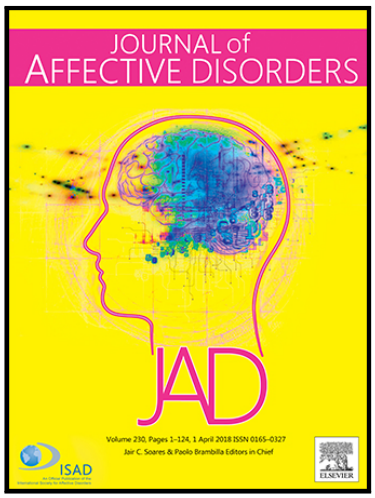

Predictors of Emotional Distress in People with Multiple Sclerosis: A Systematic Review of Prospective Studies

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Highlights

- We conducted the first systematic review of predictors of emotional distress in people with multiple sclerosis (MS)
- The only reliable predictors of emotional distress were baseline emotional distress and stress-coping variables
- Heterogeneity in predictor and outcome variables limits the conclusions that can be drawn
- For psychological treatment efficacy to advance, a better understanding of the psychological processes which underpin and maintain emotional distress in people with multiple sclerosis is needed.

Predictors of Emotional Distress in People with Multiple Sclerosis: A Systematic Review of Prospective Studies

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Abstract

Background: Emotional distress (defined as any negative mood state, including anxiety, depression, trauma symptoms and global distress) is common in people with multiple sclerosis (PwMS). To develop more integrated care for PwMS requires a better understanding of causal variables underlying persistent emotional distress. This systematic review critically appraised and synthesised the findings of prospective studies investigating predictors of emotional distress in PwMS. **Method:** CINAHL, Medline, and PsycINFO, were systematically searched for: i) prospective cohort studies with ≥1-month follow-up period, which; ii) evaluated baseline clinical and demographic, social and/or psychosocial predictors of emotional distress; iii) presented results for adults with MS; and iv) used validated measures to assess emotional distress. Risk of bias was assessed using an adapted version of the Newcastle-Ottawa Scale. **Results:** Thirteen studies, reported in 17 papers, were included. A wide range of outcome measures and statistical methods were used. The most reliable finding was that baseline emotional distress and stress-coping variables predicted emotional distress. Less robust support was found for income, negative cognitive illness appraisals and poor social support. No other variable often predicted emotional distress. **Limitations**: Lack of consistency across included studies may limit confidence in the results obtained. **Conclusions:** Little is currently known about how or why some people become and remain distressed following a diagnosis of MS, whilst others do not. However, psychological and social factors such as emotional distress and stress-coping variables appear to be important. A better understanding of the psychological factors underpinning distress in PwMS is needed.

Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disease estimated to affect approximately 2.5 million people worldwide (Dennison, Moss-Morris, & Chalder, 2009; Multiple Sclerosis Trust, 2020). In MS, multifocal areas of demyelination and axonal loss, believed to be due autoimmune aetiology, lead to an accumulation of damage to the central nervous system (Flachenecker, 2006; Geurts & Barkhof, 2008). MS presents with a range of motor and sensory impairments, cognitive decline, and neurological and neuropsychiatric symptoms (Rosti-Otajarvi & Hamalainen, 2013). The combination of resulting disabilities varies from person to person, depending on the location and severity of MS lesions. Many people with MS (PwMS) experience episodic symptoms or relapses, which only partially resolve, days, weeks, or months following each relapse (Flachenecker, 2006; Lublin & Reingold, 1996).

Emotional distress is more common in PwMS relative to the general population (Feinstein, Roy, Lobaugh, Feinstein, & O'Connor, 2004). Emotional distress in PwMS is commonly experienced as depression and/or anxiety but can also present as trauma symptoms or more global negative affect (Counsell, Hadjistavropoulous, Kehler & Asmundson, 2013). The lifetime prevalance rates for depression are 36% to 54% in PwMS compared to 16% in the general US population, with lifetime prevalence rates of 36% for anxiety disorders in PwMS versus 29% in the general population (Minden et al., 2014). Comparably fewer studies have examined trauma, with point prevalence estimates ranging from 5% to 16% for post-traumatic stress syndrome (Chalfant, Bryant & Fulcher, 2004; Counsell et al., 2013; Ostacoli et al., 2013). Elevated levels of emotional distress are associated with greater disease burden, affecting the quality of life of PwMS (Benito-Leon, Morales, Rivera-Navarro, & Mitchell, 2003; Janardhan & Bakshi, 2002). Furthermore, emotional distress is associated with greater use of healthcare, increased levels of fatigue and has an adverse impact on social interactions (Al-Asmi et al., 2015; Simpson et al., 2019). With at least a third of PwMS experiencing levels of anxiety or depression that are high enough to necessitate clinical intervention (Minden, 2014; Boeschoten et al., 2017), it is imperative that efficacious psychological interventions are available to PwMS. However, few psychological treatment trials for emotional distress in PwMS have been

conducted (Dennison & Moss-Morris, 2010; Ires et al., 2019; Sesel, Sharpe, & Naismith, 2018). Initial treatment evaluations indicate that cognitive behaviour therapy can reduce symptoms of depression when focused on addressing common problems arising in MS (e.g., pain, fatigue, and relationship difficulties; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). However, the magnitude of psychological treatment effects when specifically addressing anxiety and depression are limited, with small effect sizes reported in two meta-analyses (Ires et al., 2019; Sesel, Sharpe, & Naismith, 2018). The limited efficacy of psychological interventions for emotional distress in PwMS is therefore an unmet need requiring practical solutions (McCabe, Ebacioni, Simmons, McDonald, & Melton, 2015; Rieckmann, et al., 2018).

Understanding why some PwMS emotionally adjust to living with the condition, while others experience enduring clinical levels of emotional distress, necessitates more prospective research. In this way potential causal factors may be elucidated. Presently, empirical work in this area is predominantly cross-sectional (Dennison et al., 2009). While cross-sectional studies are essential for developing hypotheses regarding potential causal factors and the prevalence of emotional distress in PwMS, the findings of such studies are limited due to the problem of reverse causality. A previous attempt to synthesise research investigating psychosocial factors involved in the broader concept of adjustment, for the large part, reflected the paucity of prospective research (Dennison et al., 2009). Another previous review examined the potential role of stress in the progression of MS (Artemidis, Anagnostouli, & Alexopoulos, 2011), but none have sought to determine modifiable psychological factors which can alleviate emotional distress in PwMS.

The aim of the present study was to identify factors underlying persistent distress in PwMS, with a primary interest in uncovering modifiable psychological processes which could inform the development of more effective psychological interventions for emotional distress in PwMS. The current review therefore critically appraises and synthesises the findings of prospective studies investigating clinical and demographic, social, and psychological predictors of emotional distress in PwMS.

Method

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The protocol was registered in the PROSPERO database (reg. number CRD42016049031).

Search Strategy

MEDLINE, PsycINFO and CINAHL databases were initially searched from January 1960 to January 2017. These databases were chosen as they span medical, life sciences, psychological, social sciences and allied health literature. Search terms for 'multiple sclerosis' were combined with terms for 'distress' and 'predictor' using Boolean operators (see Table 1). Reference lists of included studies and previous relevant systematic reviews were hand-searched for additional relevant studies. Searches were repeated in January 2020 to identify any new studies of relevance.

[INSERT TABLE 1 HERE]

Eligibility Criteria

Studies were included if they: 1) were peer-reviewed, quantitative, prospective studies which; 2) evaluated demographic and clinical, social and/or psychological predictors of emotional distress; 3) with at least a one-month follow-up period; 4) used published and validated measures to assess emotional distress and; 5) presented results for adults, aged 18 years or over, with MS. No limit was placed on the length of time since being diagnosed with MS. Intervention studies and studies published in languages other than English were excluded. For the purposes of the review, 'emotional distress' was defined as any negative mood state, including, but not limited to, depression, anxiety, trauma symptoms and global distress.

Screening and Selection

Following de-duplication, the titles and abstracts of identified studies were screened against the inclusion criteria. Studies that did not meet the eligibility criteria were excluded. Full-text copies of

potentially relevant papers were obtained and examined for relevance. At both stages, screening was performed by PHR/MGC, with a random sample of fifty percent dual screened by a second reviewer (JR). Disagreements were resolved through discussion, with the views of the wider review team consulted where necessary.

Data Extraction

Sample characteristics, distress measures, predictors, statistical methods and results (including *r* values, beta coefficients or odds ratios and/or percentage variance explained) were extracted by PHR/CH using a standardised data extraction form and tabulated. Data extraction was cross-checked by JR/MGC; disagreements were resolved through discussion. Data from studies reported in multiple publications were extracted and reported as a single study with all relevant publications listed. Where studies reported multiple analyses, only data from the most complex relevant multivariate analyses (i.e. analyses which included the most predictors of emotional distress) were extracted.

Risk of Bias

The methodological quality of the studies were independently assessed and cross-checked by PHR, MGC and JR using a modified version of the Newcastle-Ottawa Scale for cohort studies (NOS; Wells et al., 1999). For the purpose of the review, items relating to control groups were removed, and samples were considered representative where the proportion of each clinical course of MS matched prevalence estimates (i.e., 80-95% RRMS, 5-15% PPMS; Flachenecker, 2006). In line with guidance from the Centre for Reviews and Dissemination (2009), no study was excluded based on the results of the risk of bias assessment; rather, risk of bias was considered when interpreting findings.

Data Synthesis

Predictors of distress were grouped into three broad categories (clinical and demographic, social, and psychological). A narrative rather than a meta-analytic synthesis was undertaken due to considerable variability in predictors, outcome measures and analytical methods. This approach was

adopted in a prior synthesis of clinical and demographic, social, and psychological predictors of distress in cancer patients (Cook et al., 2018).

3 Results

The search identified 1,205 papers after removing duplicates, of which 986 were excluded by title and the remaining 195 by abstract. Twenty-four papers were screened for inclusion by scrutinising the full-text articles. Of these, 15 papers, reporting data from 11 primary studies, met eligibility criteria. Two additional studies (Berzins et al., 2017; Cadden, Arnett, Tyry, & Cook, 2018) were identified via the updated search, resulting in the inclusion of 17 papers, reporting 13 primary studies. Figure 1 outlines the search results and article selection process.

[INSERT FIGURE 1 HERE]

Overview of the Included Studies

Table 2 displays the characteristics of the 13 included studies. Six studies were conducted in Australia, three in the USA, and one each in Canada, Sweden, United Kingdom and Serbia. Mean sample age ranged from 35.9 to 58.3 years; most participants were female. Mean time since diagnosis ranged from 4.7 years to 19.82 years. Ten studies reported the clinical course of MS, of which RRMS was the most prevalent, followed by chronic progressive types (i.e., SPMS/PPMS). Level of disease severity was reported in 12 studies; most participants had mild or moderate MS. Disease severity was determined by self-report measures or by physician reports of the number of symptoms that a person was experiencing (see Table 2).

[INSERT TABLE 2 HERE]

Self-report measures were primarily used to assess clinical and demographic, social, and psychological predictors across the included studies. All emotional distress outcomes were assessed using self-report questionnaires (Table 3). Twelve of the 13 studies assessed depression (Aikens et al., 1997; Berzins et al., 2017; Cadden et al., 2018; Johansson et al., 2016; Kneebone et al., 2015; McCabe, 2005; Pakenham, 1999, 2006, 2007; Pakenham & Cox, 2009; Schiaffino et al., 1998;

Tepavcevic et al., 2013; Weiland et al., 2018; Simpson et al., 2019; Taylor et al., 2018). Three studies assessed anxiety (McCabe, 2005; Pakenham, 2005, 2006, 2007; Pakenham & Cox, 2009), whilst three studies assessed global emotional distress (Johansson et al., 2016; Pakenham, 1999, 2005, 2006; Pakenham & Fleming, 2011). Only one study (Cadden et al., 2018) used a questionnaire (North American Research Committee on Multiple Sclerosis-Depression Scale, NARCOMS-D) designed specifically to assess emotional distress in PwMS.

[INSERT TABLE 3 HERE]

The duration of follow-up ranged from 3 months to 3 years (Table 2). Four studies collected data at three time-points and the remaining studies at two time-points. Attrition rates ranged from 6.59% to 24% over the total duration of prospective data collection (i.e., baseline to final follow-up; Table 2). Eleven studies controlled for significant covariates (e.g., disease variables and demographics) identified through preliminary bivariate analyses. Seven studies controlled for baseline levels of distress in multivariate analyses.

Risk of Bias

Risk of bias is presented in Table 4 for the 13 included studies. Four studies did not adequately describe the clinical characteristics of their samples, whilst seven of the remaining nine studies recruited samples that appeared adequately reflective of an average community sample of PwMS. Seven studies relied on patients self-reporting an MS diagnosis. All studies used either validated measures or subscales of validated measures to assess emotional distress. All except two studies (Pakenham, 2005, 2006; Schiaffino et al., 1998) reported follow-up periods of six months or greater. Most studies (n = 10/12; 83.3%) reported less than 20% attrition over the course of prospective data collection. It should be noted that one study did not report the attrition rate.

Clinical and Demographic Predictors

As shown in Table 5, clinical and demographic predictors of emotional distress were examined in all studies except one (McCabe, 2005).

Age, gender, ethnicity and education level.

There was limited evidence that age, gender, ethnicity or educational level predicted emotional distress. Age only predicted distress in two out of six studies, with younger age predicting more severe anxiety (Pakenham, 2006, 2007) and depression (Pakenham, 2006). Of the six studies which assessed if gender predicted distress, one study (Berzins et al., 2017) found males had a greater probability of being depressed. Ethnicity, assessed in one study, and education level, assessed in three studies, did not predict emotional distress.

Employment status and income.

Three studies considered employment status as predictors of emotional distress (Cadden et al., 2018; Johansson et al., 2016; Pakenham & Fleming, 2011), whilst two studies considered income (Berzins et al., 2017; Schiaffino et al., 1998). Employment status predicted mood in one study (Johansson et al., 2016), whereas income negatively predicted depression in both studies that assessed it (Berzins et al., 2017; Schiaffino et al., 1998), indicating that higher income was associated with lower levels of depression.

Relationship status.

Relationship status was assessed in two studies, reported in three papers, and did not predict global emotional distress (Pakenham, 2005; Pakenham & Fleming, 2011), anxiety (Pakenham, 2006) or depression (Pakenham, 2006).

Negative or stressful life events.

Negative or stressful life events predicted emotional distress in only one of three studies. Specifically, self-reported recent negative life changes predicted depression (Kneebone et al., 2015) but the number of self-reported negative or stressful life events did not predict either depression (Berzins et al., 2017; Pakenham, 1999) or global distress (Pakenham, 1999).

Religious beliefs.

Religious and spiritual beliefs were assessed in one study and did not predict anxiety (Pakenham, 2007; Pakenham & Cox, 2009) or depression (Pakenham, 2007; Pakenham & Cox, 2009).

Other demographic predictors.

One study assessed provision of insurance and found that it did not predict depression (Cadden et al., 2018).

Clinical characteristics.

There was limited evidence that any of the clinical variables assessed in the included studies predicted emotional distress. Physical disability status of MS was evaluated in 10 studies but was predictive of depression and anxiety in only three (Aikens et al., 1997; Kneebone et al., 2015; Pakenham, 2007). Cognitive functioning was examined in three studies, but did not predict depression (Aikens et al., 1997; Johansson et al., 2016), mood (Johansson et al., 2016) or global emotional distress (Pakenham & Fleming, 2011). Time since diagnosis or symptom onset was examined in two studies, but was not predictive of global emotional distress (Pakenham, 2005), anxiety (Pakenham, 2006, 2007; Pakenham & Cox, 2009) or depression (Pakenham, 2006, 2007; Pakenham & Cox, 2009). Poor sleep and fatigue levels were examined in three studies but were predictive of depression in only one (Berzins et al., 2017). Neither of the two studies examining MS type/course found it to predict either depression (Cadden et al., 2018) or global emotional distress (Pakenham, 2005).

Single studies examined different additional clinical characteristics. The perceived physical and psychological impact of MS on health predicted mood (Johansson et al., 2016), and severity of MS symptoms predicted global distress, anxiety and depression (Pakenham, 2005, 2006). Time since exacerbation of MS predicted depression (Kneebone et al., 2015). Overall physical health status did not predict depression (Tepavcevic et al., 2013), nor did recent relapse (i.e. relapse within the preceding six months; Cadden et al., 2018) or disease modifying therapy (Cadden et al., 2018). Neither smoking nor degree of physical exercise predicted depression (Cadden et al., 2018). Perception of general health status did not predict depression (Pakenham, 1999).

Social Predictors

Three studies broadly considered social and lifestyle predictors of emotional distress (Johansson et al., 2016; Pakenham, 1999; Tepavcevic et al., 2013). Of these, two found significant results; higher levels of social support and engagement in leisure and lifestyle activities predicted lower levels of depression (Pakenham, 1999) whilst lower social activity quality of life predicted greater depression (Tepavcevic et al., 2013).

Psychological Predictors

Baseline emotional distress.

Seven of the 13 studies examined whether baseline emotional distress predicted emotional distress at follow-up. With the exception of one study, which did not report whether baseline emotional distress was predictive of later distress (Cadden et al., 2018), all studies reported significant findings (McCabe, 2005; Pakenham, 1999, 2007; Pakenham & Cox, 2009; Pakenham & Fleming, 2011; Tepavcevic et al., 2013), with higher levels of emotional distress at baseline predictive of subsequent emotional distress.

Stress and coping.

Both studies testing stress levels or appraisals found stress to predict emotional distress (Aikens et al., 1997; Pakenham, 2005, 2006). Specifically, higher MS-related stress predicted higher levels of depression, anxiety and global emotional distress (Pakenham, 2005, 2006), whilst general life stress predicted depression (Aikens et al., 1997). Furthermore, five of the six studies that tested the effects of coping on distress found coping style to be a significant predictor of emotional distress (Aikens et al., 1997; Berzins et al., 2017; Johansson et al., 2016; Pakenham, 1999, 2006). Emotion-focused and avoidant coping styles, which broadly refer to a tendency to suppress or avoid unpleasant emotions, predicted higher general distress, anxiety and depression (Aikens et al., 1997; Berzins et al., 2017; Pakenham, 1999, 2006), whilst acceptance coping styles, in which an individual shows a willingness to accept unpleasant internal experiences, predicted lower levels of anxiety and depression (Pakenham, 2006). Finally, a weak coping capacity (poor ability to identify internal and external resources to overcome a stressor) predicted depression (Johansson et al., 2016).

Negative cognitive illness appraisals.

Negative cognitive illness appraisals predicted emotional distress in two out of three studies (Pakenham, 2007; Schiaffino et al., 1998). Appraisals of high illness variability (i.e. the controllability and changeability of MS over time) predicted higher levels of depression (Schiaffino et al., 1998), whilst sense-making appraisals, such as redefining life purpose (e.g., "I have new life goals because of my MS"), predicted lower depression and anxiety (Pakenham, 2007). However, Pakenham (1999) found threat, challenge and controllability illness appraisals (i.e. appraising MS as something threatening, uncontrollable and which limits opportunities for personal growth) not to predict global distress or depression.

Dispositional hope and benefit-finding.

The two studies measuring dispositional hope and benefit-finding reported contradictory findings. Pakenham (2005) found dispositional hope and benefit-finding did not predict global distress, whilst Pakenham and Cox (2009) found benefit-finding in the form of higher lifestyle gains (e.g. learning more about healthy lifestyles) predicted lower levels of anxiety and depression.

Self-efficacy and attributional style.

The single study that assessed attributional styles (Kneebone et al., 2015) found both global and stable attributions predicted depression after separately controlling for the effect of negative recent life events and time since exacerbation of MS symptoms. Furthermore, an interaction between a history of negative life events and a greater tendency to make global attributions (i.e., adversely influences other areas of life) was predictive of higher subsequent depression after controlling for the effects of recent negative life events. Self-efficacy was assessed in one study (Berzins et al., 2017) and was not directly predictive of depression, although an interaction between self-efficacy and sex was.

Additional psychological variables.

Lower self-esteem predicted depression in one study out of two (Berzins et al., 2017; McCabe, 2005). Increased perceived stigma predicted depression (Cadden et al., 2018), but psychological reserve, defined as feelings of belonging, social support and sense of control, did not predict lower levels of depression (Cadden et al., 2018).

Discussion

This review critically appraised and synthesised prospective research investigating demographic and clinical, social, and psychological predictors of emotional distress in PwMS. Thirteen studies, reported in 17 papers, were included in the review. Overall, baseline levels of emotional distress and stress-coping variables were the most frequently assessed variables and consistently predicted subsequent emotional distress. These findings are in keeping with other literature (Cook, Salmon, Hayes, Byrne, & Fisher, 2018; Dennison et al., 2009) and indicate that, for many PwMS, emotional distress is a persistent problem which may result, in part, from cognitive illness appraisals, coping strategies/responses and coping resources (Lazarus & Folkman, 1984; Leventhal et al., 1997; Leventhal, Nerenz, & Steel, 1984). This finding lends credence to the importance of routinely assessing for emotional distress at an early stage, and offering appropriate intervention, as recommended by clinical guidance, to PwMS experiencing emotional distress (National Institute for Health and Care Excellence, 2014).

Poor social support and employment status/income were assessed less frequently. Income negatively predicted depression in both studies that considered it as a predictor. Gallo and Matthews (2003) argue that low socio-economic environments reduce the capacity of individuals with physical health problems to manage stress, thereby increasing vulnerability to negative emotions and cognitions. The relationship between socio-economic factors and emotional distress – and the potential mediating role of cognitive-emotional factors and social support - is something that would benefit from further research.

There was little evidence that any other demographic, clinical, social or psychological variable predicted emotional distress. In particular, disease severity was assessed in 11 studies but only

predicted anxiety and depression in three. This is consistent with the findings of a systematic review of predictors of emotional distress in cancer (Cook et al., 2018) and supports the notion that emotional distress is more closely linked to psychological processes which may influence perception of, or ways of coping with, specific clinical difficulties, rather than clinical factors themselves. However, although a range of psychological processes were investigated, most were considered in very few studies, making it difficult to draw conclusions about their predictive value. Single studies suggest a role for stigma, benefit-finding, attributional style, self-esteem and self-efficacy, although confidence in these findings is limited. For treatment efficacy to advance, a better understanding of the psychological processes which underpin and maintain emotional distress is needed.

Limitations of the Review

The review focused exclusively on prospective designs, meaning that only 13 studies were included in the final synthesis of evidence. However, we do not see this as a limitation as it highlights the need to conduct further prospective studies. Although a comprehensive search strategy was used, it is feasible that relevant studies were not included especially given the bias towards publishing studies with significant findings. There was considerable variation in the methodology across the studies, such as the range and nature of the covariates controlled for, the reliability and validity the measures assessing the predictors, the duration of prospective data collection and rates of attrition. Furthermore, we chose not to focus the review solely on depression and anxiety, but rather to consider emotional distress more broadly, as is reflective of the range of difficulties experienced by PwMS. Although this is a strength of the review, the breadth in outcomes and outcome measures limit our ability to draw nuanced conclusions about risk factors for specific types of emotional distress. Although conclusions drawn from multiple studies can be robust, conclusions about variables investigated in a small number of studies cannot be viewed so confidently, particularly given the range of outcomes studied. Furthermore, most studies used hierarchical regression to establish incremental changes in distress prospectively, whilst controlling for demographic and clinical covariates. This approach is vulnerable to higher false positive rates since it does not account for measurement error (Westfall & Yarkoni, 2016). Moreover, some studies (for example, Aikens et al.,

1997) had small sample sizes, which means that some of the inconsistencies observed across studies may be actually reflective of lack of power (i.e. Type II errors produce the superficial appearance of contradicting studies with larger samples which report positive findings). It will be necessary for future prospective studies to use more sophisticated designs with appropriate statistical modelling strategies (Cook et al., 2015) to provide greater clarity on clinical, psychological and sociodemographic factors involved in the maintenance of emotional distress.

Conclusion

The paucity of studies assessing predictors of distress in PwMS means that little is currently known about how or why some people become and remain distressed following a diagnosis of MS, whilst others do not. However, psychological and social variables such as baseline emotional distress and stress-coping variables, and to a lesser extent negative cognitive illness appraisals, poor social support and income, appear to be important. There was little evidence that any other demographic, clinical, social or psychological variable predicted emotional distress. There are many emerging psychological models of distress yet to be tested in propsective designs in PwMS (e.g relational frame theory; Hayes, Barnes-Holems, & Roche 2001, or the metacognitive model; Wells & Matthews, 1996). Overall the results highlight the importance of developing a better comprehension of the psychological factors underpinning distress in PwMS and ensure that assessment and interventions for emotional distress continues.

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Author Contributions: PF conceptualised the study. PHR conducted the review and drafted the initial draft of the paper. JR and CH cross-checked screening, quality assessment and data extraction. MGC revised the manuscript and contributed to analysis. PF and PS provided detailed feedback on iterations of the manuscript. All authors take responsibility for the integrity of the data analysis.

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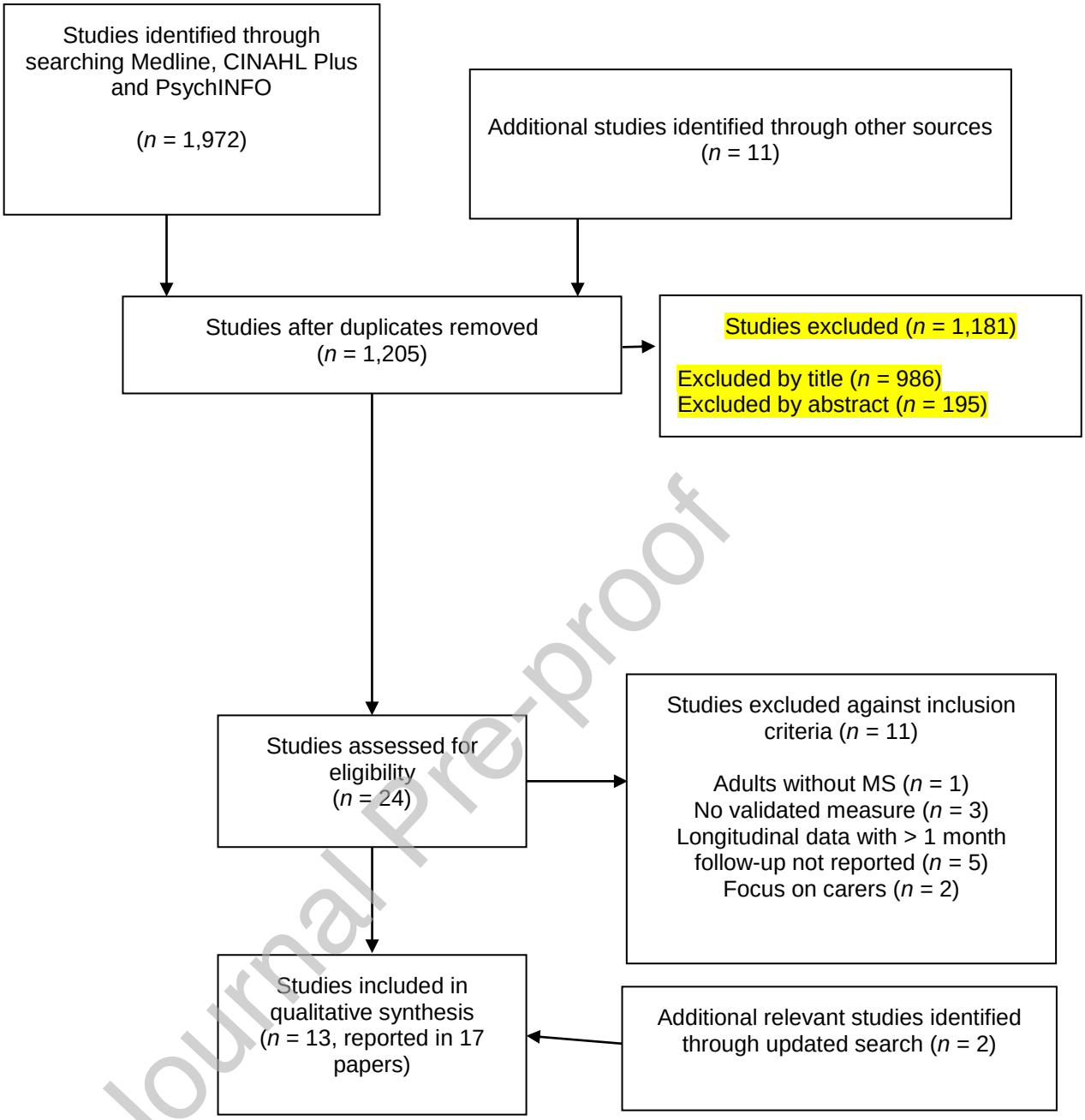

Figure 1. Flow of studies through the review

Table 1: Search Terms Used

Boolean Operator	***Search Terms***	***Search Fields***
	multiple sclerosis OR demyelinating disease OR disseminated sclerosis OR encephalomyelitis disseminata	All fields
AND	emotional distress OR psychological distress OR anxiety OR depress* OR posttraumatic stress OR PTSD OR psychological morbidity OR psych*, adjustment OR emotional adjustment OR mood OR adjustment disorder OR acute stress disorder OR fear of relapse	All fields
AND	predict* OR risk factors OR caus* OR vulnerability	All fields
NOT	childhood multiple sclerosis OR adolescent multiple sclerosis OR palliative OR paed*carers	Abstract
NOT	genetic testing OR genetic screening	Title
NOT	advanced multiple sclerosis OR survival OR mortality	Title

Table 2. Study and participant characteristics

First author and year	Demographics	Sample % disease course	Time since diagnosis (years)	Disability	Duration of follow-up (months)	Sample Size	Attrition (%)	Country
Aikens 1997	60% female $\bar{x}$ age (years) =35.9 (SD = 6.2)	Not reported	$\bar{x}$ = 4.7 (SD = 3.7)	$\bar{x}$ EDSS = 2.2 (mild), SD = 1.4	T2 = 6 T3 = 12	T1 = 27 T2 = 22 T3 = 22	18.52	USA
Berzins 2017	75.5% female $\bar{x}$ age (years) =52.9 (SD = not reported)[a]	Not reported	$\bar{x}$ = 14.6 (SD = not reported)[a]	Not reported	T2 = 6	T1 = 182 T2 = 170	6.59	Canada
Cadden 2018	78.4% female $\bar{x}$ age (years) =58.27 (SD = 10.19)	55.7% RRMS 32.2% PPMS 12.1% unknown	$\bar{x}$ = 19.82 (SD = 9.69)	$\bar{x}$ PDDS = 3.6 (moderate), SD = 2.4	T2 = 12	5369[b]	Not reported	USA
Johansson 2016	68% female 51% <47 years	61% RRMS 39%	$\bar{x}$ = 14 (SD = 10)	EDSS 63% mild	T2 = 12 T3 = 24	199[c]	Not reported	Sweden

First author and year	Demographics	Sample % disease course	Time since diagnosis (years)	Disability	Duration of follow-up (months)	Sample Size	Attrition (%)	Country
		PPMS or SPMS		17.5% moderate 19.5% severe				
Kneebone 2015	81% female $\bar{x}$ age (years) = 45.8 (SD = 9.25)	45% RRMS 32.5% PPMS 18% Unknown	$\bar{x}$ =7 (SD = not reported)	Not reported	T2 = 12 T3 = 24	T1 = 495 T2 = 396 T3 = 386	22.02	United Kingdom
McCabe 2005	67% female $\bar{x}$ age (years) = 45.27 (males); 44.86 (females; SD not reported for either group)	Not reported	Not reported	Not reported	T2 = 6 T3 = 18	T1 = NR T2 = NR T3 = 243	Not reported	Australia
Pakenha	78% female	50%=RRMS	$\bar{x}$ =16	$\bar{x}$ EDSS=5.	T2 = 12	T1 = 122	21.31	Australia

First author and year	Demographics	Sample % disease course	Time since diagnosis (years)	Disability	Duration of follow-up (months)	Sample Size	Attrition (%)	Country
m 1999	$\bar{x}$ age = 48.66 (SD = 11.32)	50%=CPMS	(SD = 10.79)	15 (moderate), SD=1.98		T2 = 96		
Pakenham 2005, 2006	77% female $\bar{x}$ age (years) = 47.77 (SD = 11.48)	73% RRMS 27% CPMS	$\bar{x}$= 9.78 (SD = 8.2)	$\bar{x}$ number of self-reported symptoms =2.62, SD=1.94	T2 = 3	T1 = 477 T2 = 404	15.3	Australia
Pakenham 2007, 2009	81% female $\bar{x}$ age (years) = 49.33 (SD=11.31)	67% RRMS 33% CPMS	$\bar{x}$ =10.56 (SD = 8.32)	$\bar{x}$ number of self-reported symptoms =3.93, SD=2.45	T2 = 12	T1 = 388 T2 = 296	23.71	Australia
Pakenham 2011	84% female $\bar{x}$ age (years) = 43 (SD = 6.5)	Not reported	$\bar{x}$ =7.67 (SD = 5.75)	$\bar{x}$ ADL =4.12, SD=0.8	T2 = 12	T1 = 145 T2 = 128	11.72	Australia
Schiaffino 1998	90% female $\bar{x}$ age	Not reported	Not reported	$\bar{x}$ AIMS = 2.63,	T2 = 4	66[d]	Not reporte	USA

First author and year	Demographics	Sample % disease course	Time since diagnosis (years)	Disability	Duration of follow-up (months)	Sample Size	Attrition (%)	Country
	(years) = 42 (SD = 12)			SD=2.61			d	
Tepavcevic 2013	72% female $\bar{x}$ age (years) = 41.6 (SD = 8.6)	69.1% RRMS 5.1% PPMS 25.8% SPMS	$\bar{x}$ = 9.3 (SD = 6.5)	$\bar{x}$ EDSS=4.4 (moderate), SD=1.6	T2 = 36	T1 = 109 T2 = 97	11.01	Serbia
Weiland 2018 Taylor 2018 Simpson 2019	83% female $\bar{x}$ age (years) = 45.9 (SD = 10.5)	63.3% RRMS 7.2% PPMS 10.4% SPMS 1.3% PRMS	$\bar{x}$ =5.4 (25-75th percentile= 2.4 – 11.4)	PDDS: 'mild' = 56.2%, 'moderate' = 31.6%, 'Severe' = 8.4%	T2 = 30	T1 = 2466 T2 = 1403	43.11	International (Australasia, Europe, North America)

Note. ADL = Activities of Daily Living Self-care Scale; AIMS = Physician rated measure of functional health status CPMS = Chronic Progressive MS; EDSS = Expanded Disability Status Scale; PDDS = Patient Determined Disease Steps; PPMS = Primary Progressive MS; PRMS = Progressive Relapse Remitting MS; RRMS = Relapse Remitting MS; SD = Standard Deviation; SPMS = Secondary Progressive MS; T# = Time point; [a] based on sample of 188; [b] analyses conducted on 5369 who completed measures at T1 and T2; [c] analyses conducted on 199 who completed Beck Depression Inventory at least one time point; [d] analyses conducted on 66 who completed measures at both time points. EDSS severity based on description provided by the included studies.

Table 3. Measurement of dependent variables in included studies

Dependent Variable	**Measure**	**Used by**	**Mean score (SD, range)**
Anxiety	POM-SF anxiety/tension subscale	McCabe (2005)	MNE: 13.38 (6.04; NR); FNE: 11.42 (4.81; NR); MWE: 11.97 (4.21; NR); FWE: 14.83 (6.89; NR)
	SCL-90 anxiety subscale	Pakenham (2006) Pakenham (2007, 2009)	5.60 (5.05; 0-24) NR
Depression	BDI	Aikens (1997) Johansson (2016) Pakenham (1999)	9.1 (7.4; 0-28) NR 6.67 (5.28; NR)
	CES-D	Kneebone (2015) Schiaffino (1998)	22.1 (12.56; 0-59) 16.19 (11.67; NR)
	HRSD	Tepavcevic (2013)	12.2 (5.4; 3–33)
	NARCOMS-D	Cadden (2018)	1.16 (1.16; NR)
	PHQ-2	Weiland (2018) Simpson (2019) Taylor (2018)	NR[b] NR[c] NR[b]
	PHQ-9	Berzins (2017) Weiland (2018) Simpson (2019) Taylor (2018)	NR NR[b] NR[c] NR[b]
	POM-SF depression subscale	McCabe (2005)	MNE: 16.34 (8.36; NR); FNE: 13.68 (6.28; NR); MWE: 14.11 (5.60; NR); FWE: 17.36 (9.13; NR)

	SCL-90 depression subscale	Pakenham (2006) Pakenham (2007, 2009)	5.72 (5.73; 0-24) NR
Global distress	DASS-21	Pakenham (2011)	NR
	BSI[a]	Pakenham (1999) Pakenham (2005)	27.34 (22.13; NR) 13.84 (12.32; NR)
Mood	BDI – mood subscale	Johanssen (2016)	NR

[a] two somatization items excluded; [b] scores collapsed into bands; [c] prevalence of 'positive screening' reported; BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; CES-D = Centre for Epidemiologic Studies – Depression scale; DASS-21 = Depression, Anxiety and Stress Scale – 21; FNE = Females with no exacerbation of MS; FWE = Females with exacerbation of MS; HRDS = Hamilton Rating Scale for Depression; MNE = Males with no exacerbation of MS; MWE = Males with exacerbation of MS; NARCOMS-D = North American Research Committee on Multiple clerosis – Depression scale; NR = not reported; PHQ-9 = Patient Health Questionnaire – 9; POMS-SF = Profile of Mood States – Short Form; SCL-90 = Symptom Checklist – 90

Table 4. Risk of bias using adapted Newcastle-Ottawa Scale

Study	**Selection**		**Outcome**		
	Representative cohort?	**Ascertainment of exposure?**	**Adequate assessment of outcome?**	**Adequate length of follow-up?**	**Adequacy of follow-up?**
Aikens 1997	Not reported	Yes – assessed by clinician	Yes – validated measure of distress	Yes – 12 months	Yes – description of those lost
Berzins 2017	Not reported	Yes – participants recruited from MS clinic	Yes – validated measure of distress	Yes – 6 months	Yes – description of those lost; proportion small
Cadden 2018	Yes – majority relapse-remitting MS	No – self-report	Partially – validated measure of distress but only single item	Yes – 12 months	Yes – description of those lost; proportion small
Johansson 2016	Yes – majority relapse-remitting MS	Yes – assessed by clinician	Yes – validated measure of distress	Yes – 24 months	Yes – description of those lost; proportion small
Kneebone 2015	Partially – just under half with relapse-remitting MS but missing data	No – self-report	Yes – validated measure of distress	Yes – 24 months	Yes – description of those lost; proportion small
McCabe 2005	No – participants experiencing an exacerbation excluded	No – self-report	Partially – subscales of validated measure of distress used	Yes – 18 months	Yes – description of those lost; proportion small
Pakenham 1999	Yes – half with relapse-	Yes – structured interview	Yes – validated measure of	Yes – 12 months	Yes – description of

	remitting MS		distress		those lost; proportion small
Pakenham 2005, 2006	Yes – majority relapse-remitting MS	No – self-report	Yes – validated measure of distress	No – 3 months	Yes – description of those lost; proportion small
Pakenham 2007, 2009	Yes – majority relapse-remitting MS	No – self-report	Partially – non-MS related items from validated measure of distress used	Yes – 12 months	Partially – description of those lost; proportion moderate (27%)
Pakenham 2011	Not reported	No – self-report	Yes – validated measure of distress	Yes – 12 months	Yes – description of those lost; proportion small
Schiaffino 1998	Not reported	Yes – assessed by clinician	Yes – validated measure of distress	No – 4 months	Not reported
Tepavceik 2013	No – participants experiencing relapse within last month excluded	Yes – assessed by clinician	Yes – validated measure of distress	Yes - 36 months	Yes – description of those lost; proportion small
Weiland 2018 Taylor 2018 Simpson 2019	Yes – majority relapse-remitting MS	No – self-report	Yes – validated measure of distress	Yes – 30 months	Partially – description of those lost; proportion high (43%)

Table 5. Summary of study design and significant findings from included papers, grouped by dependent variable

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
	DV - Caseness							

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Berzins 2017	6	Depression	No	Cox proportional hazard models	Sex; Income; Sleep disturbance; Fatigue impact (NR); Negative life events (NR); Physical disability status of MS (EDSS).	None	Coping (CISS); Self-efficacy (NR); Self-esteem (NR).	DV: Depression, PHQ-9 ≥ 10 *Psychosocial*: High emotion-focused coping (HR = 2.7); low self-esteem (HR = 5.6). *Non-psychosocial*: Sex/male (HR = 2.8); Fatigue (HR = 8.7); Problems staying asleep (HR = 2.9); low mobility (HR = 4.0); Income (HR = 0.2). *Interactions*: Low self-efficacy x sex (HR = 0.1); Emotion-coping x life events (HR =

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Johansson 2016	24	Depression Mood	No	Binary logistic regression	Sex, age, working status; Physical disability status of MS (EDSS); Fatigue (FSS); Cognitive function (SDMT); Physical impact of MS (MSIS-P).	Social activities (FAI).	Coping capacity (SOC); perceived psychological impact of MS (MSIS-Psy).	DV: Depression, BDI ≥ 13 *Psychosocial*: Coping capacity (OR = 4.90); perceived psychological impact of MS x time (OR = 3.89 to 5.78). *Non-psychosocial*: Working status (OR = 2.50) DV: Mood (subset of 6 BDI items) ≥ 5 *Psychosocial*: Coping capacity (OR = 5.81); perceived psychological impact of MS x time (OR = 3.79 to 6.37).

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings ($p < .05$)**
Taylor 2018	30	Depression	No	Log-multi-nominal regression	Smoking tobacco; Alcohol intake; Alcohol load; DHQ (99-100); Meat consumption; Dairy consumption; Vitamin D consumption; Omega-3 consumption; IPAQ (High); Mediates (weekly).	None.	None	<u>DV: Depression, PHQ-2 > 2</u> Non-psychosocial: Current smoker of tobacco (Adj. PR = 1.63); DHQ (Adj. PR = 0.50); Vitamin D consumption (PR = 0.61); IPAQ (PR= 0.49). <u>DV: Depression, PHQ-9 > 9</u> Non-psychosocial: Current smoker of tobacco (PR = 1.96); DHQ (PR = 0.36); Meat consumption (PR = 1.41);

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings ($p < .05$)**
Simpson 2019 [Same study as Taylor 2018]	30	Depression	No	Log-multi-nominal regression	*Demographic predictors*: Age; Married; Number of people in support network (0, 1, 2-5, > 5); Employment; Level of education; Perceived socio-economic status relative to peers; *Clinical predictors*: Weight (BMI > 30); Number of comorbidities at baseline; Taking prescription ADM at baseline; Type of MS at baseline; Number of doctor-diagnosed relapses in past 12 months; P-MSSS > 6;	None.	None	DV: Depression, PHQ-2 > 2 (demographic predictors) Married (Y, Adj. RR = 0.62); Number of people in support network (2-5, Adj. RR = 0.45, > 5 Adj. RR = 0.42); Perceived socio-economic status (lower, Adj. RR = 1.61) relative to peers. DV: Depression, PHQ-2 > 2 (clinical predictors) Taking prescription ADM at

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings ($p < .05$)**
	DV - Continuous							

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Aikens 1997	12	Depression	No	Linear regression	Physical disability status of MS (EDSS); Cognitive status (QMSE); Negative life stress (LES).	None	Coping style (WOCQ-R).	<u>DV: Depression (BDI) at 6 months (all Time 1/Time 1 predictors)</u> *Psychosocial*: Negative life stress (β = .53). *Non-psychosocial*: Physical disability status of MS (β = .44). <u>DV: Depression (BDI) at 12 months (all 6 month/Time 2 predictors)</u> *Psychosocial*: Negative life stress (β = .54); Coping style – escape-avoidance (β = .64).

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Cadden 2018	12	Depression	Yes	Linear regression	Age, sex, ethnicity, education, employment status, smoking status, physical activity, recent relapse, insurance, MS type, disease modifying therapy (DMT); Level of disability (PDDS).	None	Stigma (MS-S); Psychological reserves (idiosyncratic scale).	DV: Depression (NARCOM S-D; controlling for Time 1 depression) Stigma (β = NR); other variables NR.

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Kneebone 2015	24	Depression	No	Linear regression	Disability (FASQ-R); Time since MS exacerbation (TSE; model 1 only); Recent negative life changes (RLCQ; model 2 only)	None	Stability of attributional style for negative events (STAB); Globality of attributional style for negative events, (GLOB)	Model 1: DV: Depression (CES-D) *Psychosocial*: Globality (β = .23); Stability (β = .14). *Non-psychosocial*: Disability (β = -.24); Time since exacerbation (β = -.87). Model 2: DV: Depression (CES-D) *Psychosocial*: Globality (β = .20); Stability (β = .15). *Non-psychosocial*: Disability (β = -.26); Recent negative life

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
McCabe 2005	18	Anxiety/tension, Depression	Yes	Linear regression	None	None	Global distress (POMS-SF); Self-esteem (WHOQOL-100-SE); Coping style (WOCQ).	<u>DV: POMS-SF-Anxiety/Tension subscale</u> *Psychosocial*: Time 1 Anxiety/Tension (β = NR). *Non-psychosocial*: None. <u>DV: POMS-SF-Depression subscale</u> *Psychosocial*: Time 1 Depression (β = NR). *Non-psychosocial*: None.

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Pakenham 1999	12	Global distress, Depression	Yes	Linear regression	Age, duration of illness; Stressful life events (SRRS); Illness severity of MS (EDSS); Physical disability (SIP-P)	Social support (SSS).	Global distress (BSI; model 1 only); depression (BDI; model 2 only); Appraisals (TCC); Coping style (WCC).	<u>Model 1: DV: Global Distress (BSI)</u> *Psychosocial*: Time 1 BSI (β = .69); Coping – emotion-focused (β = .23). *Non-psychosocial*: None. <u>Model 2: DV: Depression (BDI)</u> *Psychosocial*: Time 1 BDI (β = .64); Coping – emotion-focused (β = .28). *Non-psychosocial*: SSS (β = -.18).

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Pakenham 2005	3	Global distress	No	Linear regression	Marital status; Age; Time since symptom onset; Course; Number of symptoms; Number of problems	None	Benefit finding (BFS); Stress appraisal (idiosyncratic)	DV: Global Distress (BSI-18) *Psychosocial*: Stress appraisal (β = .44). *Non-psychosocial*: Illness – number of symptoms (β = .25); Illness – number of problems (β = .19). *Interactions*: Stress appraisal x Benefit finding - family relations growth (β = -.15).

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Pakenham 2006 [Same study as Pakenham 2005]	3	Anxiety Depression	No	Linear regression	Marital status; Age; Gender; Time since diagnosis; Course; Number of symptoms; Number of problems	None	Appraisal of stress (idiosyncratic); Coping with MS (CMSS)	DV: Anxiety (SCL-90-Anxiety subscale[a]) *Psychosocial*: Appraisal of stress (β = .30); Coping – avoidance (β = .14); Coping – acceptance (β = -.13). *Non-psychosocial*: Age (β = -.14); Course (β = -.12); Number of problems (β = .20); Number of symptoms (β = .16). DV: Depression (SCL-90-Depression subscale[a]) *Psychosocial*: Appraisal of stress (β

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Pakenham 2007	12	Anxiety Depression	Yes	Linear regression	Age; Religious-spiritual beliefs; Time since diagnosis; Symptoms experienced; Time 2 disability and self-care (ADL).	None.	Anxiety (SCL-90; model 1 only)[b]; Depression (SCL-90; model 2 only)[b]; Sense making (SMS).	<u>Model 1: DV: Anxiety (SCL-90-Anxiety subscale[b])</u> *Psychosocial*: Time 1 anxiety (β = .61); Sense making – changed values and priorities (β = .18); acceptance (β = -.27). *Non-psychosocial*: Age (β = -.16); Time 2 self-care (β = -.17). <u>Model 2: DV: Depression (SCL-90-Depression subscale[b])</u> *Psychosoci*

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
								al: Time 1 depression (β = .66); Sense making – redefined life purpose (β = -.25); Sense making – changed values and priorities (β = .11); acceptance (β = -14). *Non-psychosocial*: Time 2 self-care (β = -.14).

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Pakenham 2009 [Same study as Pakenham 2007]	12	Anxiety Depression	Yes	Linear Regression	Age; Religious-spiritual belief; Time since diagnosis; Time 2 social desirability (MCSDS)	None.	Anxiety (SCL-90; model 1 only)[b]; Depression (SCL-90; model 2 only)[b]; Benefit finding (BFI)	Model 1: DV: Anxiety (SCL-90-Anxiety subscale[b]) *Psychosocial*: Time 1 anxiety (β = .62); benefit finding – lifestyle gains (β = -.19). *Non-psychosocial*: Time 2 social desirability (β = -.13). Model 2: DV: Depression (SCL-90-Depression subscale[b]) *Psychosocial*: Time 1 Depression (β = .66); benefit finding – lifestyle gains (β = -.18). *Non-*

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Pakenham 2011	12	Global distress	Yes	Linear regression	Employment; Marital status; Gender; Disability (ADL); Cognitive impairment (MPAI).	None .	Time 1 global distress (DASS); Acceptance – action, willingness (MSAQ).	DV: Distress (DASS-21) *Psychosocial*: Time 1 distress (β = .66); Acceptance – action (β = -.23). *Non-psychosocial*: none.

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Schiaffino 1998	4	Depression	Yes	Linear regression	Age, education, income, illness severity (AIMS),	None.	Depression (CES-D); illness representations (IMIQ).	DV: Depression (CES-D) *Psychosocial*: Time 1 depression (β = .65 to .66); Illness representation (β =.25; only variability significant). *Non-psychosocial*: Income (β = -.34 to -.35). *Interaction*: severity x illness representation (β = .NR).

					Multivariate Predictors			
First author and year	**Longest follow-up period (months)**	**DV**	**DV at T1 controlled**	**Analysis**	**Demographic and Clinical**	**Social**	**Psychological**	**Significant findings (p < .05)**
Tepavcevic 2013	36	Depression	Yes	Linear regression	Age; Gender; Fatigue (FSS); Disability severity (EDSS)	Social functioning (social functioning scale of MSQoL; model 2 only).	Depression (HRSD); Mental health – composite score (MHC of MSQoL; model 1 only).	<u>Model 1: DV: Depression (HRSD)</u> *Psychosocial*: Time 1 depression (β = -.40); Mental health composite score (β = .19). *Non-psychosocial*: Disability severity (β = .40). <u>Model 2: DV: Depression (HRSD)</u> *Psychosocial*: Time 1 depression (β = -.44); social functioning (β = -.23). *Non-psychosocial*: Disability severity (β = .38).

Notes. Adj. = Adjusted; ADL = Activities of Daily Living Self-care Scale; ADM=Antidepressant Medication; AIMS = physician rated measure to assess functional health status; = ;; BDI = Beck Depression Inventory; BFS = Benefit Finding Scale; BMI= Body Mass Index; BSI = Brief Symptom Inventory; BSI-18 = Brief Symptom Inventory-18; CES-D = Centre for Epidemiologic Studies-Depression Scale; CISS = Coping in Stressful Situations Scale; CMSS = Coping with Multiple Sclerosis Scale; DASS =Depression Anxiety and Stress Scale; DASS-21=Depression Anxiety Scale-21; DHQ = Diet History Questionnaire; EDSS = Expanded Disability Status Scale; FAI = Frenchay Activities Index; FASQ-R = Functional Assessment Screening Questionnaire – Revised; FSS = Fatigue Severity Scale; GLOB = Globality of attributions for negative events; HRSD = Hamilton Rating Scale for Depression; HR = Hazard Ratio (scores < 1 are protective factors, scores > 2 are risk factors); IMIQ=Implicit Models of Illness Questionnaire; IPAQ = International Physical Activity Questionnaire; LES = Life Experiences Survey; MASQ = Mood and Anxiety Symptoms Questionnaire; MCSDS = Marlowe-Crown Social Desirability Scale; MPAI-C = Mayo-Portland Adaptability Inventory – Cognition subscale; MSIS = Multiple Sclerosis Impact Scale; MSIS-P = MSIS-Physical subscale; MSIS-Psy = MSIS Psychological subscale; MS = Multiple Sclerosis; MSQoL=Multiple Sclerosis Quality of Life: MSQoL-MHC= Multiple Sclerosis Quality of Life-Mental Health Component; NARCOMS-D = North American Research Committee on Multiple Sclerosis – Depression scale; NR = Not Reported; OR = Odds Ratio; PAIS-SR = Psychosocial Adjustment to Illness Scale – Self-Report; PDDS = Patient Determined Disease Steps; P-MSS=Performance MS Scale;; PHQ-2 = Patient Health Questionnaire – 2; PHQ-9 = Patient Health Questionnaire – 9; POMS-SF = Profile of Mood States–Short Form; PR = Prevalence Ratio;QMSE = Quantitative Mental Status Exam; RLCQ = Recent Life Changes Questionnaire; RR = Risk Ratio; SCL-90 = Symptom Checklist – 90 (a = 6 items from depression and anxiety subscales – does not specify which items, b = 4 items from depression and anxiety scale – does not specify which); SDMT = Single Digit Modalities Test; SHS = Subjective Health Status; SLS = Satisfaction with Life Scale; SMS = Sense Making Scale; SOC = Sense of Coherence Scale; SIP-P = Sickness Impact Profile – Physical dimension; SPMS=Secondary Progressive Multiple Sclerosis; SRRS = Social Readjustment Rating Scale; SSS = Social Support Scale; STAB = Stability of attributions for negative events; TCC = Threat, Challenge, Controllability Scale; TSE; Time since MS exacerbation; WCC = Ways of Coping Checklist; WHOQOL-100-SE = World Health Organisation Quality of Life-100Self-esteem subscale; WOCQ-R = Ways of Coping Questionnaire – Revised.

Please note that psychological and social factors were categorised as psychosocial factors and that clinical and demographic variables were categorised as non-psychological factors.