

Stress and multiple sclerosis: A systematic review considering potential moderating and mediating factors and methods of assessing stress

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Abstract

Research about the effects of stress on multiple sclerosis has yielded contradictory results. This study aims to systematically review the evidence focusing on two possible causes: the role of stress assessment and potential moderating and mediating factors. The Web of Knowledge (MEDLINE and Web of Science), Scopus, and PsycINFO databases were searched for relevant articles published from 1900 through December 2014 using the terms “stress*” AND “multiple sclerosis.” Twenty-three articles were included. Studies focused on the effect of stress on multiple sclerosis onset ($n=9$) were mostly retrospective, and semi-structured interviews and scales yielded the most consistent associations. Studies focused on multiple sclerosis progression ($n=14$) were mostly prospective, and self-reported diaries yielded the most consistent results. The most important modifying factors were stressor duration, severity, and frequency; cardiovascular reactivity and heart rate; and social support and escitalopram intake. Future studies should consider the use of prospective design with self-reported evaluations and the study of moderators and mediators related to amount of stress and autonomic nervous system reactivity to determine the effects of stress on multiple sclerosis.

Keywords

moderating and mediating factors, multiple sclerosis, stress, stress evaluation

Introduction

Multiple sclerosis (MS) is a chronic, progressive, autoimmune disease that affects the central nervous system (Lutton et al., 2004). About 2.5 million people worldwide have MS, it is one of the most common neurological disorders and cause of disability of young adults (WHO, 2006). Although the etiology is unknown, MS is a complex disease that probably involves multiple genes and environmental factors. The most widely studied environmental factors include vitamin D deficiency (Munger et al., 2004), Epstein–Barr virus (Ascherio and Munger, 2010), and stress (Artemiadis et al., 2011).

Stress is the factor that has generated the most controversial results. Some studies report an association between stress and MS (Buljevac et al., 2003; Mohr et al., 2000;

Warren et al., 1982) but others failed to find this association or only found a quasi-significant relationship (Gasperini et al., 1995; Riise et al., 2011). These disparate results can be explained by heterogeneity in study design (Artemiadis et al., 2011) as well as by the indirect way stress affects MS

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through other variables (Mohr et al., 2002). Factors proposed as potential moderators and mediators between stress and MS include stressor properties, environmental factors, and patients' biological, social, and psychological characteristics (Mohr et al., 2002).

Some studies have reviewed articles published on the relationship between stress and MS. In 1999, the American Academy of Neurology found class II evidence both for and against an association between stress and the onset or exacerbation of MS, concluding that a relationship between MS and psychological stress was possible but data were insufficient for reasonable medical certainty (Goodin et al., 1999). In 2004, Mohr et al. analyzed 14 studies and found a consistent association between stressful life events and subsequent exacerbation in MS. Finally, in a recent systematic review, Artemiadis et al. (2011) found that 15 of 17 studies reported a significant stress–MS relationship; however, they pointed out that the heterogeneity in the measurement of stress precluded secure conclusions. Other authors highlight the need to identify factors that might modify the stress–MS association (Ackerman et al., 2002; Brown et al., 2006b). All these reviews focused on the quality and main results of the studies, but none examined the results in function of the way stress was measured or of potential moderators and mediators.

This study aims to review the evidence on the association between stress and MS, focusing on the methods used to evaluate whether stress affects MS and the role of potential moderator and mediator factors on this association. This knowledge can be useful for the design of future studies and for developing better interventions in MS patients.

Methods

Literature search

We searched the Web of Knowledge (MEDLINE and Web of Science), Scopus, and PsycINFO databases for relevant articles published from 1900 through December 2014. We searched for the terms *stress** AND *multiple sclerosis*. To obtain additional eligible articles, we also examined the reference lists of the articles located.

Selection criteria

We selected articles that met the following inclusion criteria: (1) published in international peer-reviewed academic journals (book chapters, abstracts of conference proceedings, and dissertations were excluded), (2) published in English or Spanish, (3) measuring psychosocial stress in everyday situations (induced stress studies were excluded), (4) evaluating MS onset, relapse rate during a period of time, or MS-related health status, and (5) observational and non-stress interventional studies in human subjects (stress-interventional and animal studies were excluded).

Two reviewers (L.B.B. and R.M.V.) independently selected articles and examined titles and abstracts to exclude those out-of-scopes. When the first two reviewers disagreed, three reviewers (L.B.B., R.M., and F.X.A.N.) reached a consensus about disagreements. Then, full papers were reviewed and selected for this study. All the processes were done following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (Moher et al., 2009).

The qualitative appraisal was based on Newcastle–Ottawa quality assessment scale recommended by the Cochrane Non-Randomized Studies Methods Working Group (Wells et al., 1999), following the adaptation for stress and MS made by Artemiadis et al. (2011).

Data extraction

We arranged papers into chronological order and extracted details on (1) source (authors, year, and country); (2) whether the study measured onset, relapse, or both; (3) design; (4) sample; (5) diagnostic criteria for MS, relapse, and health status; (6) study period; (7) qualitative assessment; (8) the instruments used to measure stress; (9) modifying factors considered; and (10) results regarding the relationship between stress and MS and influences of modifying factors.

Following Mohr et al. (2002), we classified modifying factors according to the following criteria: the nature of the stressor; the environmental context; and the patient's biological, social, and psychological characteristics. We classified articles according to whether they evaluated disease onset or progression; however, we decided not to analyze disease type and process because the disease process cannot be controlled and almost all the papers reviewed dealt with remittent-recurrent or secondary-progressive clinical types.

Risk of bias

Our approach carries a risk of different biases. First, the selection process is susceptible to publication bias. Second, there is a risk of excluding papers using different terms to refer to the same concepts, for example, disseminated sclerosis instead of MS or anxiety instead of stress. Third, we may have missed other potential modifying factors because we only analyze factors included in studies that first focused on the relationship between MS and stress.

Results

Study selection

The initial database search provided 5030 records and we identified 11 records from other sources. After we removed duplicate studies and irrelevant titles, 336 unique and potentially relevant abstracts remained (Figure 1). After excluding out-of-scope records, we checked the full texts

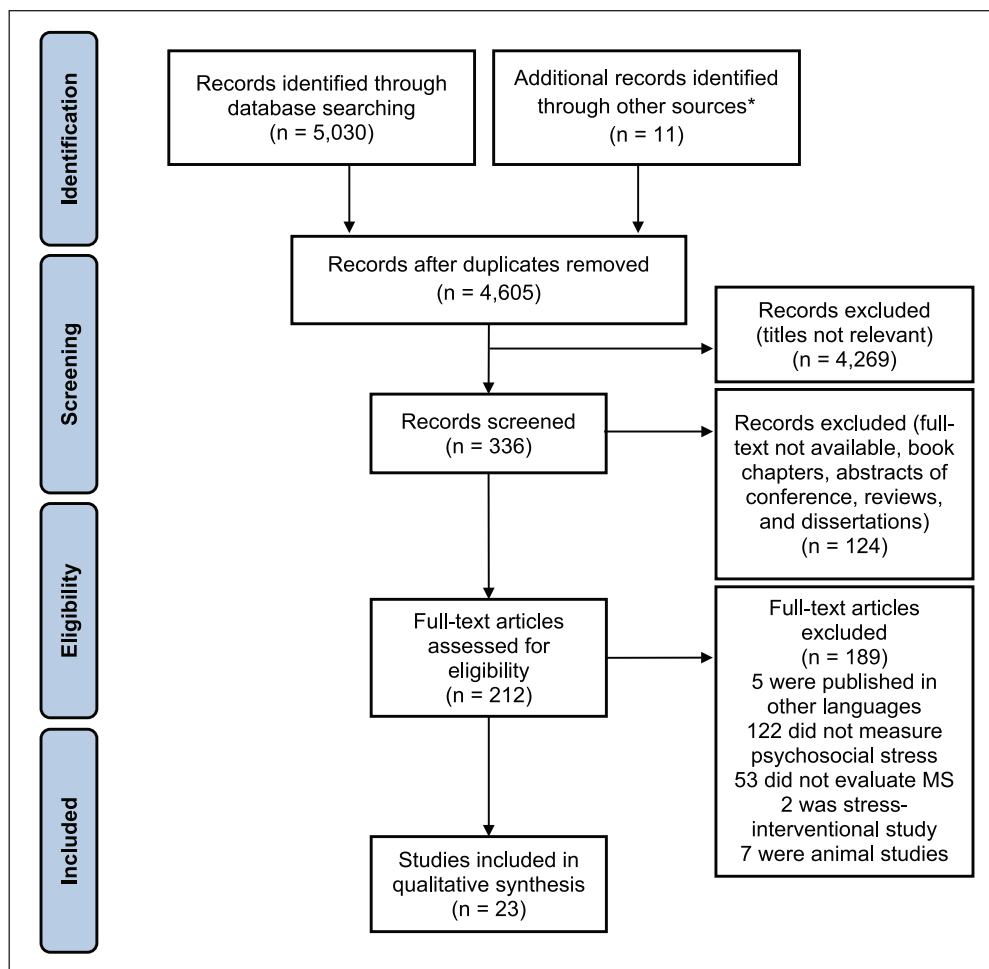


Figure 1. Search and exclusion process.

*References of other papers.

of 212 records. We excluded 189 articles because they did not meet the inclusion criteria: 5 (2.6%) were not published in English or Spanish; 122 (64.6%) did not measure psychosocial stress in everyday situations; 53 (28%) did not evaluate MS onset, relapse rate, or health status; 2 (1.1%) were stress-interventional studies; and 7 (3.7%) were animal studies. Thus, 23 studies were included.

Characteristics of the studies

Table 1 reports the main characteristics of the selected papers. When we grouped papers according to whether they evaluated the effects of stress on onset or progression, we found 9 papers evaluating the effects of stress on onset (Grant et al., 1989; Liu et al., 2009; Mei-Tal et al., 1970; Nielsen et al., 2014a, 2014b; Palumbo et al., 1998; Pratt, 1951; Riise et al., 2011; Warren et al., 1982) and 14 evaluating the effects on disease progression, of which 13 focused on relapses (Ackerman et al., 2002, 2003; Brown et al., 2006a, 2006b; Buljevac et al., 2003; Gasperini et al., 1995; Mitsonis et al., 2008, 2010; Mohr et al., 2000, 2002;

Oveisgharan et al., 2014; Potagas et al., 2008; Warren et al., 1991) and 1 on health status (Schwartz et al., 1999).

A wide variety of countries were represented, but nine (39%) were done in or in collaboration with the institutions in the United States.

Despite the broad range of years searched, all the papers selected were published after 1950. One paper was published in the 1950s, 1 in the 1970s, 2 in the 1980s, 4 in the 1990s, 10 in the 2000s, and 5 from 2010 to 2014.

The samples in the studies ranged from 23 to 170 participants with MS, with the exceptions of the three large cohort studies (Nielsen et al., 2014a, 2014b; Riise et al., 2011), which followed between 230,000 and 30 million people initially healthy participants. The control/comparison groups consisted of other individuals with MS in three studies (Gasperini et al., 1995; Mitsonis et al., 2010; Warren et al., 1991), of healthy individuals in three studies (Grant et al., 1989; Liu et al., 2009; Schwartz et al., 1999), and of individuals with other diseases in three studies: organic diseases of the central nervous system (Pratt, 1951), rheumatologic/neurologic

Table 1. Main characteristics of papers selected (sorted by onset/relapse in chronological order).

Author, year, and country	Onset/relapse	Study design	Sample	Diagnostic criteria	Relapse criteria	Study period of time	Quality assessment
Papers measuring disease onset							
Pratt (1951), United Kingdom	Onset and relapse	Case-control (retrospective)	n = 100 MS n = 100 controls (organic CNS diseases) (n = 50/50 females/males)	Not mentioned	Not mentioned	Onset: unspecified time to onset Relapse: since onset to interview	Selection: 3 Comparability: 1 Exposure: 1
Mei-Tal et al. (1970), Israel/United States	Onset and relapse	Cross-sectional/cohort (retrospective)	n = 32 MS (n = 22 females/n = 10 males)	Not mentioned	Not mentioned	Onset: unspecified time to onset Relapse: since onset to interview	Selection: 1 Comparability: 0 Outcome: 1
Warren et al. (1982), Canada	Onset	Case-control (retrospective)	n = 100 MS n = 100 controls (rheumatology/neurology) (females 2.3:1 males)	Schumacher	Not mentioned	Two years before onset	Selection: 3 Comparability: 1 Exposure: 2
Grant et al. (1989), United States/United Kingdom	Onset	Case-control (retrospective)	n = 39 MS n = 40 controls (healthy) (n = 29/30 females/n = 10 males)	Poser	Not mentioned	One year before onset	Selection: 3 Comparability: 1 Exposure: 1
Palumbo et al. (1998), Italy	Onset	Case-control (retrospective)	n = 65 MS n = 27 controls (non-genetic chronic PNP) (n = 40/12 females/n = 25/15 males)	Not mentioned	Not mentioned	One year before onset	Selection: 1 Comparability: 0 Exposure: 2
Liu et al. (2009), China/United States	Onset	Case-control (retrospective)	n = 41 MS n = 41 controls (healthy) (n = 26 females/n = 15 males)	Poser	Not mentioned	Three years before onset	Selection: 3 Comparability: 1 Exposure: 1
Riise et al. (2011), Norway/United States	Onset	Cohort (prospective)	nC1 = 121,700 nC2 = 116,671 (healthy female nurses)	Poser	Not mentioned	Follow-up 30 years	Selection: 3 Comparability: 1 Outcome: 3
Nielsen et al. (2014a), Denmark	Onset	Cohort (prospective)	nC3/nC4 = 30 million people (healthy people)	McDonald	Not mentioned	Follow-up 28 years	Selection: 4 Comparability: 1 Outcome: 3

Table 1. (Continued)

Author, year, and country	Onset/relapse	Study design	Sample	Diagnostic criteria	Relapse criteria	Study period of time	Quality assessment
Nielsen et al. (2014b), Denmark	Onset	Cohort (prospective)	nC5 = 2.9 million people (healthy people)	McDonald	Not mentioned	Follow-up 18 years	Selection: 4 Comparability: 1 Outcome: 3
Papers measuring disease progression							
Warren et al. (1991), Canada	Relapse	Case-control (retrospective)	n = 95 MS in exacerbation n = 95 MS in remission (2.3 females: 1 males)	Poser	Clinical criteria ²	Three months prior relapse (exacerbation group) or interview (remission group)	Selection: 4 Comparability: 1 Exposure: 2
Gasparini et al. (1995), Italy	Relapse	Case-control (prospective)	n = 89 MS in exacerbation n = 89 MS in remission (n = 62 females/n = 27 males)	Poser	Clinical criteria ³	Follow-up 1 year 3 months before exacerbation	Selection: 4 Comparability: 1 Exposure: 2
Schwartz et al. (1999), United States	Health status	Cohort (prospective)	n = 101 MS n = 96 controls (healthy) (n = 75 females/n = 26/21 males)	Poser	Not mentioned	Follow-up 6 years	Selection: 3 Comparability: 1 Outcome: 2
Mohr et al. (2000), United States	Relapse	Cohort (prospective longitudinal)	n = 36 MS (n = 22 females/n = 14 males)	Poser	Clinical criteria ⁴ New MRI Gd+ lesions	Follow-up for 28–100 weeks	Selection: 3 Comparability: 1 Outcome: 3
Ackerman et al. (2002), United States	Relapse	Cohort (prospective longitudinal)	n = 23 MS (females)	Poser	Clinical criteria ⁶	Follow-up 1 year	Selection: 4 Comparability: 0 Outcome: 3
Mohr et al. (2002), United States	Relapse	Cohort (prospective longitudinal)	n = 36 MS (n = 22 females/n = 14 males)	Poser	New MRI Gd+ lesions	Follow-up for 28–100 weeks	Selection: 3 Comparability: 2 Outcome: 2
Ackerman et al. (2003), United States	Relapse	Cohort (prospective longitudinal)	n = 50 MS (females)	Poser	Clinical criteria ⁶	Follow-up 1 year	Selection: 4 Comparability: 1 Outcome: 3
Buijveac et al. (2003), The Netherlands	Relapse	Cohort (prospective longitudinal)	n = 73 MS (n = 56 females/16 males)	Not mentioned	Clinical criteria ⁵	Follow-up 1.4 years (average 74 weeks, range 8–120 weeks)	Selection: 3 Comparability: 1 Outcome: 3

(Continued)

Table 1. (Continued)

Author, year, and country	Onset/relapse	Study design	Sample	Diagnostic criteria	Relapse criteria	Study period of time	Quality assessment
Brown et al. (2006a), Australia	Relapse	Cohort (prospective longitudinal)	n = 101 MS (n = 81 females/n = 20 males)	Poser	Clinical criteria ⁶	Follow-up 2 years	Selection: 4 Comparability: 2 Outcome: 2
Brown et al. (2006b), Australia	Relapse	Cohort (prospective longitudinal)	n = 101 MS (n = 81 females/n = 20 males)	Poser	Clinical criteria ⁶	Follow-up 2 years	Selection: 4 Comparability: 2 Outcome: 2
Mitsonis et al. (2008), Greece	Relapse	Cohort (prospective longitudinal)	n = 26 MS (females)	McDonald	Clinical criteria ⁵	Follow-up mean 56.3 weeks	Selection: 4 Comparability: 0 Outcome: 3
Potagas et al. (2008), Greece/France	Relapse	Cohort (prospective longitudinal)	n = 37 MS (females)	McDonald	Clinical criteria ⁵	Follow-up 1 year	Selection: 3 Comparability: 2 Outcome: 3
Mitsonis et al. (2010), Greece	Relapse	Cohort (prospective)	n = 24 MS (SSRI) n = 24 MS (no SSRI) (females)	McDonald	Clinical criteria ⁵	Follow-up 1 year	Selection: 1 Comparability: 1 Outcome: 3
Oveisgharan et al. (2014), Iran	Relapse	Cohort (prospective)	n = 57 MS patients (n = 46 females/n = 11 males)	McDonald	Clinical criteria ¹ unspecified	Follow-up 1 year	Selection: 1 Comparability: 0 Outcome: 3

MS: multiple sclerosis; CNS: central nervous system; PNP: polynuropathy; nC1: n cohort 1; nC2: n cohort 2; nC3: n cohort of persons who became parents between 1968 and 2010; nC4: n cohort of persons who married between 1968 and 2010; nC5: n cohort of people born from 1968 to 2011; MRI: magnetic resonance imaging; Gd+: gadolinium; SSRI: selective serotonin reuptake inhibitor (escitalopram); EDSS: Expanded Disability Status Scale.

Clinical criteria for relapses: 1. Unspecified. 2. Sudden appearance of a symptom typical of MS, which may have been new to participants or experienced during a previous relapse. Remission was defined as no symptoms in the previous 6 months. 3. New neurological symptom associated with a change of at least 1.0 point in EDSS which lasted more than 24 hours. 4. Increase of 1.0 point on the EDSS from the previous examination. 5. A worsening of existing symptoms or appearance of new symptoms, lasting more than 24 hours and after at least 30 days of improvement or stability not associated with fever. 6. Occurrence, recurrence, or worsening of symptom(s) of neurological dysfunction, associated with confirmatory change on neurological examination, lasted more than 48 hours, not associated with fever and occurred after at least 30 days of improvement or stability.

diseases (Warren et al., 1982), and polyneuropathy (Palumbo et al., 1998).

Study design. Six of the nine studies examining the relationship between stress and the onset of MS were retrospective: one (Mei-Tal et al., 1970) was cross-sectional and five (Grant et al., 1989; Liu et al., 2009; Palumbo et al., 1998; Pratt, 1951; Warren et al., 1982) case-control; these studies focused on a period from 1 to 3 years before onset or on an unspecified period of time before onset (Mei-Tal et al., 1970; Pratt, 1951). Three prospective studies that examined the relationship between stress and the onset of MS were longitudinal, following a cohort of initially healthy people from 18 to 30 years (Nielsen et al., 2014a, 2014b; Riise et al., 2011).

The 14 studies examining the relationship between stress and progression of MS were all prospective; 12 of these were cohort studies (Ackerman et al., 2002, 2003; Brown et al., 2006a, 2006b; Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Mohr et al., 2000, 2002; Oveisgharan et al., 2014; Potagas et al., 2008; Schwartz et al., 1999) and 2 were case-control studies (Gasperini et al., 1995; Warren et al., 1991). The duration of these studies ranged from 28 weeks to 8 years, but in most it was about 1 year.

Criteria for diagnosing MS and relapse. The criteria for the initial diagnosis of MS have evolved from those in Schumacher et al., (1965) publication, which were updated by Poser et al. (1983), and more recently by McDonald et al. (2001), last reviewed by Polman et al. (2011).

The criteria for diagnosing relapse varied widely. Whereas some articles used biological criteria (new lesions on gadolinium-enhanced magnetic resonance imaging (MRI)) to determine disease progression (Mohr et al., 2000, 2002), most studies used clinical criteria to define relapse, either changes in Expanded Disability Status Scale score (Gasperini et al., 1995; Mohr et al., 2000) or worsening or new symptoms (Ackerman et al., 2002, 2003; Brown et al., 2006a, 2006b; Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Oveisgharan et al., 2014; Potagas et al., 2008; Warren et al., 1991), with some variation in the definition of these concepts. Nevertheless, the most commonly used clinical criteria describe relapse as a worsening of the existing symptoms or appearance of new ones lasting more than 24 hours (labeled clinical criteria 5 in Table 1) or more than 48 hours (labeled clinical criteria 6 in Table 1) after at least 30 days of improvement or stability not associated with fever.

Regarding relapse criteria, we observed that studies that used biological criteria (new gadolinium-enhanced lesions) or changes in Expanded Disability Status Scale found a positive but not significant association (odds ratio (OR)=2.3, 95% confidence interval (CI)=0.9–5.6) between stress and MS (Gasperini et al., 1995) or an association not sufficiently robust (OR=1.64, 95% CI=1.22–2.20) to predict clinical exacerbations (Mohr et al., 2000).

Methods used to evaluate stress and results: onset studies

Two studies (Mei-Tal et al., 1970; Pratt, 1951) used non-validated interviews; both found more emotional stress before onset (unspecific period of time), although in Pratt (1951) the difference was not significant ($\chi^2=1.8, p>.05$).

Two other studies (Grant et al., 1989; Warren et al., 1982) used semi-structured interviews designed on the basis of previous information about stress; both showed a temporal relationship between greater emotional stress and MS. In the study by Grant et al. (1989), compared to matched controls without MS, more MS patients had experienced marked adversity in the year prior to onset of symptoms, (77% vs. 35% of controls; $\chi^2=14.08, p<.001$). Similarly, Warren et al. (1982) found that MS patients had more unwanted stress than controls in the 2 years before onset (79% vs. 54%; $\chi^2=12.93, p<.001$).

Two studies (Palumbo et al., 1998; Riise et al., 2011) used ad hoc questionnaires to determine the amount of stress. Palumbo et al. (1998) observed a nonsignificant trend toward more stressful events in MS patients than in patients with polyneuropathy (24.6% vs. 14.8%) in the year before onset. Riise et al. (2011) observed no effect of stress on MS development in 30 years' follow-up of a large cohort of initially healthy subjects.

One study used a rating scale of stressful events. Liu et al. (2009) found significant differences ($p<.01$) between MS and controls in different symptoms related to stress such as mental health symptoms, negative life events, family problems, and social support.

Finally, two studies (Nielsen et al., 2014a, 2014b) used data about specific stressful events from the National Multiple Sclerosis Registry and observed little evidence for a causal association between major stressful events and MS risk. Only parental divorce in childhood increased modestly the risk of MS (Nielsen et al., 2014b).

Methods used to evaluate stress and results: progression studies

Progression studies can be classified into two categories: those that evaluated the stress patients experienced in a period of time before a relapse retrospectively after the relapse occurred (Gasperini et al., 1995; Warren et al., 1991) and those that evaluated stress systematically before the relapse occurred (Ackerman et al., 2002, 2003; Brown et al., 2006a, 2006b; Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Mohr et al., 2000, 2002; Oveisgharan et al., 2014; Potagas et al., 2008; Schwartz et al., 1999).

In the first category, Warren et al. (1991) used a questionnaire and different scales and observed a significant positive relationship between stress and MS exacerbation: patients scoring 5 or above in Goldberg and Hillier's General Health

Questionnaire-28 (Goldberg and Hillier, 1979) had a relative risk (RR) of exacerbation of 3.1 (95% CI). In contrast, Gasperini et al. (1995) used a structured interview to determine whether patients had undergone a single stressful event and found no differences between MS patients who had relapsed and those who had not, although cumulated stressful events were associated with a nonsignificantly higher risk of MS relapse (OR=2.3, 95% CI=0.9–5.6).

In the second category, eight studies used different combinations of questionnaires, scales, and interviews. Mohr et al. (2000, 2002) used different scales to evaluate stressful events and hassles monthly, considering the 8 weeks after every stressful event a period at risk for relapse; these studies found that *Conflict and disruption in routine* increased the odds of developing new gadolinium-enhanced lesions (OR=1.64, 95% CI=1.22–2.20, $p < .001$), but was not robust enough to reliably predict clinical exacerbations. Oveisgharan et al. (2014) used a tri-monthly questionnaire and observed no differences in stressful events between patients with or without subsequent relapses. Ackerman et al. (2002, 2003) used a weekly questionnaire and a semi-structured interview at the beginning and end of the study. Both studies showed that stress was a potential trigger of MS exacerbations and vice versa; considering the 6 weeks after an stressful event as a period at risk for relapse, 85 percent of relapses were associated with an stressful event and 49 percent of stressful events were associated with relapses. Brown et al. (2006a, 2006b) found similar results using the same semi-structured interview at the beginning and every 3 months, also confirming the bidirectional hypothesis.

Schwartz et al. (1999) using a self-reported stressful event scale every 6 months also found a bidirectional relationship between stress and MS exacerbation, in which MS progressed after stress and stress increased after MS exacerbations in a vicious cycle. More than one stressful event increased the risk of disease progression (OR=1.13, $p < .001$) and disease progression increased the risk of self-reported stress (OR=2.13, $p < .001$).

Finally, four studies (Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Potagas et al., 2008) used self-reported diaries. All these studies showed increased risk for exacerbation during the 4 weeks after a stressful event. Buljevac et al. (2003) found that one or more stressful events were associated with a 2-fold risk of relapse (RR=2.2, 95% CI=1.2–4.0, $p < .05$), concluding that the increased risk of relapse was not “dose-dependent.” In contrast, Mitsonis et al. (2008) and Potagas et al. (2008) found that cumulative stressful events (three or more) increased the risk of MS relapse (from OR=5.36 to OR=16.78, 95% CI).

Moderating and mediating factors: evaluation and results

All but 2 of the 23 studies took into account potential modifying factors of the relationship between stress and MS

(Table 2). We classified these factors into three main categories: stressor properties, individual characteristics, and environmental factors.

Stressors properties. Thirteen studies analyzed stressor properties such as type, duration, severity, valence, source, and frequency. Among the different stressor properties, type and source (for example, work stress) were the least significant (Ackerman et al., 2002; Grant et al., 1989; Meital et al., 1970; Mitsonis et al., 2008). However, Mohr et al. (2000) observed that only the type of stressor referred to as “Conflict and disruption in routine” was associated with new gadolinium-enhanced lesions. The duration of exposure to a stressor was more important. Stressors associated with relapses were mainly sustained and protracted or long-term stressors (versus acute stressors), lasting more than 48 hours (Ackerman et al., 2002; Brown et al., 2006a; Grant et al., 1989; Meital et al., 1970). With regard to severity of the stressor, most studies found a stronger association with MS relapses for intermediate-to-severe intensity stressors (Ackerman et al., 2002; Grant et al., 1989; Warren et al., 1991). Finally, frequency was important; in general, studies found that cumulated stress or the presence of various stressful events increased the risk of relapse compared with a single stressful event (Brown et al., 2006a; Gasperini et al., 1995; Mitsonis et al., 2008; Oveisgharan et al., 2014; Potagas et al., 2008; Schwartz et al., 1999).

Patients' characteristics. Eight studies evaluated the impact of different patient characteristics on the stress–MS relationship. Seven considered psychosocial factors such as premorbid personality (Pratt, 1951), coping style (Brown et al., 2006b; Mohr et al., 2002; Warren et al., 1982, 1991), and mental health symptoms (anxiety, depression, optimism) (Brown et al., 2006b; Liu et al., 2009; Potagas et al., 2008). Only one study (Ackerman et al., 2003) evaluated biological factors (cardiovascular reactivity, resting heart rate, and blood pressure).

Personality did not seem to affect disease progression (Pratt, 1951), but other psychosocial factors differed significantly between MS patients and controls (Liu et al., 2009), including a trend toward worse mental health in MS patients. In a recent study by Potagas et al. (2008), a Hamilton Rating Scale for Anxiety (Hamilton, 1959) score ≥ 18 was associated with a hazard rate of 2.9 (95% CI=1.3–6.4, $p < .05$) for MS relapse.

There seems to be modest evidence that coping style affects MS; Mohr et al. (2002) found greater use of distraction had a protective effect against MS (OR=0.69, 95% CI=0.49–0.98, $p < .05$), but instrumental coping was only marginally associated with a decrease in the strength of the stress–MS relationship (OR=0.77, 95% CI=0.57–1.04, $p > .05$). Other coping styles showed no effects on the relationship. Warren et al. (1982) neither found differences in coping styles between MS patients and controls but, in a more recent study of Warren et al. (1991) comparing MS

Table 2. Stress measuring instruments, moderator factors and results.

Author/year	Instruments used to measure stress	Moderating mediating factors	Instruments to measure moderating/mediating factors	Results (1, stress–MS relationship; 2, moderating/mediating factors)
Papers measuring disease onset				
Pratt (1951)	Non-validated interview (life story)	Premorbid personality	Allotting each patient in the personality schemes of Jung (extraversion–introversion) and Sheldon (viscerotonia, somatonia, cerebrotonia)	(1) Emotional stress antedates onset or relapse but no significant differences between MS and controls ($\chi^2 = 1.8, p > .05$). (2) No specific premorbid personality type was defined in patients of MS.
Mei-Tal et al. (1970)	Non-validated interview (life story)	Stressor typology and duration	Classifying SLEs into: a) Sudden and transient b) Sudden and sustained c) Gradual and protracted	(1) 28 of 32 patients reported data indicating the illness was preceded by an SLE. (2) Stressor duration is mainly sustained and protracted; stressor typology is indifferent.
Warren et al. (1982)	Interview based on a modified version of Holmes and Rahe Social Readjustment Rating Scale	Early life stress, coping style	Questions in the interview: a) Emotional climate at home during childhood/adolescence b) Assess how to react to life problems prior to onset age	(1) There is a relationship between emotional stress and MS onset. More unwanted stress in MS patients (79%) than in controls (54%) ($\chi^2 = 12.93, p < .001$). (2) Early life stress and coping style: no differences between MS patients and control group.
Grant et al. (1989)	Semi-structured interview LEADS	Stressor severity, typology, and duration	Classifying SLEs into: a) Severely threatening events (punctual event + long-term > 48 hours + very or moderately severe threat + self-focus) b) Marked difficulties (difficulty \geq 4 weeks + very, moderately, or severe threat)	(1) Temporal relationship between marked adversity and MS symptoms (77% MS patients vs. 35% non-patients, $\chi^2 = 14.08, p < .001$). (2) More marked life adversity (severely threatening events and marked difficulties) in MS patients 1 year before onset but most evident from 6 months to onset.
Palumbo et al. (1998)	Non-validated questionnaire modeled on DSM-IV	No		No significant differences but more SLE in MS patients (24.6%) than in PNP patients (14.8%) the year before onset.
Liu et al. (2009)	Questionnaire, once: LES	Personality, social support, and mental health symptoms	Questionnaires, once: Eysenck Personality Questionnaire Social Support Reevaluate Scale Symptom Check List 90	(1) and (2) significant differences ($p < .01$) were found between MS and control group in mental health symptoms, negative life events, family problems, and social support. Negative correlation of social support with negative emotions suggesting lack of ability in MS patients to use social support.
Riise et al. (2011)	Questionnaire including questions on stress at home and work	Early life stress	Questionnaire including 22 questions on physical and sexual abuse in childhood and adolescence Questions on physical abuse adapted from the Revised Conflict Tactics Scale	(1) No increased risk of MS associated with severe stress at home or work (HR 0.85 (95% CI) 0.32–2.26). (2) Elevated but not significant risk among women having been forced into sexual activity several times during childhood (OR 1.51 (95% CI) 0.90–2.55) and adolescence (OR 1.25 (95% CI) 0.70–2.23).

(Continued)

Table 2. (Continued)

Author/year	Instruments used to measure stress	Moderating mediating factors	Instruments to measure moderating/mediating factors	Results (1, stress-MS relationship; 2, moderating/mediating factors)
Nielsen et al. (2014a)	Stressful life events: lose a child get divorced or widowed	No		No increased risk of MS in bereaved parents compared to those who did not lose a child. No increased risk in divorced or widowed persons compared with married persons.
Nielsen et al. (2014b)	Stressful life events: parental divorce parental death death of sibling	Early life stress	SLEs (until age 18 years): parental divorce parental death death of sibling	(1) and (2) Persons exposed to any SLE in childhood were at 11% elevated risk for MS (RR 1.11 (95% CI) 1.03–1.20), compared to non-exposed persons. Parental death and death of sibling were not associated. Persons exposed to parental divorce were at 13% increased risk (RR 1.13 (95% CI) 1.04–1.23).
Papers measuring disease progression				
Warren et al. (1991)	Questionnaires: Goldberg and Hillier's GHQ-28 Hassles' Scale Uplifts' Scales	Coping style, stressor severity, and frequency	Questionnaires: Ways of Coping Checklist Stressor intensity measured by Hassles Scale Stressor frequency is the number of SLEs in a 3-month period	(1) Relative risk of an exacerbation associated with a score of 5 or above in GHQ was 3.1 (95% CI), suggesting an emotional stress-exacerbation relationship. (2) Daily hassles: more severity in patients in exacerbation, no differences in frequency, suggesting that perceived impact is more important than number. No significant differences in coping strategies, but patients in exacerbation who favored emotion-focused coping were consistently higher ($\chi^2 = 8.4, p < .01$).
Gasperini et al. (1995)	Structured interview about SLEs	Stressor frequency	Number of SLEs in a period of 3 months	(1) No differences between groups for a single SLE. (2) Cumulated SLEs were associated with higher risk of relapse but not significant (OR 2.3 (95% CI) 0.9–5.6).
Schwartz et al. (1999)	Self-reported stressful events every 6 months following: Holmes and Rahe checklist	Stressor frequency	Number of SLEs (evaluated every 6 months)	(1) and (2) Increased risk of disease progression by level of stress (more than one SLE) (OR 1.13, $p < .001$). Increased risk of reported stress by rate of disease progression (OR 2.13, $p < .001$). Vicious cycle "stress progression."
Mohr et al. (2000)	Questionnaires (monthly): Modified SRRS Hassles Scale Profile of Mood States	Stressor frequency and typology	Number of SLEs (evaluated every 4 weeks) Classification of typology: a) Major negative events b) Conflict and disruption in routine c) Positive life events	(1) and (2) <i>Conflict and disruption in routine</i> increased odds (OR 1.64 (95% CI) 1.22–2.20, $p = .00083$) of developing new MRI Gd+ lesions (8 weeks later). Not sufficiently robust to predict clinical exacerbations reliability.

Table 2. (Continued)

Author/year	Instruments used to measure stress	Moderating mediating factors	Instruments to measure moderating/mediating factors	Results (1, stress–MS relationship; 2, moderating/mediating factors)
Ackerman et al. (2002)	Questionnaire, weekly: Psychiatric Epidemiologic Research Interview Semi-structured interview at the beginning/end of the study: LEDS	Stressor severity, duration, frequency, and source	Classifying SLEs by severity: a) Likert scale: <i>more severe</i> (1) to <i>less severe</i> (4) Duration: a) Short-term < 15 days b) Long-term ≥ 15 days Source (different categories) Frequency (number of SLEs)	(1) Stress is a potential trigger of exacerbations in patients with MS. 85% of relapses were associated with an SLE and 49% of SLEs were associated with relapses in a 6-week time frame. (2) An increase in frequency of life events was associated with greater likelihood of MS exacerbations (HR 13.18 (95% CI) 1.67–104.39, $p < .05$).
Mohr et al. (2002)	Questionnaire (monthly): Modified Social Readjustment Rating Scale	Coping style	Coping with Health Injuries and Problems questionnaire	(1) and (2) Modest support for that coping can moderate stress–MS relationship. Greater use of distraction (OR 0.69 (95% CI) 0.49–0.98, $p = .037$) and instrumental coping (OR 0.77 (95% CI) 0.57–1.04, $p = .81$) was marginally associated with decreased stress–MS relationship. Other coping forms did not.
Ackerman et al. (2003)	Questionnaire, weekly: Psychiatric Epidemiologic Research Interview Semi-structured interview at the end of the study: LEDS	Cardiovascular reactivity, resting heart rate, and blood pressure	Measures on: cardiovascular reactivity to an acute experimental stressor (Stroop task) resting heart rate blood pressure	(1) Stress is a potential trigger of relapse. They are more likely at-risk periods (6 weeks after SLE). Deteriorating cycle. (2) Participants with higher cardiovascular reactivity to acute stress and higher baseline heart rate had a greater number of exacerbations ($r(47) = 0.320$, $p < .05$) and weeks ill ($r(47) = 0.350$, $p < .05$).
Buljevac et al. (2003)	Self-reported weekly diaries of emotionally stressful events	Stressor frequency	Number of SLEs (evaluated weekly)	(1) At least one SLE is associated with double risk for relapse (RR 2.2 (95% CI) 1.2–4.0, $p = .014$) in a risk period (4 weeks). No differences in exacerbation risk after 1 or more SLE. Not dose dependent.
Brown et al. (2006a)	Semi-structured interview, at the beginning and every 3 months: LEDS	Stressor valence, typology, frequency, duration, and severity	Classifying SLEs in typology: a) Emotional threat b) Goal frustration Duration: a) Acute events < 6 months b) Chronic difficulties > 6 months Valence (positive, negative) Severity: a) 4-point Likert scale: 0 (<i>mild or non-threatening</i>) to 4 (<i>severe</i>) Number of SLEs	(1) Bidirectional stress-illness hypothesis was confirmed. (2) Acute events predicted greater relapse risk (< 6 months) than chronic difficulties (> 6 months). The number of SLE is the most important property in relation to MS relapse risk.

(Continued)

Table 2. (Continued)

Author/year	Instruments used to measure stress	Moderating mediating factors	Instruments to measure moderating/mediating factors	Results (1, stress-MS relationship; 2, moderating/mediating factors)
Brown et al. (2006b)	Semi-structured interview, at the beginning and every 3 months: LEDS	Coping style, anxiety, depression, optimism, Health LOC, and Social Support	Questionnaires: Beck Depression Inventory STAI-T Ways of Coping Life Orientation Test MHLC Sarason Social Support	1 and 2) Exacerbation is predicted by acute stressor frequency counts and coping responses using social support but not by chronic stressors or other psychosocial factors. Seeking social support decreases the relationship stress-relapse.
Mitsonis et al. (2008)	Self-reported weekly diaries of emotionally stressful events	Stressor duration, type, frequency, and severity	Severity measure: Recent Life Change Questionnaire Type of stress (six categories) Duration (subjective measure): Short-term Long-term (10-14 days) Number of SLEs	(1) Women with cumulative SLEs (3 or more) may be at greater risk for relapse during period at risk (4 weeks). For 3 SLEs (HR 5.36 (95% CI) 1.74-6.46, $p = .003$). For 4 SLEs (HR 16.78 (95% CI) 4.64-60.56, $p < .001$). (2) Duration is the only stressor property that seems to increase risk for relapse (HR 3 (95% CI) 1.01-9.13, $p < .05$), but not stress type or severity.
Potagas et al. (2008)	Self-reported weekly diaries of emotionally stressful events	Anxiety stressor frequency	Questionnaire, every 4 weeks: Hamilton Rating Scale for Anxiety Number of SLEs (evaluated weekly)	(1) Three or more SLE increases in 6.7 times the risk of relapse in MS women (HR 6.7 (95% CI) 2.8-16.0, $p < .001$). (2) High level of anxiety (score >18 in HAM-A) is associated with 2.9 times the rate of relapse (HR 2.9 (95% CI) 1.3-6.4, $p = .008$) and with the number and severity of the SLE.
Mitsonis et al. (2010)	Self-reported weekly diaries of emotionally stressful events	SSRI intake (escitalopram), stressor duration, and frequency	Intake of escitalopram: 10 mg/day Classifying duration: a) Short-term b) Long-term (>14 days) Number of SLEs	(1) and (2) Risk for relapse was 2.9 times higher in c-group (HR 2.9 (95% CI) 1.7-5.9, $p < .001$), influenced only by long-term SLEs. In e-group only ≥ 3 long-term SLEs were related to higher relapse risk.
Oveisgharan et al. (2014)	Questionnaire, trimonthly: Paykel's checklist	Stressor severity and frequency	Severity measure: Subjective appraisal scoring SLE from 0 to 20 Frequency measure: Number of SLE	(1) No differences in SLEs between patients with or without subsequent relapses. (2) Number of stressors was the only factor which reached near significance in predicting relapses ($p = .054$).

MS: multiple sclerosis; SLE: stressful life event, which produces emotional tension, different from everyday life; LEDS: Life Events and Difficulties Schedule; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.); PNP: polyneuropathy; LES: Life Event Scale; HR: hazard ratio; CI: confidence interval; OR: odds ratio; RR: relative risk; GHQ: General Health Questionnaire; SRRS: Social Readjustment Rating Scale; MRI: magnetic resonance imaging; Gd+: gadolinium; LOC: Locus of Control; STAI-T: State Trait Anxiety Inventory - Trait; MHLC: Multidimensional Health Locus of Control Scale; SSRI: selective serotonin reuptake inhibitor (escitalopram).

patients in exacerbation with MS patients in remission, it was found that patients in exacerbation did use more emotional-focused strategies than those in remission, $\chi^2 = 8.4$, $p < .05$.

Finally, Ackerman et al. (2003) found that higher cardiovascular reactivity to an acute stressor and higher baseline

heart rate were significantly correlated with greater relapse rate ($r(47) = .320$, $p < .05$) and longer illness after relapse ($r(47) = .350$, $p < .05$).

Environmental factors. Six studies examined environmental factors such as early life stress (Nielsen et al., 2014b; Riise

et al., 2011; Warren et al., 1982), social support (Brown et al., 2006b; Palumbo et al., 1998), or escitalopram intake (Mitsonis et al., 2010).

Regarding the early life stress, Riise et al. (2011) found a nonsignificant trend toward developing MS in women who had been forced into sexual activity several times during childhood (OR=1.51, 95% CI=0.90–2.55) or adolescence (OR=1.25, 95% CI=0.70–2.23). However, Nielsen et al. (2014b) found that persons exposed to parental divorce in childhood were at 13 percent increased risk of developing MS (RR=1.13, 95% CI=1.04–1.023).

Finally, social support and intake of escitalopram seem to decrease the stress–relapse relationship. Liu et al. (2009) found a negative correlation between social support and negative emotions, suggesting that MS patients lacked the ability to use social support. Mitsonis et al. (2010) studied the effects of escitalopram on stress-related relapses in a randomized controlled trial, finding that patients in the control group (no intake) had a risk of relapse 2.9 times higher than those in the experimental group (receiving escitalopram) (hazard ratio (HR)=2.9, 95% CI=1.7–5.9, $p<.001$), but predicted only by long-term stressors (lasting more than 14 days).

Discussion

To elucidate the relationship between stress and MS and moderating and mediating factors that might influence this relationship, we analyzed the results of 23 studies in function of the methods they used to evaluate stress. We classified studies into two main categories: those that analyzed the effect of stress on the onset of MS and those that analyzed the effect of stress on the progression of MS. Studies focused on onset used a retrospective design with interviews being the main instrument to assess stress. In these studies, semi-structured interviews and scales were the instruments that showed more significant associations with the onset of MS. Studies focused on progression were mostly prospective and evaluated stress systematically prior to exacerbations using a combination of interviews, questionnaires, scales, and self-reported diaries. Almost all these studies showed a significant positive relationship between stress and progression, and self-reported diaries yielded the most consistent results. The potential moderating and mediating factors with the most consistent effect on the stress–MS relationship were the duration, severity, and frequency of the stressor; anxiety, cardiovascular reactivity, and heart rate; and social support and escitalopram intake.

As previous reviews (Artemiadis et al., 2011; Mohr et al., 2004) pointed out, one of the main problems in evaluating the evidence for the relationship between stress and MS is the wide variety of methods used to measure stress. Moreover, different studies not only used different combinations of several stress-measuring instruments but also

different study designs, temporal frameworks between stress and disease (onset or progression), and different criteria to evaluate disease onset and progression.

The studies that evaluated disease onset with a prospective design or ad hoc questionnaires failed to show a significant relationship between stress and disease onset. Only studies using interviews with a retrospective design or questionnaires and scales in a case–control design showed a significant relationship, although this approach cannot establish a causal link. To firmly confirm or rule out whether stress is a risk factor for MS onset, prospective studies that frequently assess stressors are required.

Most studies evaluating disease progression assessed stress prospectively before the changes in disease progression became evident. Almost all these studies showed a positive relationship, regardless of the instruments used or the temporal framework considered as the period “at risk” (from 4 to 8 weeks). However, the studies that used self-reported diaries or weekly assessment (Ackerman et al., 2002, 2003; Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Potagas et al., 2008) had more consistent results. Another important element for obtaining consistent results is the criteria used to measure relapse. As mentioned by Mohr and Pelletier (2006), after a stressful life event, the changes in MS manifest in the following order: first, MRI brain lesions, second, clinical symptoms or relapses, and third, the changes in the Expanded Disability Status Scale. Therefore, studies using the Expanded Disability Status Scale to evaluate MS progression after stress would probably show less progression because the scores often do not change until long after patients notice worsening symptoms or several relapses have occurred. Thus, biological or clinical criteria, or a combination of the two, are likely to provide more accurate results in early stages. In addition, since stress can affect disease without causing relapse, but only worsening symptoms, it seems necessary to add periodic functionality assessment to evaluate different categories of health status.

The relationship between stress and disease is modulated by several factors. The characteristics of the stressors have been the most widely studied. Although one study (not included in the systematic review) found that psychosocial and occupational stress were linked to a disease worsening (Strengé, 2001), overall the typology and source of stress do not apparently moderate the stress–MS relationship. In contrast, stressor duration, severity, and frequency have consistently been identified as modifying factors.

Chronic stress, defined as exposure to a stressor for more than 48 hours, had a greater effect on MS than acute stress (Ackerman et al., 2002; Brown et al., 2006a, 2006b; Grant et al., 1989; Mei-Tal et al., 1970). However, the studies reviewed often categorized duration differently. For example, for Ackerman et al. (2002), long-term stressors were those lasting at least 15 days, but for Brown et al. (2006a, 2006b), long-term stressors were those lasting

more than 6 months. The effect of chronic stress on MS could be explained by alterations in the stress-response systems of the hypothalamic–pituitary–adrenal axis and autonomic nervous system (for a review, see Gold et al., 2005).

Stressor severity is also important. Intermediate and severe stressors have shown the most consistent associations with disease progression. However, these results seem applicable only to everyday or common stress; in extremely stressing situations, such as war, relapse rate can decrease (Nisipeanu and Korczyn, 1993). The frequency of exposure to stress is also positively associated with disease progression: an increase in the number of stressful events is associated with an increase in the likelihood of relapse. The reason why stressor duration, severity, and frequency consistently modify the effects of stress on MS but source and typology do not is that the former directly determine the amount of stress, whereas the latter depend on personal assessment.

Many studies have also explored the potential modifying role of patients' individual characteristics on the effects of stress on MS. The most important factors identified are anxiety, cardiovascular reactivity, and heart rate, all of which are related to autonomic reactivity. The autonomic nervous system is one of the stress-response systems and could be involved in MS pathogenesis and progression (Gold et al., 2005). Future studies should take biological measures of stress into account, so they can analyze biological correlates of stressful situations. Biofeedback technology has been widely used to reduce stress and anxiety and might help teach people which emotional states cause greater activation of biological stress-response systems. In a recent review, Biondi and Valentini (2014) concluded that biofeedback therapies are able to produce somatic peripheral changes (neuroendocrine and neurovegetative systems).

Another patient factor that has been analyzed is coping style; however, the results for this factor have been contradictory. Whereas Mohr et al. (2002) found modest support for a moderating effect of coping style, Warren et al. (1982, 1991) found no significant differences between MS patients and control group but a tendency to use a more emotion-focused coping style in MS patients experiencing exacerbations compared to patients in remission. Brown et al. (2006b) found that only coping responses using social support had a modifying effect on stress. Other studies (not included in the systematic review) showed limited support for the stress-buffering effects of coping (Pakenham, 1999) and a tendency for people with MS, especially men, to be less likely than the general population to adopt coping styles related to problem-solving and seeking social support (McCabe et al., 2004). More research is needed to elucidate the effects of coping on stress.

Finally, the environmental factors escitalopram intake and social support decrease the effect of stress on MS (Brown et al., 2006b; Mitsonis et al., 2010). Escitalopram reduces the stress-dependent relapse rate in MS patients

(Mitsonis et al., 2010). Escitalopram regulates serotonin reuptake and blunts autonomic reactivity, resulting in lower emotional reactivity to stressful situations (Fabre and Hamon, 2003). The efficacy of escitalopram in reducing the relapse rate in Mitsonis et al. (2010) clinical trial opens new directions for the study of MS. It could be interesting to study whether disease progression is linked to genetic factors related to serotonin transporters due to that serotonergic neurotransmission in MS patients is altered in limbic and paralimbic regions as well as in the frontal cortex (Hesse et al., 2014).

Social support can attenuate responses to stress or threatening situations by reducing neural activity in regions that respond to basic survival threats while increasing activity in regions that process safety signals (Eisenberger, 2013). Other studies in MS patients have found that social support may moderate the impact of negative life events and have a positive effect on quality of life (Costa et al., 2012) and that it is a predictor of perceived health status (Krokavcova et al., 2008).

Although our systematic review showed little evidence for early life stress as a moderating factor, a recent case-control study (Spitzer et al., 2012) found that MS patients had more traumatic experiences in childhood and adolescence than healthy people. Moreover, patients with early life stress showed a higher relapse rate than those without. Early life stress can cause neuroendocrine alterations that remain into adulthood, increasing susceptibility to certain diseases (Panzer, 2008) and increasing the prevalence of severe psychological disorders (Alvarez et al., 2011) that predispose to inadequate coping in stressful situations. More prospective studies are needed to better understand the effect of early life stress in MS.

Our study has both strengths and limitations. To our knowledge, this is the first review of studies analyzing the relationship between stress and MS that takes into account how stress was evaluated and moderators of the stress–MS relationship. Although the first article included in our review dates from 1950, we searched three important databases compiling publications from 1900 to the present in an attempt to summarize all the evidence accumulated since Charcot first described MS in 1877. Moreover, we took into account English and Spanish languages, more comprehensive search than other papers. However, relatively few studies met the inclusion criteria. We did not include stress-intervention or animal studies, although these studies could surely contribute important data about the stress–MS relationship. Almost all the studies took at least one moderating factor into consideration; however, the wide variety of factors considered meant that few studies considered the same factors, precluding strong conclusions about the impact of most moderating and mediating factors. Almost all the studies reviewed were done in women, so despite the higher prevalence of MS in women, the results extracted may not be generalizable to the entire population.

Conclusion

The effect of stress on the onset of MS remains unclear. More prospective studies evaluating stress systematically are needed to better understand this effect. In stress progression studies, instruments and designs based on self-evaluation and subjective measures have shown more consistent results than objective ones or instruments based on standard stressors. This means that patients' subjective appraisal of the stress could be an important predictor of MS relapse and onset. Also, the criteria used to evaluate disease progression are important in the evaluation of results. The greatest amplifying or buffering effects on stress come from factors directly related to the amount of stress and autonomic nervous system reactivity. Future studies should clarify the biological mechanisms involved: combining self-reported measures with biofeedback technology and genetic evaluation can improve our knowledge about the relationships between stress and MS. We also strongly recommend including moderating factors in studies on the effects of stress on MS; this approach can provide information that might be useful for treating patients, since some factors such as anxiety and coping styles are potentially modifiable.

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The authors declare that they have no competing interests.

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