Yes	n.d.	Yes	Yes	Yes	No	No	n.d.	Yes	+
Mohr 2000	Yes	Yes	n.d.	Yes	Yes	Yes	No	No	n.d.	Yes	0
Ackermann 2003	Yes	Yes	n.d.	n.d.	Yes	Yes	No	No	n.d.	Yes	+
Buljevac 2003	Yes	Yes	Yes	n.d.	Yes	Yes	Yes	Yes	Yes	Yes	+
Brown 2006	Yes	Yes	Yes	Yes	Yes	n.d.	Yes	Yes	n.d.	Yes	+
Golan 2008	Yes	Yes	Yes	Yes	Yes	Yes	No	No	n.d.	Yes	++
Mitsonis 2008	Yes	Yes	n.d.	n.d.	Yes	Yes	Yes	Yes	Yes	Yes	++
Potagas 2008	Yes	Yes	n.d.	Yes	Yes	Yes	No	No	Yes	Yes	+
Mitsonis 2010[1]	Yes	Yes	n.d.	n.d.	Yes	Yes	Yes	Yes	Yes	Yes	+
Yamout 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	n.d.	Yes	++
Burns 2014[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	+
Oveisgharan 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	+
Kanamori 2017	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	0
Leekoff 2022	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	++
Sparaco 2022	Yes	Yes	n.d.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	+

[1]Although part of a randomized controlled trial (RCT), these two studies were treated and assessed as cohort studies as RCT groups were analyzed together.

n.d.: no data; stands for the assessment category "can´t tell" due to lack of data according to merged model of CASP Case Control Study Checklist[26] and Cohort Study Checklist[27]

(++): A clear association (effect size 0.5 and higher) was found but study methodology had some limitations or a study of high methodological quality has shown a modest association (effect size 0.3-0.49).

(+): Study indicated a minor association (effect size 0.2-0.3) of stress at sufficient study methodology.

(0): No association was found with a sufficient study methodology or a minor association with limited study methodology.

(-): Study showed a negative association of stress and MS at sufficient methodology.

Table 3:*Studies on stress and MS disability progression - quality assessment and evidence synthesis*

Studies	Quality criteria: Clear focus	Appropriate method	Acceptable case recruitment	Acceptable controls selection	Accurate exposure measure	Accurate outcome measure	Confounders mentioned	Confounders analyzed	Follow-up complete	Follow-up duration long enough	Evidence synthesis
Sibley 1987	Yes	Yes	n.d.	Yes	Yes	Yes	No	No	n.d.	Yes	0
Schwartz 1999	Yes	Yes	n.d.	Yes	Yes	n.d.	No	No	n.d.	Yes	0
Binzer 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	+
Leekoff 2022	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	+

n.d.: no data; stands for the assessment category "can´t tell" due to lack of data according to merged model of CASP Case Control Study Checklist[26] *and Cohort Study Checklist*[27]

(++): A clear association (effect size 0.5 and higher) was found but study methodology had some limitations or a study of high methodological quality has shown a modest association (effect size 0.3-0.49).
(+): Study indicated a minor association (effect size 0.2-0.3) of stress at sufficient study methodology.
(0): No association was found with a sufficient study methodology or a minor association with limited study methodology.
(-): Study showed a negative association of stress and MS at sufficient methodology.

3.1 Stress factors and MS onset risk – overview

Ten relevant studies were found which examined the association between stress and MS onset risk. Due to an overlap of five Danish registry studies[31–35], they cannot be regarded as independent datasets, therefore the included studies investigating the association between stress and MS onset risk represent only six independent cohorts. As the possibly most severe stressor, Nielsen[34] and Li[31] used patients´ loss of a child in nationwide Danish registry studies combining The Danish MS Registry with data of the National Patient Registry. While Li et al. (2004)[31] could demonstrate a significantly increased hazard ratio (HR) of 2.25 after at least 8 years of follow-up, Nielsen et al. (2014)[34] found no statistically significant association of the MS risk with bereavement (RR=1.12). They also showed no effect of widowhood, divorce or for stillbirth of a child[32,34]. The low number of MS cases among bereaved parents (n=85), widowed persons (n=42) and stillbirth mothers (n=15) was an important limitation of these studies. A graphic overview of the five most relevant stressors investigated by the Danish studies of Li et al. (2004)[31] and Nielsen[32,34,35] is displayed in figure 2.

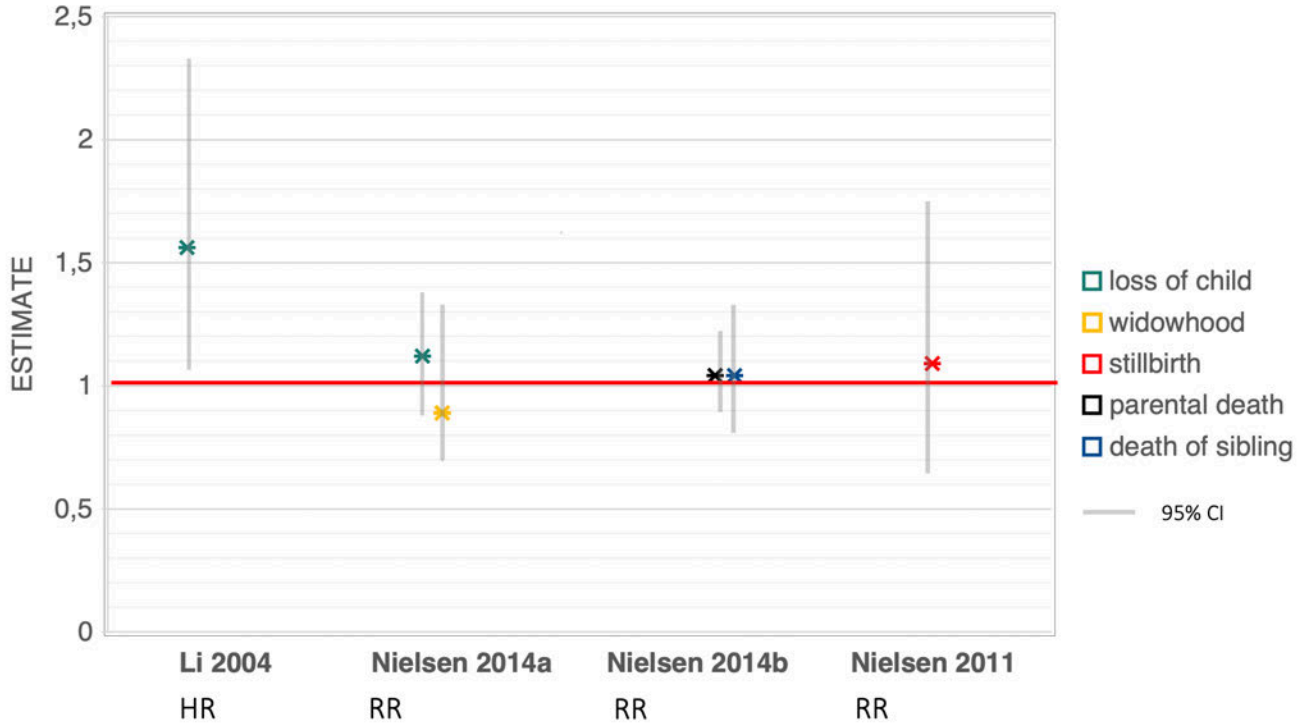


Figure 2: *Graphic synopsis of relevant Danish studies on major negative stressful life events and MS onset.*

In two large survey based studies of cohorts of US female nurses investigated and published in one paper by Riise et al. (2011)[36] no increased risk of MS associated with home stress (HR=0.87) or work stress (HR=0.52) as assessed by survey questionnaires was found. Nielsen et al. (2013, 2014)[33,35] studied childhood adversities such as socioeconomic status, parental divorce, parental death and death of a sibling with only divorce showing a slightly increased MS risk (RR=1.13). Recently, Eid et al. (2022)[37] carried out a matching analysis of a large population-based study in Norway among pregnant women compared with data from the National MS Registry. Authors found an increased MS risk for sexual abuse (HR= 1.65) and emotional abuse in childhood (HR=1.40) based on women's questionnaire responses. In addition, a dose-response relationship was found, as the MS risk was higher when exposed to several abuse categories. One major limitation of this study was the lack of information about the chronicity of the abuse events (one-time incident vs. repetitive abuse).

Three studies addressed stress-related disorders[38–40]. Two studies examined post-traumatic stress disorder (PTSD) in U.S. veterans[38,39] showing an increased MS risk

in persons with PTSD alone or in combination with other psychiatric disorders (adjusted RR=2.36 and HR=2.3). In a Swedish population- and sibling-matched retrospective cohort Song et al. (2018)[40] investigated the association between stress-related disorders (incl. PTSD) and subsequent autoimmune disease (incl. MS) and found an increased risk of MS in exposed individuals (HR=1.35) . As these studies are sufficiently similar and comparable, a meta-analysis could be performed in summary showing a 1.87-fold (CI 1.061 to 3.429) increased MS risk, as presented in figure 3. The sample size of studies varied substantially from 77 to 8.547 MS cases, the follow-up duration showed a range from 11 to 43 years.

In summary, most of the studies only found a small positive association between stress and MS onset.

All included studies investigating the association between stress and MS onset risk are presented and summarized in table 4. For reasons of better legibility, the confidence intervals in the following narrative part were mostly omitted and displayed in the mentioned table. In summary for the MS onset aspect highest evidence levels were found in the three studies on stress-related disorders and MS[38–40].

3.1.1 Description of studies on stress and MS onset according to stress factors

Major personal negative life events and MS onset risk

Li et al. (2004)[31] compared data from a cohort study with about 21.000 parents from the Danish MS registry who lost a child under age 18 years with an unexposed cohort of ca. 294.000 parents with a mean follow-up of 9.5 years. Exposed parents had an increased risk of MS onset after bereavement (HR=1.56), which was significant only in the follow-up of at least eight years (HR=2.25) compared to the length of follow up of one to seven years (HR=1.37). The subgroup of parents having lost a child unexpectedly showed a HR of 2.13. The low number of 28 MS cases in the exposed group limited the validity of the finding factor.

Ten years later **Nielsen et al. (2014)**[34] carried out a cohort study with two cohorts of about 1.8 million parents and ca. 1.6 million married persons, which were followed over 28 years, to investigate the role of loss of child, divorcement and widowhood for MS risk. In total, no MS risk was found for all three types of stress: bereavement

(RR=1.12), divorcement (RR=0.98) or widowhood (RR=0.98). The low number of MS cases among bereaved parents (n=85) and widowed persons (n=42) was a relevant limitation.

Home and work stress and MS onset risk

In a prospective study of **Riise et al. (2011)**[36] two cohorts of US female nurses were investigated. The first cohort of round about 122.000 persons were followed prospectively for 29 years asking for stress at home and at work as a risk factor for MS. The second cohort of about 117.000 nurses, which was followed for the association between physical and sexual abuse in childhood and adolescence and MS onset, was excluded due to the retrospective design. In summary, no increased risk of MS associated with home stress (HR=0.87) and work stress (HR=0.52) was found.

Stillbirth and MS onset risk

In a Danish cohort study of **Nielsen et al. (2011)**[32] 4.4 million Danish women and men were followed up to 34 years. In a subgroup of 1.39 million pregnant women with adverse pregnancy outcomes and complications authors looked for a subsequent increased MS onset risk. Among other pregnancy associated stressors stillbirth as the possibly most severe pregnancy associated stressor was selected. MS risk was not associated with this major life event (RR=1.09). The small number of MS cases (n=15) among exposed women limited the validity of the finding.

Childhood adverse experiences and MS onset risk

In another Danish study by **Nielsen et al. (2013)**[33] 1.5 million people from the national population registry were followed up over 26 years to investigate the association between the socioeconomic status in childhood at 7 and 15 years of age and the risk of MS. Among different indicators a low household income as possibly the most relevant socioeconomic stressor was selected, which showed no association with MS onset for both ages (RR 1.0).

In a further Danish study of **Nielsen et al. (2014b)**[35] a cohort of 2.9 million Danes were followed over 40 years examining the association between stressful life-events in childhood (under age of 18 years), which included parental divorce, parental

death and death of a sibling. Parental death (RR=1.04) and death of a sibling (RR= 1.04) showed no association with MS risk, but parental divorce was linked with a 13% increased risk of MS onset (RR=1.13). The fact that only deaths of siblings or parents and only divorces among formally married parents were considered, was one limitation, as deaths of other family members and separations of unmarried parents could have been valued as similar stressful.

Eid et al. (2022)[37] carried out a nationwide prospective cohort study with circa 78.000 Norwegian pregnant women to examine the association between adverse childhood experiences (sexual, emotional and physical abuse) and MS risk. About 14.500 exposed and about 63.500 unexposed women were followed for 19 years. Authors found an increased MS risk for sexual abuse (HR=1.65) and emotional abuse (HR=1.40). For the exposure to physical abuse authors described a similar tendency (HR=1.31). In addition, a dose-response relationship was found, as the MS risk was higher when exposed to several abuse categories. One major limitation of this study was the lack of information about the chronicity of the abuse events (one-time incident vs. repetitive abuse).

Stress-related disorders and MS onset risk

O´Donovan et al. (2015)[38] examined the association between PTSD and risk for autoimmune diseases including MS based on a retrospective observational study with about 666.000 US-American Iraq and Afghanistan veterans and 535 MS cases with a follow-up duration of almost 11 years. In summary, an increased MS risk in persons with PTSD alone or in combination with other psychiatric disorders was found (adjusted relative risk=2.36). The fact, that the occurrence of PTSD was only analyzed together with other psychiatric disorders with no separate data available was a limitation.

In a Swedish population- and sibling-matched retrospective cohort **Song et al. (2018)**[40] investigated the association between stress-related disorders and subsequent autoimmune disease (incl. multiple sclerosis) from Swedish registries. About 106.000 exposed patients with stress-related disorders, circa 1.065.000 matched unexposed persons and about 127.000 full siblings of these patients, who were followed up over 32 years, were studied. Beside other autoimmune diseases

also an increased risk of MS was found in exposed individuals (HR=1.35). In contrast to O´Donovan et. al. (2015)[38] here the stress exposure did not focus veterans with presumably PTSD based on experiencing war.

Similar to Leekoff et al. (2022)[41] **Bookwalter et al. (2020)**[39] analyzed the association between PTSD and MS risk based on a cohort of about 121.000 US-American military service members, who were followed for 14 years. In the cohort with about 10.000 exposed and circa 111.000 unexposed persons authors found an increased MS risk when a premorbid PTSD had been diagnosed (HR=2.3). One limitation was the lack of diagnostic security because no medical records were reviewed. Further, the fact that the assessment of PTSD was only based on patients´ report resp. patient checklist was a limiting factor.
The meta-analysis of the three studies in this section is displayed in figure 3.

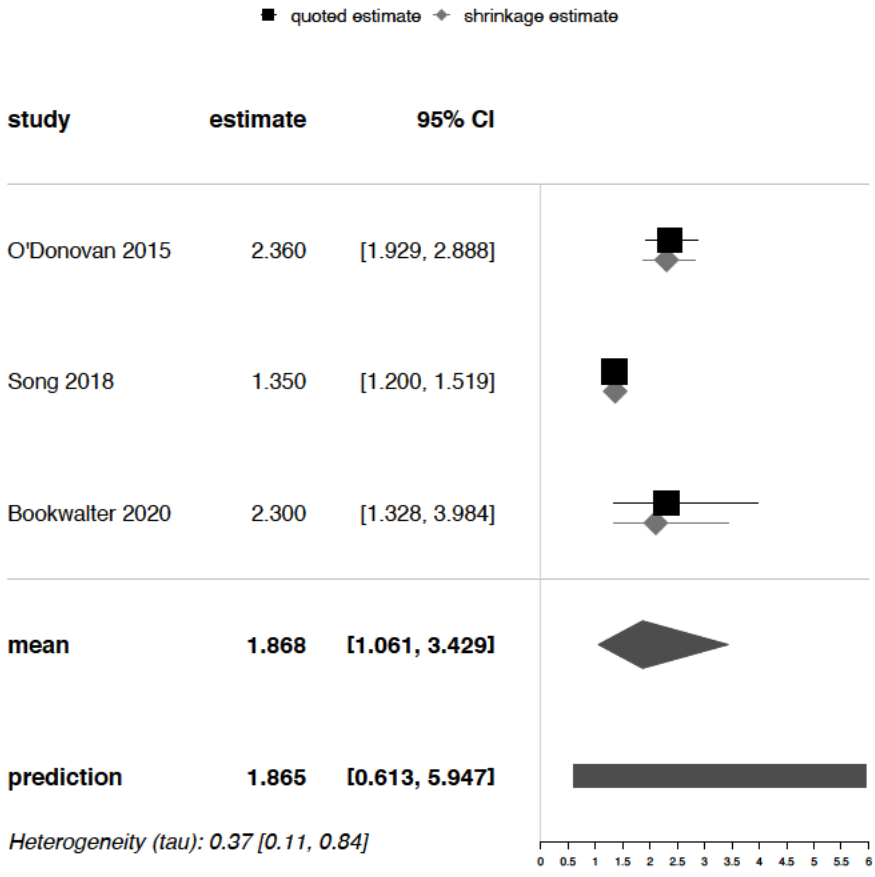


Figure 3: *Meta-analysis of studies[38–40] investigating the association between stress-related disorders and MS risk. For all three studies hazard ratios (black squares) and shrinkage estimates (grey diamonds) are displayed with 95% confidence.*

Table 4: *Included studies investigating stress and MS onset risk*

study	N	design	cohort(s)	stressor(s)	follow-up duration	main result	comment
Major personal negative life events and MS onset risk							
Li et al., 2004*	21.062 exposed 293.745 unexposed 258 MS cases (all) 28 exposed 230 unexposed	cohort study	Danish parents with child loss 1980-1996 matched with parents without child loss	loss of child age <18 yrs	17 yrs (1980-1997) Ø 9.5 yrs	HR=1.56 (1.05-2.31) **8-17 yrs follow-up:** HR=2.25 (1.32-3.81) **unexpected loss:** HR=2.13 (CI 1.13-4.03)	exposed parents with increased MS onset risk only significant when follow-up at least 8 yrs
Nielsen et al., 2014a*	**1.801.330 (cohort 1)** **loss of child:** 28.682 exposed 4.760 MS cases (all) 85 exposed 4.675 unexposed **1.618.424 (cohort 2)** **divorcement:** 442.264 exposed 3.787 MS cases (all) 626 exposed 3.161unexposed **widowhood:** 34.711 exposed 3.787 MS cases (all) 42 exposed 3.745 unexposed	cohort study	**cohort 1:** Danish people who became parents 1968-2010 **cohort 2:** Danish people who married 1968-2010	1. loss of child age <18 yrs 2. divorcement 3. widowhood	28 yrs (1982-2010)	**loss of child:** RR=1.12 (CI 0.89-1.38) **divorcement:** RR=0.98 (CI 0.89-1.06) **widowhood:** RR=0.98 (CI 0.71-1.32)	no elevated MS onset risk for selected major SLE

Home and work stress and MS onset risk							
Riise et al.**, 2011	94.185 (total cohort) **stress at home:** 7.309 exposed 77 MS cases (all) 6 exposed 71 unexposed **stress at work:** 10.296 exposed 77 MS cases (all) 4 exposed 73 unexposed	cohort study	female U.S. nurses (age 30-55 yrs)	1. severe stress at home 2.severe stress at work	22 yrs (1982-2004)	**stress at home:** HR=0.87 (CI 0.32-2.26) **stress at work:** HR=0.52 (CI 0.15-1.85)	no support for asso-ciation between stress at home and at work and MS onset risk
Stillbirth and MS onset risk							
Nielsen et al., 2011	1.39 million **(subcohort of pregnant women)** 4.004 MS cases (all) 15 exposed 3.091 unexposed	cohort study	Danish women born 1955-1989	stillbirth	34 yrs (1970-2004)	RR=1.09 (CI 0.63-1.74)	no association between stillbirth and MS onset risk
Childhood adverse experiences and MS onset risk							
Nielsen et al., 2013*	1.569.02 (total cohort) 2.205 MS cases (all) **relevant subgroup:** **SES at age** a) 7 yrs and b) 15 yrs **a) 810 MS cases (all)** 156 exposed	cohort study	Danish men and women born 1966-1992	lowest quintile of household in-come at age 7 and 15 yrs	26 yrs (1981 - 2007)	RR=1.0 for age 7 /15 yrs	no association between household income and MS onset risk

	654 unexposed **b) 2.193 MS cases (all)** 582 exposed 1.611 unexposed						
Nielsen et al., 2014b*	2.973.993 (total cohort) <u>3.260 MS cases (all)</u> 902 MS exposed 2.358 unexposed **1.parental divorce:** <u>3.260 MS cases (all)</u> 712 exposed 2.548 unexposed **2.parental death:** <u>3.260 MS cases (all)</u> 185 exposed 3.075 unexposed **3.death of sibling:** <u>3.260 MS cases (all)</u> 68 exposed 3.192 unexposed	cohort study	Danes born 1968-2011	exposure to (<18 yrs): 1.parental divorce 2.parental death 3.death of sibling	43 yrs (1968-2011)	**1.parental divorce:** RR=1.13 (CI 1.04-1.23) **2.parental death:** RR=1.04 (CI 0.90-1.21) **3.death of sibling** RR=1.04 (CI 0.81-1.32)	modestly increased MS onset risk for parental divorce for other events no association
Eid et al., 2022	<u>77.997 (total cohort)</u> 14.477 exposed 63.520 unexposed <u>300 MS cases (all)</u> 71 exposed 229 unexposed	cohort study	Norwegian pregnant women (1999-2008)	childhood abuse: -sexual -emotional -physical	19 yrs (1999-2018) Ø13 yrs	**sexual abuse:** HR=1.65 (CI 1.13-2.39) **emotional abuse:** HR=1.40 (CI 1.03-1.90)	sexual and emotional abuse in childhood with increased MS onset risk similar tendency for physical abuse

						physical abuse: HR=1.31 (CI 0.83-2.06)	
Stress-related disorders and MS onset risk							
O`Donovan et al., 2015***	666.269 (final cohort) 203.766 exposed 462.503 unexposed 535 MS cases (exposed)	retrospective cohort study	Iraq and Afghanistan veterans < 55 yrs	PTSD	11 yrs (2001-2012)	ARR=2.36 (CI 1.93-2.89)	PTSD with increased MS onset risk
Song et al., 2018***	7.689.628 (population) **Population-matched cohort:** 106.464 exposed 1.064.640 unexposed 2.834 MS cases (all) 347 exposed 2.487 unexposed	cohort study	Swedish population-matched cohort (MS and stress-related disorder)	diagnosed with stress-related disorder incl. PTSD	32 yrs (1981-2013) Ø 10 yrs	HR=1.35 (CI 1.20-1.52)	slightly increased MS onset risk
Bookwalter et al., 2020***	120.572 (total cohort) 9.875 exposed 110.697 unexposed 151 MS cases (all) 24 exposed 127 unexposed	cohort study	active duty U.S. military service members	PTSD	14 yrs (2001-2015) Ø 5.2 yrs	HR=2.3 (CI 1.3-3.9)	PTSD with increased MS onset risk

*cohort overlap of the Danish MS registry studies
**Riise et al. 2011: Data of cohort 2 was excluded due to retrospective design
***Meta-Analysis of three studies with focus on stress-related disorders and MS onset risk

ARR: adjusted relative risk
HR: hazard ratio
SES: socioeconomic status
yr: year
CI: confidence interval
PTSD: post-traumatic stress disorder
SLE: stressful life event
yrs: years
HR: hazard ratio
RR: relative risk
U.S.: United States
Ø: average

3.2 Stress factors and MS relapse risk – overview

Nineteen eligible studies were identified which focused on the association between stress and MS relapse risk. Studies with evident cohort overlap and studies with additional (secondary) analysis of data from cohorts published earlier, were not analyzed separately[42–45].

Many studies investigated the role of stressful life events in the sense of major and minor negative life events. While studies published before 2000 were substantially methodologically limited[46–49] due to small sizes and large assessment intervals they showed partial conflicting findings. Newer studies[50–56] consistently showed statistically significant associations between stress and relapse risk. However, risk estimates showed considerable variance ranging from a relative risk of 2.2[50] to an odds ratio of 38.5[52]. The sample sizes showed a range from 25 to 216 and the duration of follow-up varied from seven months to a maximum of eight years.

As in the onset section, also here the small sample sizes of several studies were a limiting factor.

Several of the studies could be classified as studying major societal threats representing pure external stressors. Three studies focused on stress by exposure to war activities with missile attacks[15,57,58] with partly contradictory results. Two of the three studies[57,58] could be meta-analyzed reporting data from the same period in 2006 from Israel and Lebanon based on an ongoing military confrontation (see figure 4). Overall, in the two studies a threefold increased relapse rate in association with missile attacks in connection with the war (rate ratio=3.0, 95% CI 1.56 to 5.81) was reported. The third small Israelian study from the 1991 gulf war[15] showed reduced relapse risk during the war, but was only compromised of 32 patients with little methodological information.

One Asian study investigated the influence of the Great East Japan Earthquake in 2011 with subsequent tsunami and meltdown of the Fukushima nuclear power plant on the MS relapse risk among 140 MS patients from Japan[59]. Overall, after the earthquake no increase of the annualized relapse rate was found, compared to the pre-disaster period.

Another recently studied societal stressor was the COVID-19 pandemic affecting societies as a whole[60]. In this study, the annual relapse rate in 2020 showed a statistically significant increase, mainly in the second and third quarter of 2020 in a

sample of 216 Italian persons with MS compared to 2019. However, the main limitation of this study is the lack of clinical relapse confirmation, as due to the restrictions of the pandemic only remote relapse evaluations could be performed.

Two further studies examined magnetic resonance imaging (MRI) inflammatory activity in relation to stressful life events[61,62]. Both studies reported a small increased risk of the occurrence of gadolinium-enhanced lesions in relation to personal stressors (odds ratio (OR)=1.12 and 1.77). As the findings from Burns et al. (2014)[62] are derived from a RCT on stress management in MS, a meta-analysis of the two studies was not justified.

Recently, Leekoff et al., 2022[41] investigated a diagnosis of PTSD antecedent to clinical MS onset and its impact on MS relapse risk and MRI activity in U.S. veterans. MS patients with PTSD prior to symptom onset had both a higher mean annual relapse rate (0.23 vs 0.06) and a higher annualized mean number of new T2 (0.52 vs 0.16) and gadolinium-enhancing MRI-lesions (0.29 vs 0.08). The external validity may be limited as the population mainly was male, had higher rates of PTSD and notably high rates of psychiatric comorbidities and often a corresponding medical treatment.

Besides stress quality and severity, some studies also investigated the role of the number of stressors and the stressor duration (short-term vs. long-term). Overall, the included studies showed a pronounced heterogeneity with sample sizes showing a range from 25 to 216, the follow up duration showed a range from almost 7 months to 8 years.

In summary major societal threats increased the MS risk up to threefold. In addition, stressful life events consistently showed small increases in relapse risk as well as increased inflammatory disease activity on MRI.

The highest evidence levels for the aspect relapse were found in the two war studies[57,58] we meta-analyzed, and also in the study of Leekoff et al. (2022)[41] examining the association between PTSD and MS relapse risk. All included studies investigating the association between stress and MS relapse risk are presented and summarized in table 5. For reasons of better legibility, the confidence intervals in the following narrative part were mostly omitted and displayed in mentioned table.

3.2.1 Description of studies on stress and MS relapse risk according to stress factors

Stressful life events and MS relapse risk

In a prospective study **Rabins et al. (1986)**[46] followed 87 MS patients from the U.S. and 16 patients with spinal cord injury as control group with a follow-up duration of one year. Besides the role of emotional disorders among MS patients, which was assessed by the General Health Questionnaire, authors investigated the temporal association between stressful life-events and MS exacerbations. In summary, authors found no evidence that stressful life-events are associated with relapses.

In an 8-year prospective U.S. American study with 170 MS patients and 134 persons as healthy controls **Sibley (1986)**[47] investigated the association between stressful life events and relapses. Over all data showed no significant influence of any stress subcategory on the relapse risk. None of the nine stress categories, of which three were classified as severe, were related to relapses.

Franklin et al. (1988)[48] carried out a prospective study with 55 RR-MS patients (25 with exacerbations, 30 without exacerbations) from the U.S. with 20 months follow-up and examined the impact of stressful life events on relapse occurrence. Patients with serious stressors had a significantly elevated likelihood for exacerbations compared to those without such events (RR=3.73). In total, the study found that rather the quality rather than the quantity of stressful life events was associated with relapses. Limitations of this study were the relatively large time interval of the stress assessment (every four months) and the small sample size.

In a Canadian prospective study **Morrison et al. (1994)**[49] followed 50 RR-MS patients for two years to examine the association between emotionally stressful events and relapse evolution. Only the data of 17 patients without immunotherapy were analyzed in this study. In summary, the annual rate of relapses in times at risk (1.8) was higher than for periods not at risk (1.4). However, there was no significant relation between stress and relapses. The very small sample size and the missing representativeness was a substantial limitation.

Buljevac et al. (2003)[50] investigated in a longitudinal prospective cohort study 73 Dutch RR-MS patients with mean follow-up period of 1.4 years to study the influence of stressful life events on MS exacerbations and showed that stress was associated with a twice increased relapse rate (RR=2.2). Limiting factor was the stress measurement in the form of diary entries instead of a validated assessment instrument.

Ackermann et al. (2003)[51] run a longitudinal study with 50 female US MS-patients (RR-MS and SP-MS) and followed them over one year to analyze the linkage of stressful life events and relapses. Relapses were significantly more likely to occur during periods at risk (estimate: 0.29). Events with modest or major level of short-term threat were related to MS relapses. In an earlier sub-cohort of 23 patients[42] it was already shown that an increase in frequency of life events was clearly related to an elevated likelihood of relapses (HR=13.18). As a limitation about 25% of the patients received psychoactive substances, which may have potentially modulated stress responses.

In a longitudinal study **Brown et al. (2006)**[52] followed 101 Australian MS patients (RR-MS and SP-MS) for two years to examine the association between stressful life events and MS exacerbations. Here acute events (OR=38.54, high stress emotional threat at three months) but not chronic difficulties predicted occurrence of relapses. The count of acute stress events predicted increased relapse risk, so that in summary the number and not the severity of acute stressors were concluded as most relevant. Chronic stressors did not predict subsequent exacerbations. A relatively high dropout rate of patients who completed the stress interviews (35% at 12 months, 49% at 24 months) substantially limited the conclusion.

In a prospective study 37 Greek female patients (RR-MS) were followed for one year (**Potagas et al., 2008)**[53], and the impact of stressful life events and anxiety levels on relapse occurrence was investigated. Results showed, that three to five stressful life events were associated with a 6.7-fold increased relapse rate (HR=6.7). The small sample size was a limitation.

In a further Greek, smaller prospective study with 26 RR-MS female patients with follow-up for a mean of about one year, **Mitsonis et al. (2008)**[54] investigated the relationship between stressful life events and relapses, also in terms of duration, type and severity of stressors. Summing up, it was found that three or more stressful life events came along with a fivefold increase of relapse rate. Further, patients with at least one long-term stressful life events had a threefold elevated risk for exacerbations during the following four weeks (HR=3.03). No significant relation between severity or type of stressor and relapse risk was ascertained. Besides the small sample size, the lack of differentiated listing of the severe stressors represented a limitation of this study. As both authors[53,54] were located at the same institution, an overlap of thew two cohorts cannot be ruled out.

In a randomized, controlled study for one year, again **Mitsonis et al. (2010)**[55] aimed to exam the impact of an antidepressant medication (Escitalopram) on the occurrence of stress-related relapses on the basis of 48 Greek women with RR-MS. They found, that the cumulative risk for relapse was nearly three times higher for controls than for patients who received Escitalopram (HR=2.9). Furthermore, the risk was only influenced by long-term stressful life events. For the patients who were on antidepressant medication three or more long-term stressful life events were related with a significant increase of the risk of exacerbation during the following four weeks (HR=16.1). In comparison the control group showed a four times higher risk. A limitation of this study was the missing differentiation regarding stress severity. Although part of a randomized controlled trial (RCT), this study was handled and assessed as a cohort study as the RCT group data was analyzed together.

In another small prospective study **Oveisgharan et al. (2014)**[56] followed 57 Iranian RR-MS patients for one year and investigated the relation between number of stressful life events and MS-exacerbations. They found, that the number of stressful life events reached near significance as a predictor for relapses, and showed a trend towards significance in predicting severe relapses, whereas stress severity had no significant effect.

Major societal threats and MS relapse risk

In a small Israelian study **(Nisipeanu and Korczyn, 1993)**[15] 32 RR-MS patients, exposed to the 1991 first gulf war, were followed over three months and showed a significant decrease in the number of exacerbations during the period at risk (war period and following two months) compared to the two preceding years ($p<0.01$). The study was substantially limited as little methodological information was provided.

Golan et al. (2008)[57] investigated 156 Israelian RR-MS patients who were exposed to war connected with missile attacks lasting 33 days between Israel and Hezbollah in Lebanon and compared the count of relapses during the war-period (plus three months after) vs. during comparable time periods over 12 months preceding the war. It was found a higher relapse rate for the war period, so the data in total suggested, that war stress with missile attacks is associated with increased relapse risk (HR=3.35, CI 2.01-5.56).

From the Lebanon perspective, **Yamout et al. (2010)**[58] examined the association between war-exposure with missile attacks (between Israel and Hisbollah in Lebanon, see also Golan et al., 2008[57]) and MS-relapses and radiological disease activity on the basis of 216 RR-MS patients. In summary, the total count of exacerbations during the war period was significantly higher than during non-war periods (HR=2.74, CI 1.76-4.25). Also, more patients had gadolinium-enhancing MRI lesions during the war period in comparison with the controls. The fact that these MRI controls were not the same patients, thus a between-subject design was a substantial limitation for this aspect.

Overall, in the two war-studies of **Golan et al. (2008)**[57] and **Yamout et al. (2010)**[58] a threefold increased risk for relapses in association with the war (HR=3.0, CI 1.56-5.81) was found. The metanalytic calculation is shown in figure 4.

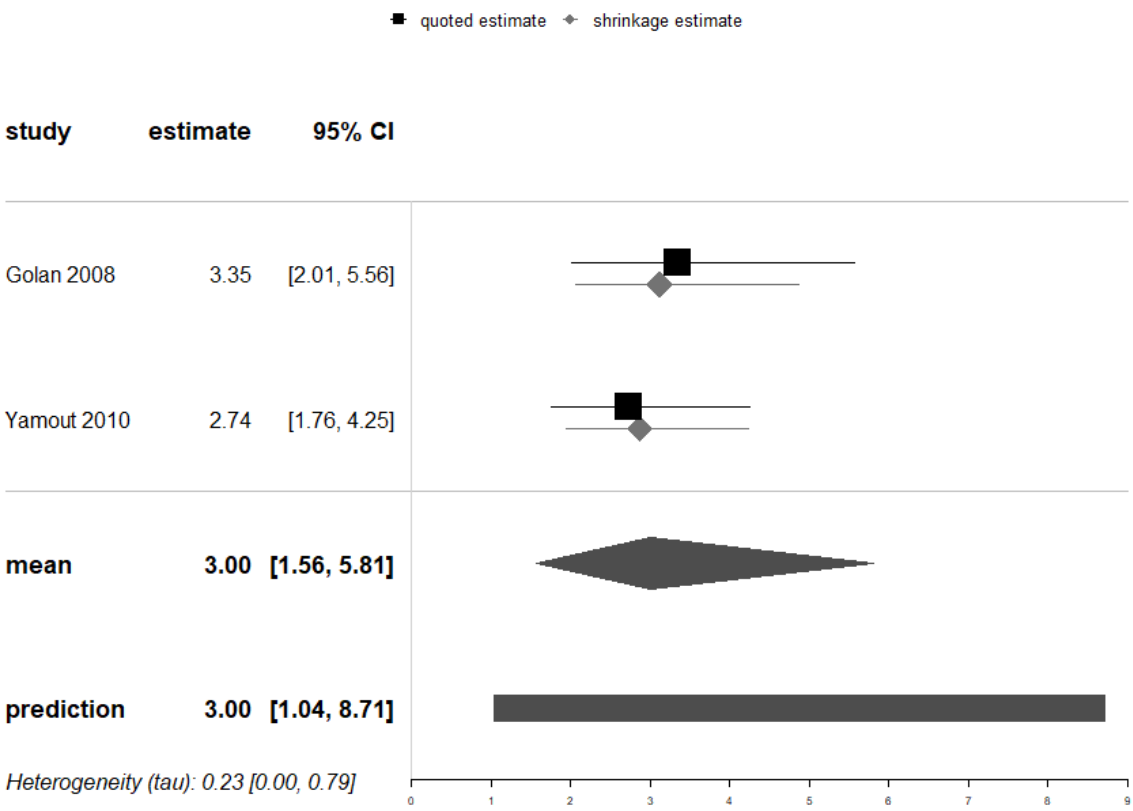


Figure 4: *Meta-analysis of two studies[57,58] investigating the association of war exposure with missile attacks and MS relapse risk. For both studies hazard ratios (black squares) and shrinkage estimates (grey diamonds) are displayed with 95% confidence interval.*

Kanamori et al. (2017)[59] investigated in a retrospective study with 140 Japanese MS patients the influence of the Great East Japan Earthquake in 2011 with subsequent tsunami and meltdown of the Fukushima nuclear power plant on the relapse risk[59] by comparing the annualized relapse rate one year before and one year after the event. Overall, after the earthquake no increase of the annualized relapse rate was found, compared to the pre-disaster period. Limited was the study by partially contradictory data reporting and the missing data about other implications of the natural disaster, e.g., physical injuries or starving situations, etc. Therefore, the stressor and its sequelae are hardly comparable with the war stress studies and therefore do not justify a joined meta-analysis.

Sparaco et al. (2022)[60] conducted an observational study with 216 Italian persons with remitting multiple sclerosis and compared the relapse rate before the COVID-

19 pandemic (2019) and in the first year after the pandemic onset (2020). In summary, the annual relapse rate in 2020 showed a significant increase (p=0.0142), mainly in the second and third quarter of 2020. Limited was the study by the lower certainty of the relapse assessment, as due to the restrictions of the pandemic only remote relapse evaluations could be performed. However, only relapses treated with steroids were considered for the analysis thereby increasing validity of the relapse rating. Although to a certain degree the pandemic represents a comparable stressor to war concerning the severe and broad impact on societies, the required extent of comparability of the stressors for including the pandemic study in the meta-analysis of the two war-studies was not given.

Studies investigating inflammatory MRI activity

In a prospective longitudinal study **Mohr et al. (2000)**[61] investigated 36 MS patients (RR-MS and SP-MS) from the U.S. for 28 to 100 weeks and analyzed the association between minor and major stressful life events, psychological distress and the subsequent appearance of new gadolinium-enhancing MRI lesions. For major negative events there was no significant relation between stressor occurrence and disease activity in the 8-week lagged analyses (OR=1.12).

Burns et al. (2014)[62] longitudinally followed 121 MS patients (RR-MS and SP-MS) from the U.S. for 48 weeks, which was a secondary analysis of a randomized controlled trial of Mohr et al. (2012)[63], who compared Stress Management Therapy for MS to a waitlist control.

Across all groups major negative stressful events were predictive for appearance of gadolinium-enhancing lesions (OR=1.77) and new or enlarging T2 lesions (OR=1.57), whereas moderate negative events, perceived stress, anxiety and depressive symptoms were not. The design of the primary study which enrolled persons in a trial including a stress management therapy, could have led to a selection of persons with specific experiences with stress compared to pwMS from cohort studies. Although part of a randomized controlled trial (RCT), this study was handled and assessed as a cohort study as RCT groups were analyzed together.

PTSD and MS relapse risk

Leekoff et al. (2022)[41] investigated the impact of a preexisting diagnosis of PTSD in a population-based cohort study with about 5.000 U.S. military veterans with multiple sclerosis on the relapse frequency and MRI activity over four years, compared to circa 25.000 MS patients from the same cohort without PTSD as controls. They were able to include 96 pwMS who had experienced PTSD before a MS diagnosis was made and matched these to 95 pwMS without PTSD. Authors compared the annual relapse rate and annualized the mean number of new T2 and gadolinium-enhancing lesions on brain MRI between the two groups. In conclusion MS patients with PTSD prior to symptom onset had both a higher mean annual relapse rate (0.23 vs 0.06) and a higher annualized mean number of new T2 (0.52 vs 0.16) and gadolinium-enhancing MRI lesions (0.29 vs 0.08). The external validity may be limited as the population mainly was male, had higher rates of PTSD and notably high rates of psychiatric comorbidities and often a corresponding medical treatment.

Table 5: *Included studies investigating stress and MS relapse risk*

study	n	design	cohorts	demographics	stressor(s)	follow-up duration	main results	comment
Stressful life events and MS relapse risk								
Rabins et al., 1986	87 MS 16 SCI	prospective study	pwMS (U.S.) CG: pwSCI (U.S.)	Ø age 39.2, 70.1 % female, 31% RR-MS, 25% RP-MS, 44% PP-MS, Ø disease duration 8.6 yrs	stressful life events	1 yr	23 individuals with exacerbation	no association btw. SLE and relapses
Sibley, 1987	170 MS 113 exp. 57 unexp. 134 HC	prospective study	pwMS (U.S.) HC (U.S.)	**patients (controls)** Ø age 43 (40), f:m = 1.6:1 (1.7:1), almost 50% mildly affected at entry with DSS 0-4	1. death of spouse or 1st relative 2. death of other close family member 3. serious illness, family member	8 yrs (Ø 5.23) CG: Ø 4.6 yrs	**Ex/yr-AR vs. NAR:** **stressor 1** 0.14 vs. 0.16 **stressor 2** 0 vs 0.25 **stressor 3** 0.33 vs. 0.29	no effect of SLE on relapse rate
Franklin et al., 1988	25 MS 30 HC	prospective study	RR-MS (U.S.)	cases (controls) Ø age 33.1 (36.6), 88 % (77%) female, all RRMS, DSS 2.0 (1.7), duration of disease 6.6 (7.1) yrs	SLE	20 months	RR=3.73 (CI 1.20-12.08)	increased likelihood of relapses for qualitatively extreme events
Morrison et Nelson, 1994	49	prospective study	RR-MS (Canadian)	73.5 % female, all RR-MS 17 on placebo, 32 on Betaseron	emotionally stressful events	2 yrs	**annual relapse rate:** (at risk period vs. not at risk period) 1.8 vs. 1.4	relapses more frequent after stressful events compared to periods not at risk

Buljevac et al., 2003	73	longitudinal, prospective cohort study	RR-MS (Dutch)	Ø age 39.9, 77.8 % female, all RRMS, Ø EDDS baseline 2.6, Ø duration of disease 5.2 yrs	SLE (incl. minor and major)	Ø 1.4 yrs	RR=2.2 (CI 1.2-4.0)	SLE associated with increased relapse rate
Ackermann et al., 2003**	50	longitudinal study	pwMS (U.S.)	Ø age 39.8, all female, 90 % RR-MS, 10 % SP-MS, EDSS baseline 2.7, Ø duration of disease 9.7 yrs	SLE	1 yr	OR=1.34 (CI 1.12-1.60)	relapses more likely during periods at risk relatively independent of threat level and type of stressor
Brown et al., 2006	101	longitudinal study	pwMS (Australian)	Ø age 42.6, 80,2 % female, 74,5 % RR-MS, 25,5 % SP-MS, Ø EDSS 3.6, Ø disease duration 8.3 yrs	SLE	2 yrs	**acute events (hi-stress emotional threat at 3 mths):** OR=38.54 (CI 1.01-1470.04) also for milder stressors elevated ORs	*acute* stressors predict relapse occurrence *chronic* stress and stress severity not relevant
Potagas et al., 2008[1]	37	prospective study	RR-MS (Greek)	Ø age 32.8, all female, all RR-MS, Ø EDSS 0,47, Ø duration of disease 3.6 yrs	SLE (incl minor and major)	1 yr	**1 SLE** HR=1.3 (CI 0.5-3.1) **2 SLE** HR=0.6 (CI 0.1-4.4) **3,4 or 5 SLE** HR=6.7 (CI 2.8-16.0)	correlation between nr of SLE and relapse rate

[1] Due to study similarities an overlap of Potagas et al. (2008) and Mitsonis et al. (2008) could not have been excluded.

Mitsonis et al., 2008[1]	26	prospective study	RR-MS (Greek)	Ø age 33.5, all female, Ø EDSS baseline 0.4, Ø duration of disease 6.5 yrs	SLE	1 yr	**≥ 4 SLE:** HR=16.78 (CI 4.64-60.56)	nr. of SLE associated with higher relapse risk severity or type of stressor not relevant
Mitsonis et al., 2010	48 24 e-group 24 c-group	RCT	RR-MS (Greek)	Ø age 34.2, all female, all RR-MS, Ø EDSS baseline 0.4, Ø duration of disease 6.5 yrs	1.antidepressant (Escitalopram) 2.SLE	1 yr	**no antidepressant:** 1.HR=2.9 (1.7-5.9) **≥3 long-term SLE:** 2.HR:16.1 (CI 8.0-54.6)	-higher relapse risk for group without AD - sign. increased relapse risk for ≥3 long-term SLE
Oveisgharan et al., 2014	57	prospective study	RR-MS (Iranian)	Ø age 33.5, 81 % female, all RRMS, Ø EDSS baseline 2.16	SLE	1 yr	**coefficients of:** mean of stressor severity score and relapse 0.012, p=0.648 number of stressors 0.108, p=0.054	nr of SLE, not severity with trend for prediction of severe relapses
Major societal threats and MS relapse risk								
Nisipeanu et Korczyn, 1993	32	prospective study	RR-MS (Israelian)	Ø age 38.2, 56,3 % female, all RR-MS, Ø DSS 2.6, Ø duration of disease 4.7 yrs	war exposure (missile attacks)	28 months	3 relapses during resp. post-war vs. 77 relapses in pre-war period (2 yrs)	sign. decreased relapse rate during war associated period vs. pre-war period
Golan et al., 2008[2]	156	prospective cohort,	RR-MS (Israelian)	Ø age 44 y, 78 % female, all RR-MS, Ø EDSS	war exposure (missile attacks)	16 months	HR: 3.35[3] (CI 2.01-5.56)	increased relapse risk by war stress

[2] Meta-analysis of two studies with focus on war exposure and MS relapse risk
[3] Ratios calculated as part of the current systematic review

		retrospective study		2.8, Ø duration of disease 10 yrs				
Yamout et al., 2010[2]	216	prospective cohort, retrospective study	RR-MS (Lebanese)	Ø age 39.6 y, 60,2 % female, all RR-MS, Ø EDSS 3.0, Ø duration of disease 9.25 yrs	war exposure (missile attacks)	3 yrs	HR=2.74[34] (CI 1.76-4.25)	increased relapse risk by war stress
Kanamori et al., 2017	140	retrospective study	RR-MS (Japanese)	Ø age 42.8, disease duration: 12.7 yrs	Earthquake and meltdown of nuclear power plant	2 yrs	**annualized relapse rate** pre-disaster: 0.24 (33 relapses) post-disaster: 0.22 (31 relapses)	no increase of ARR after earth-quake vs. pre-disaster
Sparaco et al., 2022	216	observational study	RR-/RP-MS (Italian)	**survey cohort (n=154):** Ø age 43.8; 70.8 % female; 84,4 % RR-MS, 15,6 % RP-MS, Ø PDSS 1.7, Ø duration of disease 16.49 yrs	COVID-19 pandemic	1 yr (2019-2020)	**annualized relapse rate** 2019: 0.209 2020: 0.357 p=0.0142	significant increase of relapse rate during COVID-19 pandemic 2020 vs. 2019
Stress and inflammatory MRI activity								
Mohr et al., 2000	36	prospective longitudinal study	pwMS (U.S.)	61.1 % female, 47.2 % RR-MS, 52.8 % SP-MS RRMS/SPMS	minor and major SLE psychological distress	28-100 weeks	**major neg. events, 8-week lag** OR=1.12 (p=0.5)	no significant re-lation btw. stress and new Gd+ brain lesions

[3] Ratios calculated as part of the current systematic review

				Ø age 39.8/48.1 y, ØEDDS base-line 1.6/5.0				
Burns et al., 2014[5]	121	RCT	RR-MS (U.S.)	Ø age 42.7, 83 % female, 98 % RR-MS, 2 % SP-MS, Ø EDDS 3.1, Ø duration of disease 7.05 yrs	SLE (incl. major and moderate)	48 weeks	**major negative events** OR=1.77 (CI 1.18-2.64)	major neg. SLE predict increased risk for Gd+ and T2 lesions
PTSD and MS-relapse risk								
Leekoff et al., 2022	**MS-PTSD** 5.350 (database) 96 incl. **MS-controls** 23.226 (database) 95 incl.	population-based cohort study	U.S. military veterans with MS and PTSD prior to symptom onset CG: MS without PTSD	**MS-PTSD (CG):** Ø age 48.9 (50.1), 55.7 % (61.8 %) female, 80.2 % (81.1) RRMS, 11.5 % (12.6) SPMS, 8.3 % (6.3) PPMS	PTSD	4 yrs (2015-2019)	Ø **ARR MS-PTSD vs. controls:** 0.23 vs. 0.06 (p<0.05) **annualized mean nr. of new T2/Gd+ MS-PTSD vs. controls:** 0.52 /0.29 vs. 0.16/0.08 (p<0.05)	MS-PTSD with higher disease activity

AD: antidepressant
CI: confidence interval
incl.: including
PP-MS: primary progressive MS
RR-MS: relapse remitting MS
SLE: stressful life event
p: probabilitas
yr: year

ARR: annualized relapse rate
Ex/yr AR: exacerbation per year at period of risk
neg.: negative
PTSD: post-traumatic stress disorder
SCI: spinal cord injuries
SP-MS: secondary progressive MS
T2: T2 weighted image
yrs: years

CG: control group
Gd+: gadolinium-enhancing
nr.: number
RCT: randomized controlled trial
SES: socioeconomic status
OR: odds ratio
vs.: versus
Ø: average

[5] Burns et al. 2014 = secondary analysis of the RCT of Mohr et al. (2012)

3.3 Stress factors and risk of MS disability progression - overview

Four studies investigated the association of stress and MS disability progression measured by EDSS score increase. Two older studies[47,64] investigated individual stressful life events in 101 and 170 patients up to 6 and 8 years with contradictory results, possibly due to small sample sizes and to the short study durations.

Two more recent studies[41,65] used psychiatric disorders (PTSD, depression) as a stress proxy. A retrospective cohort study[65] investigated disability worsening among depressed persons with MS (pwMS) compared to pwMS without depression from the Swedish MS registry. MS patients with depression had a significantly higher risk of reaching disability endpoints (EDSS 4.0: HR=1.79; EDSS 6.0: HR=1.89). As cited above, Leekoff et al. (2022)[41] studied antecedent PTSD to a MS diagnosis in U.S. veterans. In addition to MS and relapse risk also the risk for disability progression of the disease was increased. Patients with MS and a preceding PTSD diagnosis reached disability endpoints (DSS 6.0) more rapidly than pwMS without PTSD diagnosis (median 23.0 vs 30.0 years, HR=0.77).

A methodological difficulty of the work on stress and MS disability progression is the need of a relevant follow-up time after diagnosis to conclude on progression together with information of stress factors independent of MS, at best antecedent to a MS onset. The sample sizes varied from 101 to 9.692, the follow up duration showed a range from 4 to 13 years.

In summary the limited evidence indicates a minor to modest impact of stress on disability progression risk. A substantial limitation in examining progression was that only one of the included studies assessed confirmed progression, and even in this study clinical status was solely based on self-reported progressions. As in MS due to disease fluctuations and relapse a relevant number of pseudo-progressions occur all conclusions without 6 months, better 24 months confirmations of progressions should be taken cautiously.

For the progression part, highest evidence levels were obtained in the studies of Binzer et al. (2019)[65] and Leekoff et al. (2022)[41].

All included studies investigating the association between stress and MS disability progression are presented and summarized in table 6. For reasons of better legibility, the confidence intervals in the following narrative part were mostly omitted and are displayed in the mentioned table.

3.3.1 Description of studies on MS disability progression according to stress factors

Stressful life events and MS disability progression

Schwartz et al. (1999)[64] investigated in a prospective study over six years 101 MS patients (RR-MS, CP-MS) and 96 healthy controls from the U.S. They found an increased risk of MS-progression when the rate of reported stressful life events was higher (OR=1.13). The finding of a relationship between stress and disease progression however leaves the question open if disease progression induced increased susceptibility or vice versa.

Sibley´s ([47]**)** prospective study[47] with 170 MS patients from the U.S. with eight years of follow up duration investigated also the effect on disease progression. Authors compared two patient groups with two different count ranges of stressful life events and comparable baseline degrees of disability. In conclusion, there was no difference in disability evolution in both subgroups.

Psychiatric diseases and MS disability progression

Leekoff et al. (2022)[41] examined in their population-based cohort study the impact of PTSD on MS-progression (for study details see “relapse section”). In summary patients with MS and a preceding PTSD diagnosis reached disability endpoints (DSS 6.0) more rapidly than controls (23.7 vs 29.5 years), which corresponds with a self-calculated HR=0.77.

In a retrospective cohort study **Binzer et al. (2019)**[65] investigated disability worsening among depressed pwMS compared to pwMS without depression from the Swedish MS registry. Therefore, a depression diagnosis cohort of about 500 and an antidepressant exposure cohort of cicra 1.300 were formed which were followed for 13 years resp. 9 years. MS patients with depression had a significantly higher risk of reaching disability endpoints (EDSS 4.0: HR=1.79; EDSS 6.0: HR=1.89). Also, for the group of MS patients exposed to antidepressants an increased risk for progression was found (EDSS 4.0: HR=1.93; EDSS 6.0: HR=1.86). The absence of differentiation between chronic and nonchronic or situational depression was a limitation.

Table 6: *Included studies investigating stress and MS disability progression*

study	n	design	cohorts	demographics	stressor(s)	follow-up duration	main results	comment
Stressful life events and MS disability progression								
Sibley,1987	170 MS 113 exposed 157 unexposed 134 HC	prospective study	MS (U.S.) HC	**patients (controls)** Ø age 43 (40), f:m = 1.6:1 (1.7:1), almost 50% mildly affected at entry with DSS 0-4	SLE	8 yrs	**Ø change of disability (DSS) for both groups (≥ 5 vs <5 SLE) at entry vs. exit:** -1.1	no effect of frequent SLE on progression of disability no confirmation of progression required
Schwartz et al., 1999	101 MS 96 HC	prospective study	MS (U.S.) HC	Ø age 45.7, 75% female, 39% RR-MS, 19% CP-MS, 42% chronic stable, Ø EDSS 4.1, Ø duration of disease 14.2 y	SLE	6 yrs	OR=1.13 (CI 1.06-1.12)	increased risk of disease progression when higher rate of SLE self-reported neurological status
Psychiatric disorders and MS disability progression								
Binzer et al., 2019	**5.875 (cohort 1)** 502 exposed 5.373 unexposed **3.817 (cohort 2)** 1.289 exposed	retrospective cohort study	**cohort 1** Swedish pwMS with diagnosis of depression	**depression cohort (exp/unexp.):** 73.1/69.2 % female, 72.9/76.5 % RR-MS,	1. depression 2. ≥ 1 prescribed antidepressant	13 yrs (2001-2014) resp. 9 yrs (2005-2014)	**1.depression** **2. ≥1 AD** **EDSS 6.0:** HR=1.89	pwMS with comorbid depression with increased risk

	2.528 unexposed		**<u>cohort 2</u>** Swedish MS pat and ≥1 AD	11.2/7.8 % SP-MS, 5.2/6.0 % PP-MS **antidepressant cohort (exp./unexp.):** 73.7/67.4 % female, 77.5/83.1 % RR-MS, 6.9/3.6 % SP-MS, 5.8/4.4 % PP-MS)			(CI 1.38-2.57) HR=1.86 (CI 1.45-2.4) similar results für EDDS 3.0 and 4.0	of disability progression confirmed progression assessed
Leekoff et al., 2022	**MS-PTSD** 5.350 (database) 96 included **MS-controls** 23.226 (database) 95 included	population-based cohort study	U.S. military veterans with MS and PTSD prior to symptom onset CG: pwMS without PTSD	**MS-PTSD (CG):** Ø age 48.9 (50.1), 55.7 % (61.8 %) female, 80.2 % (81.1) RR-MS, 11,5 % (12.6) SP-MS, 8,3 % (6.3) PP-MS	PTSD	4 yrs (2015-2019)	**disability accrual MS-PTSD vs MS-controls** (time to DSS 6.0) Median 23.0 vs 30 yrs HR=0.77[6]	MS-PTSD with more rapidly reached disability endpoints than controls no confirmation of progression required

AD: antidepressant
exp.: exposed
m: male
pwMS: person with multiple sclerosis
SP-MS: secondary progressive MS
yrs: years

CP-MS: chronic progressive MS
f: female
MS: multiple sclerosis
resp.: respectively
U.S.: United States
Ø: average

DSS: Disability Status Scale
HC: healthy controls
PP-MS: primary progressive MS
RR-MS: relapse remitting MS
unexp.: unexposed

EDSS: Expanded Disability Status Scale
HR: hazard ratio
PTSD: post-traumatic stress disorder
SLE: stressful life event
yr: year

[6] Ratio calculated as part of the current systematic review

4. Discussion

For more than 100 years, psychological stress has been considered as a trigger of MS[7]. In 2004, Mohr et al.[17] performed a meta-analysis of a variety of studies with substantial methodological and qualitative heterogeneity. Since the publication of this meta-analysis almost 20 years ago, a number of elaborate investigations indicated a moderate association of psychological stressors or stress disorders with onset of MS, relapse rate or disability progression.

With 19 studies of reasonable quality, most studies have been performed on relapse risks. Studies investigating the perceived stress levels and relapse rate are severely limited by the possibility of reversed causality, in which preclinical relapse evolution might increase stress sensitivity. However, studies on more clearly defined external stressors such as missile attacks[57,58] reported similar hazard ratios as the latter and provided the strongest associations which have been reported in the field yet. Corroborating these findings, two studies[61,62] supported the positive association between stressful life-events and inflammatory MRI activity. However, here as well reversed causality cannot be excluded.

When analyzing the impact of the COVID-19 pandemic[60] the MS relapse risk seem to have increased as shown in an Italian study although to a smaller extent than during the missile attack threat in the Lebanon war. Regarding the variety of potential direct and indirect consequences of the pandemic the significance of this study must be considered with caution especially as no other study has confirmed this observation. Being aware that relapses are often difficult to verify, highly heterogeneous and of questionable value for the long-term prognosis of MS the relevance of the stress-relapse association is limited.

In contrast most robust data were found for the association between posttraumatic stress-disorders and MS onset. Our meta-analysis of one population-based study from Sweden and two veterans studies from U.S.[38–40] could show a small but significant increase of MS risk subsequent to an established diagnosis of a PTSD over time. Although two studies[38,39] of the meta-analysis were related to military stress events experienced by veterans and the third was based on PTSD after any severe stressor and other stress-related disorders, these studies were meta-analyzed together because their common ground was not the stressors per se, but the perceived extent of stress experience leading in all studies to diagnosed PTSD. This opens the question if being aware that stressors are hardly comparable rather

persons stressor appraisal are most relevant in mitigating stress-based biological alterations. In fact, PTSD research has consistently shown altered stress response systems such as cortisol awakening responses[66].

Childhood adverse experiences might represent one of the most severe traumatic stressors. While earlier work as summarized by Polick et al. (2022)[67] retrospectively asking for childhood adversities in established MS was presumably substantial hampered by reporting bias Eid et al. (2022)[37] recently provided the first methodologically sound evidence that sexual and emotional abuse may trigger MS. Childhood adversities with or without diagnosed PTSD might alter stress-response systems predisposing to a variety of autoimmune diseases. Timing in life as well number of stressors, severity and duration seem to influence the probability of substantial immune dysregulation[10]. Just looking at severe stressors later in life taking into account possible psychiatric sequelae the evidence is not straightforward. While the earliest publication from The Danish MS Registry[31] showed an increased risk of developing MS after loss of a child, a subsequent update[34] only found a weakly increased risk. Resilience and coping abilities could be possible modulators.

Regarding the influence of stress on disability progression, the earliest study by Schwartz et al. (1999)[64] was methodologically limited. The recent study by Leekoff et al. (2022)[41] can be regarded as the first convincing evidence that PTSD preceding clinical MS onset is not only associated with the risk of relapse but also the risk of sustained disability progression. Based on the Swedish MS registry, Binzer et al. (2019)[65] demonstrated that experienced depression as a relevant psychological stressor shortened time to EDSS milestones. However, depression is an important comorbidity in persons with MS and might in part be immunologically mediated, and can therefore not be considered solely a stress experience independent of the disease process.

The heterogeneity of the studies regarding MS progression makes any meta-analysis impossible at this stage.

Overall, external stressors are associated with the highest reliability to assess an association between stress and MS. During the last 20 years following the first meta-analysis by Mohr et al. (2004)[17] methodological quality has substantially improved with large register studies having been carried out. Differentiated according to the aspects MS onset risk, MS relapse risk and disability progression risk the onset

studies were of the highest methodological quality showing a moderate effect of stress on MS.

In summary, over the last decades the methodological quality of corresponding studies has relevantly improved, as initially studies had noticeable limitations until large register studies were performed. At this point the quality of studies´ methodology is difficult to increase.

4.1 Limitations

Stress is difficult to assess which explains the heterogeneity of the studies and the challenges to perform a meta-analysis of comparable studies. As strict high-threshold inclusion criteria for the systematic review were set and even more so for any meta-analysis the dataset for meta-analysis was substantially reduced. However, findings within the meta-analysis were homogenous.

While publication bias of unpublished studies showing no or protective effect of stressors to trigger MS or MS relapses cannot be ruled out, the consistent finding across the 31 reviewed studies is a small to moderate effect in triggering the disease.

4.2 Perspectives

More large-scale studies based on reliable data sources on childhood adversities, serious life events and diagnosed stress disorders prior to MS from other than U.S. Veterans or nationwide population-based Scandinavian registries would be helpful to confirm the reported findings on MS onset and even more importantly on the risk of progression. Being aware of the impact of stressors more effort should be made to enhance the resilience of persons with MS to stressors or to efficiently screen and treat known psychiatric disorders. This is highly relevant as receiving the diagnosis has been reported as a traumatizing event in MS[68] with a high level of stigma.[69] In fact, up to now, to our knowledge, only one study[63] has investigated the effect of stress management on MRI inflammatory disease activity showing an impressive effect in a small cohort. Mindfulness studies have shown relevant effects on patient reported outcomes, but little effort has been made to study the effects on markers of disease activity[70].

The summarized evidence is helpful for the MS clinician supporting patients to reflect on their stress behavior and encourage development of stress management techniques.

4.3 Conclusion

There is substantial evidence for a minor to modest disease triggering effect of major stressful life events in MS with the strongest evidence for PTSD antecedent to MS and exposure to missile attacks during war being a trigger factor for the disease.

4.4 Transparency statement

The manuscript is an honest, accurate, and transparent account of the study being reported without any competing interests of the author. No important aspects of the study have been omitted. The study was performed and written-up as originally planned.

4.5 Role of the funding source

This study was not funded.

5. Summary

Thirty-one studies reporting data from 27 cohorts reporting on 34.613 cases could be identified. 10 studies addressed stressors and MS disease onset showing a weak to modest effect of psychological stressors. A meta-analysis of three studies investigating diagnosed stress disorders and MS onset risk showed a 1.87-fold (CI 1.06 to 3.43) increased risk. Stress and MS relapse risk were addressed in 19 heterogeneous studies. A meta-analysis could be performed from two independent cohorts investigating the same military threat of a population. Here a threefold increased risk for relapses in association with missile attacks during war (relapse rate=3.0, CI 1.56 to 5.81) was found. In addition, two studies confirmed an association of stressful life events and MRI activity. Four studies of stressors and disability progression were included in the systematic review indicating an effect on disease progression.

Taken together studies indicate a minor to modest impact of psychological stressors on disease onset, inflammatory activity and progression of MS.

Zusammenfassung

In der vorliegenden Arbeit wurden 31 Studien mit 27 unabhängigen Kohorten mit 34.613 MS-Patienten ausgewertet.

Davon befassten sich 10 Studien mit dem Aspekt der MS-Manifestation, wobei nur ein geringer Effekt von psychologischen Stressoren auf das MS-Erkrankungsrisiko gezeigt werden konnte. In einer Meta-Analyse von drei Studien, die den Zusammenhang zwischen diagnostizierten Belastungsstörungen und MS-Risiko untersuchten, fand sich ein 1.87-fach (KI 1.06 – 3.43) erhöhtes Risiko.

Der Zusammenhang zwischen Stress und MS-Schubrisiko wurde in 19 heterogenen Studien untersucht. Eine Meta-Analyse von zwei unabhängigen Kohorten, die unter kriegerischer Bedrohung, inklusive Raketenangriffe standen, ergab ein dreifach erhöhtes Schubrisiko (Schubrate=3.0, KI 1.56 – 5.81). Darüber hinaus konnten zwei Studien einen Zusammenhang zwischen belastenden Lebensereignissen und MRT-Aktivität zeigen.

Schließlich wurden vier Studien eingeschlossen, in denen ein Effekt von psychologischem Stress auf die Krankheitsprogression bei MS beobachtet werden konnte.

Zusammenfassend wurde nur ein geringer Effekt von psychologischen Stressoren auf das MS-Erkrankungsrisiko, das Schubrisiko sowie die Krankheitsprogression bei MS gefunden.

6. Lists

6.1 List of abbreviations

AD	*Antidepressant*
ARR	*Annualized relapse rate*
ARR	*Adjusted relative risk*
ca.	*Circa*
c-group	*Control group*
CASP	*Critical Appraisal Skills Programme*
CG	*Control group*
CI	*Confidence interval*
COVID-19	*Coronavirus disease 2019*
CP-MS	*Chronic progressive multiple sclerosis*
DSS	*Disability Status Scale*
e-group	*Escitalopram group*
e.g.	*Exempli gratia*
EDSS	*Expanded Disability Status Scale*
Ex/yr AR	*Exacerbation per year at period of risk*
exp.	*Exposed*
f	*Female*
f.e.	*For example*
Gd+	*Gadolinium enhancing*
HC	*Healthy controls*
HPA	*Hypothalamic-pituitary-adrenal*
HR	*Hazard ratio*
i.e.	*Id est*
incl.	*Including*
KI	*Konfidenzintervall*
M	*Male*
MR	*Magnetic resonance*
MRI	*Magnetic resonance imaging*
MRT	*Magnetresonanztomografie*
MS	*Multiple Sklerose*
MS	*Multiple sclerosis*
n.d.	*No data*
NAR	*Not at risk*
NNHM	*Normal-Normal Hierarchical Model*
nr.	*Number*
OR	*Odds ratio*
p	*Probabilitas*
Pop-matched	*Population-matched*
PP-MS	*Primary progressive multiple sclerosis*
PRISMA	*Preferred Reporting Items for Syste-matic Reviews and Meta-Analyses*
PTSD	*Post-traumatic stress disorder*
pwMS	*Persons with multiple sclerosis*
RCT	*Randomized controlled trial*
resp.	*Respectively*
RR	*Relative risk*
RR-MS	*Relapse remitting multiple sclerosis*
SCI	*Spinal cord injuries*
SES	*Socioeconomic status*
SLE	*Stressful life event*
SP-MS	*Secondary progressive Multiple Scle-rosis*
SR/MA	*Systematic review/meta-analysis*
T2	*T2 weighted image*
unexp.	*Unexposed*
U.S.	*United States*
vs.	*Versus*
yr	*Year*
yrs	Years
Ø	Average

6.2 List of figures and tables

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10. Supplement

Index of supplements:

10.1 Supplement 1: Search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to July 15, 2022>

1 "acute emotional situation".mp. 1
2 "acute emotional situations".mp. 0
3 "adjustment disorder".mp. 1244
4 "child abuse".mp. 38018
5 "child neglect".mp. 792
6 "childhood abuse".mp. 2533
7 "emotional load".mp. 114
8 "emotional stimuli".mp. 3246
9 "emotional stimulus".mp. 262
10 "life difficulty".mp. 31
11 "life difficulties".mp. 155
12 "life event".mp. 2537
13 "life events".mp. 14706
14 "psychological harm".mp. 432
15 "psychological harms".mp. 105
16 "psychosocial factor".mp. 286
17 "psychosocial factors".mp. 14602
18 "stressful event".mp. 1288
19 "stressful events".mp. 3558
20 "stressful life situation".mp. 14
21 "stressful life situations".mp. 68
22 "traumatic event".mp. 4024
23 "traumatic events".mp. 5817
24 "traumatic experience".mp. 1201
25 "traumatic experiences".mp. 2879
26 "Adult Survivors of Child Abuse"/ 2579
27 "adult survivors of child abuse".mp. 2596
28 "adult survivor of child abuse".mp. 0
29 "Adult Survivors of Child Adverse Events"/ 815
30 "adult survivors of child adverse events".mp. 829
31 distress.mp. 159285
32 hassle*.mp. 1750
33 Life Change Events/ 23418
34 "life change events".mp. 23494
35 "life change event".mp. 20
36 "life changing event".mp. 174
37 "life changing events".mp. 67
38 "childhood maltreatment".mp. 2474
39 "childhood maltreatments".mp. 14
40 posttraumat*.mp. 42951
41 stress*.mp. 1171973
42 "Trauma and Stressor Related Disorders"/ 119
43 "trauma related disorder".mp. 37
44 "trauma related disorders".mp. 360
45 "war-related injuries".mp. or War-Related Injuries/ 600
46 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or

29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 1379354
47 "Multiple Sclerosis".mp. or Multiple Sclerosis/ 94290
48 Multiple Sclerosis, Relapsing-Remitting/ 7690
49 Demyelinating Diseases/ 12682
50 "relapsing remitting multiple sclerosis".mp. 5016
51 "remitting-relapsing multiple sclerosis".mp. 52
52 "remitting relapsing, multiple sclerosis".mp. 52
53 "multiple sclerosis, relapsing-remitting".mp. 7712
54 "multiple sclerosis, relapsing remitting".mp. 7712
55 "acute relapsing multiple sclerosis".mp. 4
56 "relapsing multiple sclerosis".mp. 914
57 "multiple sclerosis, acute relapsing".mp. 1
58 "progressive relapsing multiple sclerosis".mp. 12
59 "progressive relapsing, multiple sclerosis".mp. 12
60 "multiple sclerosis, progressive relapsing".mp. 0
61 "demyelinating disease".mp. 5249
62 "demyelinating diseases".mp. 15101
63 "demyelinating disorder".mp. 663
64 "demyelinating disorders".mp. 914
65 "Encephalomyelitis disseminata".mp. 64
66 "encephalitis disseminata".mp. 7
67 MS.ti. 41813
68 RRMS.ti. 130
69 (Myelitis, Transverse or Encephalomyelitis, Acute).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 3690
70 Multiple Sclerosis, Relapsing-Remitting.mp. or Demyelinating Diseases/ 20220
71 Optic Neuritis/ 6323
72 "relapsing remitting multiple sclerosis".mp. 5016
73 "optic neuritis".mp. 9291
74 "devic disease".mp. 64
75 "clinically isolated syndromes".mp. 328
76 "clinically isolated syndrome".mp. 1565
77 "transverse myelitis".mp. 2620
78 "encephalomyelitis".mp. 27609
79 "neuromyelitis".mp. 5705
80 "CIS".ti. 17915
81 "chronic progressive multiple sclerosis".mp. 255
82 "chronic progressive, multiple sclerosis".mp. 255
83 "primary progressive multiple sclerosis".mp. 623
84 "secondary progressive multiple sclerosis".mp. 841
85 "progressive relapsing multiple sclerosis".mp. 12
86 "progressive relapsing, multiple sclerosis".mp. 12
87 "multiple sclerosis, progressive relapsing".mp. 0
88 "multiple sclerosis, secondary progressive".mp. 12
89 SPMS.ti. 43
90 PPMS.ti. 54

91 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 187664

92 46 and 91 5455

93 limit 92 to humans **3180**

10.2. Supplement 2: PRISMA checklist[21]

(From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5-8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5-8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 8-10
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 8+ Supplement S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 10-11
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 10-11
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 10-11
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 10-11

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11-12
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 10-11
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 12
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 12
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 12 + Figure 3+4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 12+ Figure 3+4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 12
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 12
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplement S5
Study characteristics	17	Cite each included study and present its characteristics.	Page 17-44
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 1-3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 4-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 17-19; 27-28; 41

Section and Topic	Item #	Checklist item	Location where item is reported
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figure 3+4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 17-44
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	not performed
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 45-47
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 4-6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 45-47
	23b	Discuss any limitations of the evidence included in the review.	Page 47
	23c	Discuss any limitations of the review processes used.	Page 47
	23d	Discuss implications of the results for practice, policy, and future research.	Page 47-48
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 8
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 48
Competing interests	26	Declare any competing interests of review authors.	Page 48
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplement S1-S5

10.3. Supplement 3: CASP items definition adapted for studies on MS onset risk[26]

Definitions of the items of the quality assessment by CASP Case Control Study Checklist (for MS onset studies)

1. Did the study address a clearly focused issue?

Yes:	MS onset triggered by stressful life events as main study topic data for MS or MS subgroup separately available
Can´t tell:	MS onset triggered by stressful life events was a minor aspect/partially addressed
No:	MS onset triggered by stressful life events not as study focus

2. Did the authors use an appropriate method to answer their question?

Yes:	case control design
Can´t tell:	control group not matched, other methodological problems
No:	no control group

3. Were the CASES recruited in an acceptable way?

Yes:	cohort clearly defined cases representative for a defined population (geographically, temporally) reliable selection system study time window relevant for MS disease existing power calculation 100 cases or more
Can´t tell:	cohort not ideal, but sufficient < 100 cases
No:	no clearly defined cohort cohort not representative no appropriate study time window

no existing power calculation
< 10 cases

4. Were the CONTROLS selected in an acceptable way?

Yes:	representative and population-based control group matched control group sufficient large control group, in general 1000 or more
Can´t tell:	number of controls too low, in general between 100 and 1000
No:	not representative and not population-based control group selection by random mechanism no sufficient number of controls, in general 100 or less

5. a) Was the EXPOSURE accurately measured to minimize bias?

Yes:	clearly defined and exactly measured exposure suitable, validated measurement tools comparability between cases and controls reliable prospective recording of trigger events
Can´t tell:	only self-reported stress exposure before MS onset assessed
No:	not clearly defined, not exactly measured exposure not suitable, not validated measurement tool no comparability between cases and controls self-reported stress exposure after MS onset

5. b) Was the OUTCOME accurately measured to minimize bias?

Yes:	MS diagnosis according to valid diagnosis criteria at the time of publication
Can´t tell:	no stated diagnosis criteria, but objective measurement tools
No:	outcomes solely based on self-reporting

6. (a) What confounding factors have the authors accounted for?

6 (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?

Yes:	nearly complete analyses of confounders, feasible evaluation of confounders

Can´t tell:	only partial analysis of confounders
No:	no confounders assessed and no analyses confounder not controllable, evaluable, accountable

The **items of Section B and C** are not displayed, because it was focused on items concerning the quality and conduct of the study.

10.4. Supplement 4: CASP items definition adapted for studies on MS relapse risk and disability progression[26,27]

Definitions of the items of the quality assessment by merged model of CASP Case Control Study Checklist and CASP Cohort Study checklist (for MS relapse and progression studies)

1. Did the study address a clearly focused issue?

Yes: MS relapse/progression triggered by stressful life events as main study topic

data for MS or MS subgroup separately available

Can´t tell: MS relapse/progression triggered by stressful life events was a minor study aspect/partially addressed

No: MS relapse/progression triggered by stressful life events not as study focus

2. Did the authors use an appropriate method to answer their question?

Yes: case control design

Can´t tell: control group not matched, other methodological problems

No: no control group

3. Were the CASES recruited in an acceptable way?

Yes: cohort clearly defined
Sufficient number of cases
cases representative for defined population (geographically, temporally)
reliable selection system
study time window relevant for MS disease
available power calculation

Can´t tell: cohort not ideal, but sufficient

No: cohort not clearly defined
cohort not representative
study time window not appropriate

no existing power calculation

4. Were the CONTROLS selected in an acceptable way?

Yes:	representative and population-based control group matched control group sufficient large control group, in general 100 or more
Can´t tell:	number of controls too low, in general between 10 and 100
No:	not representative and not population-based control group not sufficient number of controls, in general less than 10

5. a) Was the EXPOSURE accurately measured to minimize bias?

Yes:	clearly defined and exactly measured exposure suitable, validated measurement tools comparability between cases and controls reliable prospective recording of trigger events
Can´t tell:	only self-reported stress exposure before MS relapse/progression
No:	not clearly defined, not exactly measured exposure not suitable, not validated measurement tools

5. b) Was the OUTCOME accurately measured to minimize bias?

Yes:	validated neurological assessment, clinical/radiological documentation or self-reported relapse/progression with confirmation by expert
Can´t tell:	only self-reported relapse/progression without confirmation by expert
No:	no defined criteria for relapse/progression

6. (a) Have the authors identified all important confounding factors?

Yes:	important confounding factors included
Can´t tell:	only some confounding factors included
No:	none/missing important confounding factors included

6 (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?

Yes:	analysis of most important confounders feasible evaluation of confounders
Can`t tell:	only partial analysis of confounders, or data presentation unclear
No:	no confounders assessed and no analysis confounder not controllable, evaluable accountable

7. (a) Was the follow up of subjects complete enough?

Yes:	80 % of participants remaining during follow-up
Can´t tell:	50-80 % of participants remaining during follow-up
No:	< 50 % of participants remaining during follow-up

7. (b) Was the follow up of subjects long enough?

Yes:	follow up at least 1 year
Can´t tell:	follow up >6 months <1 year
No:	follow up < 6 months

For external severe threats: follow-up at least 3 months

The **items of Section B and C** are not displayed, because it was focused on items concerning the quality and conduct of the study.

10.5. Supplement 5: List of excluded studies at full-text stage

	Author	Year	Title	Reason for exclusion
1.	Apel	2006	Stress und Krankheitsverlauf der Multiplen Sklerose	review
2.	Artemiadis	2011	Stress as a risk factor for multiple sclerosis onset or relapse: a systematic review	review
3.	Gulick	2007	Postpartum Functioning in Mothers With Multiple Sclerosis	inappropriate study focus
4.	Grant	1985	The social environment and Neurological Disease	no data
5.	Belbasis	2015	Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses	review
6.	Firth	2014	Effectiveness of psychologically focused group interventions for multiple sclerosis: A review of the experimental literature	review
7.	Confavfreux	2014	The clinical course of multiple sclerosis	no data
8.	Corthals	2011	Multiple sclerosis is not a disease of the immune system	no data
9.	Carvalho	2009	The mosaic of autoimmunity: the role of environmental factors	no data
10.	Dennison	2009	A review of psychological correlates of adjustment in patients with multiple sclerosis	review
11.	Dennison	2010	Cognitive-behavioral therapy: what benefits can it offer people with multiple sclerosis?	review
12.	Esch	2002	The role of stress in neurodegenerative diseases and mental disorders	review
13.	Heesen	2007	Stress regulation in multiple sclerosis current issues and concepts	review
14.	Heesen	2007	Stress and hypothalamic–pituitary–adrenal axis function in experimental autoimmune encephalomyelitis and multiple sclerosis—A review	review
15.	Gold	2006	Stress and disease progression in multiple sclerosis and its animal models	review

16.	Gold	2005	The role of stress-response systems for the pathogenesis and progression of MS	review
17.	Bras	2008	Relationship between combat related posttrau- matic stress disorder (PTSD) and multiple sclerosis (MS)	qualitative study
18.	Briggs	2015	Role of socioeconomic position in multiple sclerosis etiology	review
19.	Brown	2005	A review of stress/relapse interactions in multiple sclerosis: important features and stress-mediating and -moderating variables	review
20.	Lovera	2013	Stress in Multiple Sclerosis: Review of New Developments and Future Directions	review
21.	Marrie	2004	Environmental risk factors in multiple sclerosis aetiology	review
22.	Mitsonis	2009	The Effects of Stressful Life Events on the Course of Multiple Sclerosis: A Review	review
23.	Karagkouni	2013	Effect of stress on brain inflammation and multiple sclerosis	review
24.	Pereira	2018	Basal cortisol levels and the relationship with clinical symptoms in multiple sclerosis: a systematic review	review
25.	Mohr	2004	Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis	review
26.	Mohr	2007	Stress and multiple sclerosis	review
27.	Mohr	2005	A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis	review
28.	Mohr	2001	Multiple Sclerosis: Empirical Literature for the Clinical Health Psychologist	review
29.	Simpson	2014	Mindfulness based interventions in multiple sclerosis--a systematic review	review
30.	VanderPlate	1984	Psychological Aspects of Multiple Sclerosis and Its Treatment: Toward a Biopsychosocial Perspective	review
31.	Sandyk	1996	TRYPTOPHAN AVAILABILITY AND THE SUSCEPTIBILITY TO STRESS IN MULTIPLE SCLEROSIS: A HYPOTHESIS	review

32.	Schulz	2005	Das Stresskonzept von Allostase und Allostatic Load: Einordnung psychoneuroimmunologischer Forschungsbefunde an Beispielen zur Autoimmunität und Onkologie	no data
33.	Sharif	2018	The role of stress in the mosaic of autoimmunity: An overlooked association	review
34.	Weatherby	2003	Does trauma trigger multiple sclerosis? 1: A controversy	review
35.	Taylor	1998	Neuropsychologic aspects of multiple sclerosis.	review
36.	Strenge	2001	Zur Beziehung von psychologi schem Stress und klinischem Verlauf der multiplen Sklerose	review
37.	Rabin	2002	Can Stress Participate in the Pathogenesis of Autoimmune Disease?	review
38.	Paulley	1985	Psychosomatic aspects of multiple sclerosis	review
39.	Leray	2016	[Epidemiology of multiple sclerosis and new diagnostic criteria]	different language
40.	Lowis	1990	THE SOCIAL EPIDEMIOLOGY OF MULTIPLE SCLEROSIS	review
41.	Martinelli	2000	Trauma, stress and multiple sclerosis	review
42.	Mason	1991	Genetic variation in the stress response: susceptibility to experimental allergic encephalomyelitis and implications for human inflammatory disease	review
43.	Minderhoud	1974	[Multiple sclerosis]	different language
44.	D´hooge	2010	Modifiable factors influencing relapses and disability in multiple sclerosis	review
45.	Hart	2008	Relationships Among Depressive Symptoms, Benefit-Finding, Optimism, and Positive Affect in Multiple Sclerosis Patients After Psychotherapy for Depression	inappropriate study focus
46.	Schumann	2012	Stress, Depression and Antidepressant Treatment Options in Patients Suffering from Multiple Sclerosis	review
47.	Pucak	2007	Neuropsychiatric manifestations of depression in multiple sclerosis: neuroinflammatory, neuroendocrine, and	review

			neurotrophic mechanisms in the pathogenesis of immune-mediated depression	
48.	Ifantopoulou	2015	Self-esteem is asscociated wih perceived stress in multiple sclerosis patients	inappropriate study focus
49.	Munoz	2016	Intervenciones psicoterapéuticas y psicosociales para el manejo del estrés en esclerosis múltiple: aportación de intervenciones basadas en mindfulness	different language
50.	Mollaoglu	2009	Fatigue in multiple sclerosis patients	inapproriate study focus
51.	Carletto	2018	Prevalence of Posttraumatic Stress Disorder in Patients With Multiple Sclerosis	inappropriate study focus
52.	Georgopoulos	2017	Gulf War illness (GWI) as a neuroimmune disease	inappropriate study focus
53.	Verhaak	1997	SOMATIC DISEASE AND PSYCHOLOGICAL DISORDER	inappropriate study focus
54.	Lemke	1951	[On posttraumatic multiple sclerosis]	inappropriate study focus
55.	Anonymous	1970	Stress, multiple sclerosis, and corticosteroids	review
56.	Prick	1972	[Clinical, autoimmunological and neuropathological aspects of multiple sclerosis. I]	different language
57.	Müller	1973	[Etiology of multiple sclerosis]	inappropriate study focus
58.	Pulton	1977	Multiple sclerosis: a social-psychological perspective	review
59.	Paulley	1977	The psychological management of multiple sclerosis	qualitative study
60.	Poser	1979	Trauma, stress, and multiple sclerosis	review
61.	Poser	1980	[Physical trauma and psychological stress in multiple sclerosis (author's transl)]	different language
62.	Mandel	1986	Stress management in rehabilitation	inappropriate study focus
63.	Henningsen	1993	[Psychoneuroimmunologic research in psychosomatic medicine]	review
64.	Stip	1988	Affective disorder and stress in multiple sclerosis.	no data

65.	Stip	1994	[Organic personality syndrome in multiple sclerosis and effect of stress on recurrent attacks]	different language
66.	Djokic	1998	[Association of manifestations of chronic post-traumatic stress disorders and disseminated demyelinating disease of the central nervous system]	different language
67.	Schreiber	1998	[Endocrinology 1996-1997]	different language
68.	Martinez	2001	[Exogenous factors in the aetiology of multiple sclerosis in Cuba. A study of cases and controls]	different language
69.	Moreau	2001	[Daily life activities and multiple sclerosis]	different language
70.	Leger	2002	[Anxiety and physical limitation: a complex relation]	different language
71.	Galea	2004	Stress and exacerbations in multiple sclerosis: whether stress triggers relapses remains a conundrum	no data
72.	Van Alstine	1983	Emotional stress and the development of multiple sclerosis.	no data
73.	Goodin	2004	Relationship between multiple sclerosis exacerbations and stress	no data
74.	Lehrer	2004	The relationship of MS to physical trauma and psychological stress: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology	no data
75.	Chaudhuri	2004	The relationship of MS to physical trauma and psychological stress: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology	no data
76.	Poser	2004	The relationship of MS to physical trauma and psychological stress: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.	no data
77.	Poser	1984	MS and postpartum stress	no data

78.	Chelmicka	1994	Nervous system-immune system interactions and their role in multiple sclerosis	review
79.	Rapaport	2012	Multiple sclerosis and stress	no data
80.	Heesen	2012	Don't stress about it! Is stress management a disease-modifying therapy for multiple sclerosis?.	no data
81.	Krone	2011	Paradigms in multiple sclerosis: time for a change, time for a unifying concept.	review
82.	Benito-Leon	2011	Stress and multiple sclerosis: what's new?	no data
83.	Goodin	2008	The impact of war-stress on MS exacerbations.	no data
84.	Schulz	2006	[Psychological stress, immune function and disease development. The psychoneuroimmunologic perspective].	review
85.	Schad	2013	Stress caused adverse entanglement of the nervous and autoimmune systems: A case for MS	no data
86.	Green	2019	Systematic Review of Yoga and Balance: Effect on Adults With Neuromuscular Impairment	review
87.	Simpson	2019	Mindfulness-based stress reduction for people with multiple sclerosis - a feasibility randomised controlled trial	review
88.	Gulick	2003	Adaptation of the postpartum support questionnaire for mothers with multiple sclerosis	inappropriate study focus
89.	LaRocca	1984	Psychosocial factors in multiple sclerosis and the role of stress.	review
90.	Krone	2011	Paradigms in multiple sclerosis: time for a change, time for a unifying concept	review
91.	Pape	2019	Immunoneuropsychiatry - novel perspectives on brain disorders	review
92.	Simpson	2015	Mindfulness-based interventions for people with multiple sclerosis	no data
93.	Goodin	1999	The relationship of MS to physical trauma and psychological stress: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.	review

94.	Frontoni	1992	Effect of stress on cardiovascular regulation in neurological diseases with dysautonomia	inappropriate study focus
95.	Procter	1999	The children of toxic families: what can be done	inappropriate study focus
96.	Boman	1971	Effect of emotional stress on spasticity and rigidity	inappropriate study focus
97.	Kos	2016	The effectiveness of a self-management occupational therapy intervention on activity performance in individuals with multiple sclerosis-related fatigue : a randomized-controlled trial	inappropriate study focus
98.	Freeman	2003	Chronic sorrow	inappropriate study focus
99.	Harrison	2015	Beyond a physical symptom: the importance of psychosocial factors in multiple sclerosis pain	inappropriate study focus
100.	Ackroyd	2011	Adversarial Growth in Patients with Multiple Sclerosis and their Partners: Relationships with Illness Perceptions, Disability and Distress	inappropriate study focus
101.	Kern	2014	Time matters – Acute stress response and glucocorticoid sensitivity in early multiple sclerosis	inappropriate study focus
102.	Kern	2013	Cortisol Awakening Response Is Linked to Disease Course and Progression in Multiple Sclerosis	inappropriate study focus
103.	Strober	2005	An examination of four models predicting fatigue in multiple sclerosis	inappropriate study focus
104.	Flensner	2013	Work capacity and health-related quality of life among individuals with multiple sclerosis reduced by fatigue: a cross-sectional study	inappropriate study focus
105.	Enns	2018	The association of fatigue, pain, depression and anxiety with work and activity impairment in immune mediated inflammatory diseases	inappropriate study focus
106.	Till	2012	Factors associated with emotional and behavioral outcomes in adolescents with multiple sclerosis	inappropriate study focus
107.	Noy	1995	A New Approach to Affective Symptoms in Relapsing-Remitting Multiple Sclerosis	inappropriate study focus

108.	Powell	2015	Circadian cortisol and fatigue severity in relapsing-remitting multiple sclerosis	inappropriate study focus
109.	Barlow	2009	A randomised controlled trial of lay-led self-management for people with multiple sclerosis	inappropriate study focus
110.	Alosaimi	2017	The Relationship between Psychosocial Factors and Cognition inMultiple Sclerosis	inappropriate study focus
111.	Brickner	1950	Emotional stress in relation to attacks of multiple sclerosis	qualitative study
112.	Heesen	2005	Altered cytokine responses to cognitive stress in multiple sclerosis patients with fatigue.	inappropriate study focus
113.	Brenner	2018	Depression and fatigue in multiple sclerosis: Relation to exposure to violence and cerebrospinal fluid immunomarkers	inappropriate study focus
114.	Heesen	2002	Endocrine and cytokine responses to acute psychological stress in multiple sclerosis.	inappropriate study focus
115.	Ackermann	1998	Stressor-Induced Alteration of Cytokine Production in Multiple Sclerosis Patients and Controls	inappropriate study focus
116.	Ackermann	1996	Immunologic response to acute psychological stress in MS patients and controls	inappropriate study focus
117.	Janssens	2004	Perception of prognostic risk in patients with multiple sclerosis: the relationship with anxiety, depression, and disease-related distress	inappropriate study focus
118.	Bogart	2015	Disability Identity Predicts Lower Anxiety and Depression in Multiple Sclerosis	inappropriate study focus
119.	Dennison	2010	Cognitive and behavioural correlates of different domains of psychological adjustment in early-stage multiple sclerosis	inappropriate study focus
120.	Senders	2014	Perceived stress in multiple sclerosis: The potential role of mindfulness in health and wellbeing	inappropriate study focus
121.	Kern	2009	Neurological disability, psychological distress, and health-related quality of life in MS patients within the first three years after diagnosis	cross sectional design

122.	Janssens	2003	Impact of recently diagnosed multiple sclerosis on quality of life, anxiety, depression and distress of patients and partners	inappropriate study focus
123.	D´Hooge	2012	Self-reported health promotion and disability progression in multiple sclerosis	inappropriate study focus
124.	Grech	2016	Coping Mediates and Moderates the Relationship Between Executive Functions and Psychological Adjustment in Multiple Sclerosis	inappropriate study focus
125.	Gilchrist	1994	DEPRESSION, COGNITIVE IMPAIRMENT AND SOCIAL STRESS IN MULTIPLE SCLEROSIS	cross sectional design
126.	Trojan	2007	Fatigue in multiple sclerosis: association with disease-related, behavioural and psychosocial factors	inappropriate study focus
127.	Chalfant	2004	Posttraumatic Stress Disorder Following Diagnosis of Multiple Sclerosis	inappropriate study focus
128.	Buelow	1991	A Correlational Study of Disabilitities, Stressors and Coping Methods in Victims of Multiple Sclerosis	cross sectional design
129.	Ostacoli	2013	Prevalence and Significant Determinants of Post-traumatic Stress Disorder in a Large Sample of Patients with Multiple Sclerosis	inappropriate study focus
130.	Yalachkov	2019	Determinants of quality of life in relapsing-remitting and progressive multiple sclerosis	cross sectional design
131.	Zorzon	2001	Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects.	inappropriate study focus
132.	Lamis	2018	Perceived cognitive deficits and depressive symptoms in patients with multiple sclerosis: Perceived stress and sleep quality as mediators	inappropriate study focus
133.	Kenealy	2000	Autobiographical memory, depression and quality of life in multiple sclerosis.	inappropriate study focus
134.	Waliszewska-Prosół	2018	The relationship between event-related potentials, stress perception and personality type in patients	inappropriate study focus

			with multiple sclerosis without cognitive impairment: A pilot study	
135.	Figved	2007	Caregiver burden in multiple sclerosis: the impact of neuropsychiatric symptoms	inappropriate study focus
136.	Larsen	1990	Psychosocial adjustment in multiple sclerosis.	inappropriate study focus
137.	Feinstein	2000	Depression associated with multiple sclerosis. Looking beyond diagnosis to symptom expression.	inappropriate study focus
138.	Shin	2019	Comparison of psychiatric disturbances in patients with multiple sclerosis and neuromyelitis optica.	cross sectional design
139.	Heffer-Rahn	2018	The clinical utility of metacognitive beliefs and processes in emotional distress in people with multiple sclerosis	inappropriate study focus
140.	Ritvo	1996	Psychosocial and neurological predictors of mental health in multiple sclerosis patients.	inappropriate study focus
141.	McCabew	2005	The Effects of Economic Disadvantage on Psychological Wellbeing and Quality of Life among People with Multiple Sclerosis	inappropriate study focus
142.	Evers	2001	Beyond unfavorable thinking: the illness cognition questionnaire for chronic diseases.	inappropriate study focus
143.	Schwartz	1999	The role of spouse responses to disability and family environment in multiple sclerosis.	inappropriate study focus
144.	Ron	1989	Psychiatric morbidity in multiple sclerosis: a clinical and MRI study	cross sectional design
145.	Johnson	2004	The cost and benefits of employment: a qualitative study of experiences of persons with multiple sclerosis.	qualitative study
146.	Fazekas	2013	No impact of adult attachment and temperament on clinical variability in patients with clinically isolated syndrome and early multiple sclerosis.	cross sectional design
147.	Sorenson	2013	Psychological stress and cytokine production in multiple sclerosis: correlation with disease symptomatology.	inappropriate study focus

148.	Beeney	2008	Stress and memory bias interact to predict depression in multiple sclerosis.	inappropriate study focus
149.	Bassi	2014	The coexistence of well- and ill-being in persons with multiple sclerosis, their caregivers and health professionals.	inappropriate study focus
150.	Passamonti	2009	Neurobiological mechanisms underlying emotional processing in relapsing-remitting multiple sclerosis.	inappropriate study focus
151.	Hyphantis	2008	Disability status, disease parameters, defense styles, and ego strength associated with psychiatric complications of MS	cross sectional design
152.	Klevan	2014	Health related quality of life in patients recently diagnosed with multiple sclerosis.	inappropriate study focus
153.	Kirchner	2011	stress and depression symptoms in patients with multiple sclerosis: the mediating role of the loss of social functioning	inappropriate study focus
154.	Nocentini	2009	An exploration of anger phenomenology in multiple sclerosis.	cross sectional design
155.	Boyle	1991	Empirical support for psychological profiles observed in multiple sclerosis.	cross sectional design
156.	Vickrey	1995	A health-related quality of life measure for multiple sclerosis	inappropriate study focus
157.	Devins	1993	Restless sleep, illness intrusiveness, and depressive symptoms in three chronic illness conditions: rheumatoid arthritis, end-stage renal disease, and multiple sclerosis	inappropriate study focus
158.	Yafang	2019	The mediating effect of health-related hardiness on the degree of physical disability and perceived stress in Chinese female patients with neuromyelitis optica spectrum disorder	inappropriate study focus
159.	Gullo	2019	Cognitive and physical fatigue are associated with distinct problems in daily functioning, role fulfilment, and quality of life in MS	inappropriate study focus
160.	Wilski	2019	Health locus of control and mental health in patients with multiple sclerosis: Mediating effect of coping strategies.	inappropriate study focus
161.	Tyszka	2010	Exploring the Relation of Health-Promoting Behaviors to Role Participation and Health-Related	inappropriate study focus

			Quality of Life in Women With Multiple Sclerosis: A Pilot Study	
162.	White	2008	Invisible and Visible Symptoms of Multiple Sclerosis: Which Are More Predictive of Health Distress?	inappropriate study focus
163.	Panda	2018	Psychiatric comorbidity in multiple sclerosis.	cross sectional design
164.	Logsdail	1988	Psychiatric morbidity in patients with clinically isolated lesions of the type seen in multiple sclerosis: a clinical and MRI study	inappropriate study focus
165.	Gulick	2001	Emotional Distress and Activities of Daily Living Functioning in Persons with Multiple Sclerosis	cross sectional design
166.	Beier	2019	Relationship of perceived stress and employment status in individuals with multiple sclerosis	cross sectional design
167.	Spitzer	2012	Childhood Trauma in Multiple Sclerosis: A Case-Control Study	cross sectional design
168.	Warren	1982	EMOTIONAL STRESS AND THE DEVELOPMENT OF MULTIPLE SCLEROSIS: CASE-CONTROL EVIDENCE OF A RELATIONSHIP	cross sectional design
169.	Warren	1982	How multiple sclerosis is related to animal illness, stress and diabetes	cross sectional design
170.	van der Hiele	2012	Daily hassles reported by Dutch multiple sclerosis patients	cross sectional design
171.	Kroencke	1999	Stress and coping in multiple sclerosis: exacerbation, remission and chronic subgroups	cross sectional design
172.	Bishop	2015	Quality of life among people with multiple sclerosis: Replication of a three-factor prediction model	inappropriate study focus
173.	Eftekharian	2016	Frequency of viral infections and environmental factors in multiple sclerosis	cross sectional design
174.	Warren	1991	Emotional stress and coping in multiple sclerosis (MS) exacerbations.	cross sectional design
175.	Crawford	1987	Stress management for multiple sclerosis patients.	inappropriate study focus
176.	Weygandt	2016	Stress-induced brain activity, brain atrophy, and clinical disability in multiple sclerosis.	inappropriate study focus

177.	Bach	1990	[Life stress events preceding illness episodes in multiple sclerosis and ulcerative colitis--a comparison].	cross sectional design
178.	Grant	1989	Severly threatening events and marked life difficultiues preceding onset or exacerbation of multiple sclerosis	cross sectional design
179.	Mei-Tal	1970	The Role of Psychological Process in a Somatic Disorder: Multiple Sclerosis	qualitative study
180.	Simpson	2019	Mindfulness-based interventions for mental well-being among people with multiple sclerosis: a systematic review and meta-analysis of randomised controlled trials	review
181.	Liu	2009	Relationship between Psychosocial Factors and Onset of Multiple Sclerosis	cross sectional design
182.	Saul	2017	Stressful life events and the risk of initial central nervous system demyelination	cross sectional design
183.	Abbasi	2017	Multiple sclerosis and environmental risk factors: a case-control study in Iran	cross sectional design
184.	AlZahrani	2019	Association of acute stress with multiple sclerosis onset and relapse in Saudi Arabia	cross sectional design
185.	Palumbo	1998	Stressful life events and multiple sclerosis: a retrospective study	cross sectional design
186.	Abdollahpour	2018	Stress-full life events and multiple sclerosis: A population-based incident case-control study	cross sectional design
187.	Gunnarsson	2015	Characteristics in childhood and adolescence associated with future multiple sclerosis risk in men: cohort study	inappropriate stressor
188.	Aikens	1997	A Replicated Prospective Investigation of Life Stress, Coping, and Depressive Symptoms in Multiple Sclerosis	inappropriate study focus
189.	Janssens	2006	Prediction of anxiety and distress following diagnosis of multiple sclerosis: a two-year longitudinal study	inappropriate study focus
190.	Johnson	1999	A controlled Investigation of bodywork in MS	inappropriate study focus
191.	Brown	2009	Longitudinal assessment of anxiety, depression, and fatigue in people with multiple sclerosis	inappropriate study focus

192.	Ribbons	2017	Anxiety Levels Are Independently Associated With Cognitive Performance in an Australian Multiple Sclerosis Patient Cohort	inappropriate study focus
193.	Anagnostouli	2019	A novel cognitive-behavioral stress management method for multiple sclerosis. A brief report of an observational study	inappropriate study focus
194.	Beier	2015	Beyond Depression: Predictors of Self-Reported Cognitive Function in Adults Living With MS	inappropriate study focus
195.	Artemiadis	2012	Stress Management and Multiple Sclerosis: A Randomized Controlled Trial	inappropriate study focus
196.	bombardier	2008	The efficacy of telephone counseling for health promotion in people with multiple sclerosis: A randomized Controlled Trial	inappropriate study focus
197.	Senders	2019	Impact of mindfulness-based stress reduction for people with multiple sclerosis at 8 weeks and 12 months: A randomized clinical trial.	inappropriate study focus
198.	Kasser	2003	Variability in constraints and functional competence in adults with multiple sclerosis.	inappropriate study focus
199.	Foley	1987	Efficacy of stress-inoculation training in coping with multiple sclerosis	inappropriate study focus
200.	O`Connor	1994	Effect of diagnostic testing for multiple sclerosis on patient health perceptions. Rochester-Toronto MRI Study Group	inappropriate study focus
201.	Pakenham	2005	Benefit Finding in Multiple Sclerosis and Associations With Positive and Negative Outcomes	inappropriate study focus
202.	Carletto	2017	The Effectiveness of a Body-Affective Mindfulness Intervention for Multiple Sclerosis Patients with Depressive Symptoms: A Randomized Controlled Clinical Trial	inappropriate study focus
203.	Foley	1992	A prospective study of depression and immune dysregulation in multiple sclerosis	inappropriate study focus
204.	Simmons	2004	What affects your MS? Responses to an anonymous, Internet-based epidemiological survey	cross sectional design

205.	Snyder	2013	Psychological and physical predictors of illness intrusiveness in patients with multiple sclerosis	inappropriate study focus
206.	Zeldow	1984	Physical disability, life stress, and psychosocial adjustment in multiple sclerosis	inappropriate study focus
207.	Wilken	2007	Recognizing and Treating Common Psychiatric Disorders in Multiple Sclerosis	review
208.	van der Hiele	2012	The relationship between self-reported executive performance and psychological characteristics in multiple sclerosis	inappropriate study focus
209.	Simpson	2018	Optimising mindfulness based stress reduction for people with multiple sclerosis	inappropriate study focus
210.	Pakpoor	2018	Psychiatric disorders in children with demyelinating diseases of the central nervous system	inappropriate study focus
211.	van Kessel	2008	A Randomized Controlled Trial of Cognitive Behavior Therapy for Multiple Sclerosis Fatigue	inappropriate study focus
212.	Stuifbergen	2016	Selected health behaviors moderate the progression of functional limitations in persons with multiple sclerosis: Eleven years of annual follow-up	inappropriate study focus
213.	Mohr	2012	"A randomized trial of stress management for the prevention of new brain lesions in MS"	inappropriate study focus
214.	Pakenham	1999	Adjustment to Multiple Sclerosis: Application of a Stress and Coping Model	inappropriate study focus
215.	Gale	1999	Mortality from Parkinson’s disease and other causes in men who were prisoners of war in the Far East	inappropriate study focus
216.	Ackermann	2002	Stressful life events precede exacerbations of multiple sclerosis	overlap
217.	Somer	2010	Patients with multiple sclerosis in a war zone: coping strategies associatedwith reduced risk for relapse	additional study with differenz focus
218.	Mohr	2002	Moderating Effects of Coping on the Relationship Between Stress and the Development of New Brain Lesions in Multiple Sclerosis	additional study with differenz focus

219.	Brown (part II)	2006	Relationship between stress and relapse in multiple scleros: part II. Direct and indirect relationships	additional study with differenz focus

10. 6 **Supplement 6:** PRISMA Abstract Checklist[21]

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

11. Statutory declaration - Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe. Eine statistische Beratung erfolgte durch Herrn Prof. Tim Friede (Abteilung Medizinische Statistik, Universitätsmedizin Göttingen).
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....