The Role of Metacognition in Emotional Distress in People with Multiple Sclerosis

Phillip E. Heffer-Rahn[a*]

Supervisors: Peter L. Fisher[a] & Peter Salmon[ab]

[a]*Institute of Psychology, Health and Society, University of Liverpool, UK*

[b]*The Royal Liverpool and Broadgreen University Hospitals NHS Trust, UK*

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Thesis Overview

Multiple sclerosis (MS) is one of the most common neurological diseases, affecting approximately 2.5 million people worldwide (Haussleiter, Brüne, & Juckel, 2009). Many people living with the condition experience clinical depression and anxiety (Garfield & Lincoln, 2012; Jones et al., 2014). Investigating the psychological factors and processes underpinning emotional distress is an important avenue of empirical work, in order to develop effective psychological interventions.

The first chapter in this thesis is a systematic review that aimed to synthesise prospective studies that have measured demographic, clinical, and psychosocial variables over time, assessing their influence on emotional distress in people with multiple sclerosis (PwMS). In doing so, the review aims to identify psychosocial variables that predict distress in PwMS prospectively. This chosen aim was established in light of there being no previous systematic reviews that have focused principally on prospective evidence, which in the last decade has been an emerging area of psychosocial research in PwMS. Previous attempts have summarised a large body of cross-sectional evidence, and included a broad range of adjustment outcomes, limiting the conclusions that could be drawn specifically relating to emotional distress (Dennison, Moss-Morris, & Chalder, 2009).

The review reports the findings from 15 longitudinal studies exploring a range of psychosocial factors. In this evidence, the key factors that emerged as predictive of emotional distress were derived from the stress-coping model (Lazarus & Folkman, 1984), cognitive-behavioural conceptualisations (Leventhal et al., 1997; Leventhal, Nerenz, & Steel, 1984), and contructs from positive psychology (Pakenham, 2007; Snyder, Lehman, Kluck, & Monsson, 2006). The review discusses the clinical implications with respect to potential psychological interventions that could be utilised to address high levels of emotional distress in PwMS. For example, cognitive-behavioural strategies to help PwMS to identify and reframe maladaptive stress-related cognitions, and third wave therapies, such as Acceptance and Commitment Therapy (Hayes, Follette & Lineham, 2004) and Mindfulness-Based

Cognitive Therapy (Segal, Williams, & Teasdale, 2002), to address avoidance-based coping by promoting cognitive flexibility.

The review was prepared for submission to the British Journal of Health Psychology, and has been formatted in line with the author guidelines (see Appendix A). This journal was chosen because it focuses on psychological aspects related to health, health-related behaviour and illness across the lifespan. Findings are intended to have potential clinical implications for the future development of novel psychological approaches to treating persistent distress in PwMS.

In chapter two, an empirical paper is reported that tests for the first time the predictions of a psychological model of emotional distress in PwMS, the Self-Regulatory Executive Function (S-REF) model (Wells & Matthews, 1994, 1996). The S-REF asserts that psychological disorders can be accounted for by top-down processes, positioning a person's style of thinking and responding as of central importance in the maintenance of emotional distress (Fisher & Wells, 2009). From this perspective the model places emphasis on the conscious processes involved in the appraisal of thoughts, threats and emotions (Fisher & Wells, 2009). Two types of metacognitive beliefs are predicted to influence these processes, positive metacognitive beliefs which concern a person's beliefs about advantages of worry and rumination (e.g., "Worrying helps me to prepare for my condition deteriorating"), and negative metacognitive beliefs which concern appraisals about the dangerous and uncontrollable nature of perseverative thinking in the form of worry and rumination (e.g., "Thinking constantly about having a relapse will make me lose my mind" and "I have no control over my worry").

To build on the current theoretical understanding of emotional distress in PwMS, the empirical paper incorporates the S-REF perspective with an existing cognitive-behavioural conceptualisation, the common-sense model (CSM) (Leventhal et al., 1997). At the heart of the CSM is the notion that a person's representations or appraisals of their illness (e.g., "The symptoms of my MS are puzzling to me") enables them to make sense of their illness and in turn guide their coping responses and adaptive behaviour. Therefore the model places the greatest weight of importance on illness appraisals, whereas the S-REF asserts that such appraisals occur in the form of worry and rumination and are less

important than the top-down processes believed to promote worry and rumination and unhelpful responses that backfire (e.g., thought suppression). Based on positions, the specific objective of the empirical study was to test whether metacognitive beliefs and processes predicted by the S-REF model account for emotional distress in PwMS, whilst controlling for demographic, clinical, and illness appraisal variables predicted by the CSM. Using a cross-sectional design, the paper was prepared with the intention of developing hypotheses for a further prospective study to investigate the utility of the S-REF model in predicting distress over time in PwMS.

One of the key findings from the empirical study was the significance of negative metacognitive beliefs, which explained large proportion of the variance in emotional distress, over and above illness appraisals and other important clinical factors (i.e., pain and fatigue). Additionally, further analyses supported the predicted relationships between metacognitive beliefs and maintaining factors proposed by the S-REF, known as the cognitive attentional syndrome (CAS) (i.e., worry and rumination, focusing attention on sources of threat, and coping responses that backfire). Specifically, a full mediation effect of the CAS on the relationship between positive metacognitive beliefs and emotional distress, and a partial mediation effect of the CAS on the relationship between negative metacognitive beliefs and emotional distress. This pattern of results supports the assertions of the S-REF model which predicts that positive metacognitive beliefs do not cause emotional distress *per se*, but do so by promoting aspects of the CAS. Contrastingly, negative metacognitive beliefs may cause distress independently of the CAS, because they are both intrinsically distressing when they come to mind (e.g., “My worrying thoughts persist no matter how hard I try to stop them”), but also lead to negative appraisals of worry and rumination (e.g., “My worrying could make me go mad”). The clinical implications outlined in the empirical study suggest that when delivering psychological interventions for PwMS, clinicians should consider whether these top-down processes are playing a role and appropriately implement therapies to address them.

The empirical paper will be submitted to the Journal of Psychosomatic Research, therefore it has been formatted in line with the author guidelines (see Appendix B). The selected journal focuses on publishing research that covers all relationships between psychology and medicine, with a particular

emphasis on illness populations, from basic biological and psychological research, to treatment and service evaluations.

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Chapter One

A Systematic Review of Psychosocial Predictors of Emotional Distress in People with Multiple Sclerosis

Phillip E. Heffer-Rahn[a*]

Supervisors: Peter L. Fisher[ab] & Peter Salmon[ab]

Second reviewer: James A. Reilly[a]

[a]*Institute of Psychology, Health and Society, University of Liverpool, UK*

[b]*The Royal Liverpool and Broadgreen University Hospitals NHS Trust, UK*

[*]Corresponding author at: Phillip Heffer-Rahn, Institute of Psychology, Health and Society, University of Liverpool, Whelan Building, Brownlow Hill, Liverpool UK.

E-mail address: prahn@liverpool.ac.uk

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Abstract

Purpose: Research suggests that emotional distress is common in people with multiple sclerosis (PwMS). Presently there are no systematic reviews of prospective studies that have tested the influence of psychosocial variables on distress in PwMS. These variables are important because they may be modifiable through psychological intervention. Therefore, the aim of this review was to identify psychosocial variables that predict distress in PwMS prospectively. **Method:** CINAHL, Medline, and PsycINFO, were systematically searched to obtain studies relevant to the research question, measuring a variety of distress outcomes (depression, anxiety, global distress, self-esteem, and positive and negative affect). Studies were included if they were a prospective cohort design with at least a one-month follow-up period; evaluated psychosocial predictors of subsequent distress; presented results for adults with MS; and used validated outcome measures for emotional distress. All studies were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS). **Results:** Fifteen studies were included and summarised in a narrative synthesis. The most consistent predictors were stress and coping, cognitive appraisals, benefit finding and social and lifestyle factors. Findings related to attributional style, self-efficacy and quality of life were equivocal, partly due to methodological issues. **Conclusions:** This review provided support for the stress-coping model and common-sense model. Variables from positive psychology also emerged in the reviewed studies. Future prospective studies should be conducted to investigate psychological models of distress yet to be explored in PwMS, to support the development of more effective psychological interventions for this population.

Keywords: Multiple Sclerosis, systematic review, emotional distress, depression, anxiety, predictors, longitudinal, psychological intervention.

Refer to Appendix C for the Statement of Contribution.

1 Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disease that is estimated to affect approximately 2.5 million people worldwide (Compston & Coles, 2002; Dennison, Moss-Morris, & Chalder, 2009). 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 (Chiaravalloti & DeLuca, 2008; Compston & Coles, 2002; Rosti-Otajarvi & Hamalainen, 2013). The combination of disabilities that result vary 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). Roughly 80-95% of PwMS present with this disease course from onset, which is known as relapse-remitting MS (RRMS). After 10 years, around half of those with RRMS present with secondary-progressive form of MS (SPMS) wherein relapses are replaced with a gradual progression of disability (Weinshenker et al., 1989). The rarer disease course, primary-progressive MS (PPMS), presents in approximately 10% of cases from onset, in which there is gradual deterioration with an absence of relapses (Flachenecker, 2006).

PwMS face many challenges, including disruption to employment, leisure activities, daily living, reduced income, and issues in managing social roles and relationships (Dennison et al., 2009). Given this context, it is perhaps unsurprising that emotional difficulties are more common in PwMS compared to the general population (Feinstein, Roy, Lobaugh, Feinstein, & O'Connor, 2004). In PwMS, clinically significant levels of depression occur in 25-50% (Jones et al., 2012) and anxiety in 14-34% (Garfield & Lincoln, 2012). Such elevated levels of emotional distress lead to greater disease burden, impacting on the quality of life of PwMS (Benito-Leon, Morales, Rivera-Navarro, & Mitchell, 2003; Janardhan & Bakshi, 2002).

The National Institute for Health and Care Excellence (NICE) recommends cognitive-behavioural therapy (CBT) for depression in chronic health conditions (NICE, 2009). CBT has been found to be effective in reducing 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; Mohr et al., 2000). In contrast, CBT for anxiety has been relatively neglected in MS research (Dennison & Moss-Morris, 2010), despite evidence suggesting the prevalence of anxiety disorders is higher than depression (Garfield & Lincoln, 2012; Janssens et al., 2003). This relative paucity of research is arguably holding back the development of effective psychological treatments for PwMS, therefore empirical efforts pursuing factors maintaining emotional distress in PwMS should be a priority.

Understanding why some PwMS emotionally adjust to living with the condition, while others experience enduring clinical depression and anxiety, 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, 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 a large part reflected the paucity of prospective research (Dennison et al., 2009). The authors concluded that stress and certain avoidant-coping styles presented the greatest weight of evidence in correlating with adjustment (Dennison et al., 2009). They also concluded other psychosocial factors derived from a range of psychological theories have received empirical support, including factors from psychopathology research (e.g., attributional styles), illness cognitions or appraisals, perceptions of control, constructs from positive psychology, and health behaviours (Dennison et al., 2009).

In the last decade, more prospective studies have emerged. Therefore, the aim of this review is to identify psychosocial variables that predict distress in PwMS prospectively. Within this scope, the review explores longitudinal evidence pertaining to a range of psychosocial factors, such as stress and coping (i.e., unhelpful coping styles such as avoidance), illness appraisals (i.e., a person's beliefs and ideas about their illness), and concepts from positive psychology (e.g., dispositional hope).

2 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).

2.1 Search Strategy

MEDLINE, PsycINFO and CINALH databases were systematically searched from January 1960 to January 2017. Search terms for 'multiple sclerosis' were combined with terms for 'distress' and 'predictor' using Boolean operators (see Appendix D). References of all papers and previous systematic reviews were also hand-searched for studies relevant to the scope of the review. Screening was undertaken by reading the titles and abstracts of the records identified from the initial search. Screening focused on identifying studies that measured psychosocial and distress outcomes, collecting prospective data.

2.2 Inclusion Criteria

Included studies met the following criteria; 1) were peer-reviewed prospective studies, 2) evaluated theoretically-driven psychosocial predictors of subsequent distress with at least a one-month follow-up period, 3) presented results for adult MS samples, 4) used published and validated outcome measures for emotional distress, and 5) were published in English. No limit was placed on the length of time since being diagnosed with MS.

2.3 Data Extraction and Quality Assessment

A random sample of fifty percent of the studies selected after the screening phase were assessed against the inclusion criteria by a second reviewer (JR). Information relevant to the inclusion criteria was tabulated for all eligible studies (see Appendix E). For the included studies, data was extracted using a data extraction form (see Appendix F). This included; sample characteristics, distress

measures, psychosocial predictors and covariates, statistical methods and a summary of the results relevant to the scope of this review. A second reviewer (JR) randomly selected half of the included studies and repeated data extraction to ensure the reliability of the process.

The quality of the studies were independently assessed by the two reviewers (PHR & JR) using the Newcastle-Ottawa Scale (NOS) (G. A. Wells et al., 1999). The NOS explores the risk of bias in observational studies in three domains; 1) selection, 2) comparability, and 3) outcome. NOS domain criteria were modified for the purpose of the review (see Appendix G). Specifically, comparability items focused on the control of baseline levels of the dependent variables and covariates, and outcome items assessed adequacy of follow-up and rate of attrition. In the selection domain, a sample was rated representative where the proportion of each clinical course of MS matched prevalence estimates (i.e., 80-95% RRMS, 5-15% PPMS) (Flachenecker, 2006). If the sample consisted of over 60 per cent of relapse-remitting cases, a rating of "somewhat representative" was awarded. Domain and total scores were calculated. The higher the score, the less potential for study bias within the domains rated.

2.4 Synthesis of Results

A narrative rather than a meta-analytic synthesis was undertaken due to considerable variability in predictors, outcome measures, analytical methods and covariates accounted for across the set of studies.

3 Results

Figure 1 depicts the process for identifying and selecting the studies included in the review. The search identified 1,333 papers after removing duplicates, of these 925 were excluded by title and the remaining 187 by abstract. Twenty one papers were screened for inclusion by scrutinising the full-text articles. Six studies were excluded due to; a focus content analysis (Pakenham, 2007b), measuring carer adjustment (Pakenham, 2005b), studying clinical predictors rather than psychosocial variables (Koch et al., 2015), focusing solely on describing the clinical course of distress (Janssens et al., 2006), lacking a longitudinal analysis (Devins, Seland, Klein, Edworthy, & Saary, 1993), and employing measures that had not been validated (Brooks & Matson, 1982). Fifteen papers reporting 13 primary studies were included in the final review. A summary of the sample characteristics are given in Table 1, and the study design, extracted results, and study quality ratings are shown in Table 2.

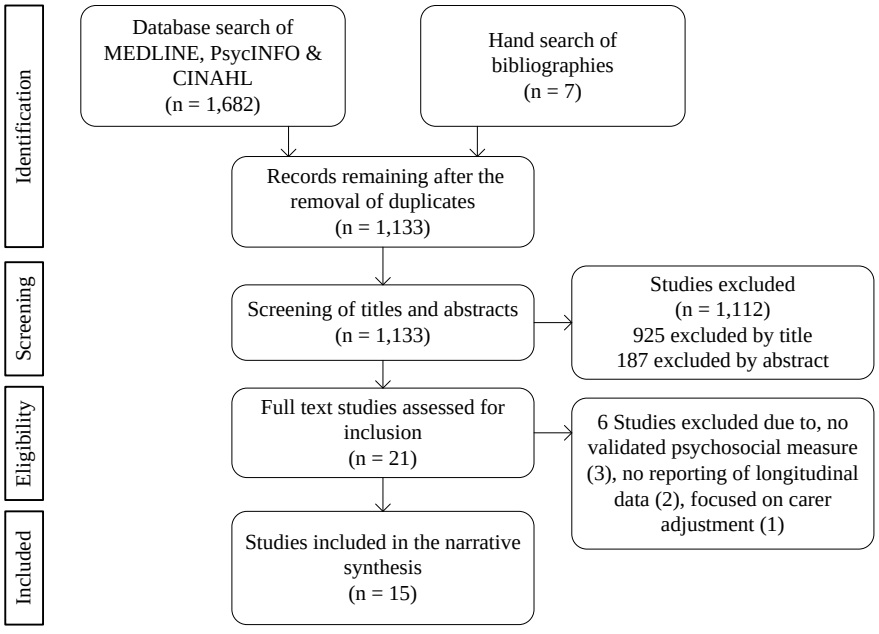

Figure 1. Flow diagram depicting the number of studies included in each stage of the search.

Table 1. Sample characteristics of the 15 included papers reporting 13 primary studies

First Author & Year	Demographics	Sample % Disease Course	Time Since Diagnosis in Years	Disability	Duration of Follow-up in months	Follow-up & Sample Size	Attrition %	Country
Aikens 1997	60% female $\bar{x}$ age in 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
Barnwell 1982	66.67% female $\bar{x}$ age in years =48 Range=25-75	Not reported	$\bar{x}$=12 Range=1-45	$\bar{x}$ SIP-P =24.5, SD=14.2	T2=2	T1=75 T2=71	5.33%	Australia
Johansson 2016	68% female 51% <47 years	61% RRMS 39% PPMS or SPMS	$\bar{x}$=14, SD=10	EDSS 63% mild 17.5% moderate 19.5% severe	T2=12 T3=24	T1=199 T1=185 T3=185	7.03%	Sweden
Kneebone 2015	81% female $\bar{x}$ age in years =45.8, SD=9.25	45% RRMS 32.5% PPMS 18% Unknown	$\bar{x}$=7.8, SD=6.5	Not reported	T2=12 T3=24	T1=495 T2=396 T3=386	22.02%	United Kingdom
Madan 2014	84.1% female $\bar{x}$ age in years =49.15, SD=11.3	64.5% RRMS 29.7% CPMS 6% Unknown	$\bar{x}$=9.9, SD=7.8	$\bar{x}$ ADL =47.85, SD=15.6	T2=12	T1=388 T2=296	23.71%	Australia
McCabe 2004	66% female $\bar{x}$ age in years =45.5, range 18-65	Not reported	Not reported	$\bar{x}$ WHOQOL-100 mobility 11.31, SD=3.07 males, 12.24, SD=3.24 female	T2=18	T1=251 T2=251	0%	Australia
McCabe 2005	67% female $\bar{x}$ age in years =45	Not reported	Not reported	Not reported	T2=6 T3=18	T1=243 T2=243 T3=243	0%	Australia
Pakenham 1999	78% female $\bar{x}$ age in years =48.66, SD=11.32	50%=RRMS 50%=CPMS	$\bar{x}$=16.12, SD=10.79	$\bar{x}$ EDSS=5.12 (moderate), SD=1.98	T2=12	T1=122 T2=96	21.31%	Australia
Pakenham 2005a	77% female $\bar{x}$ age in years =47.77, SD=11.48	73% RRMS 27% CPMS	$\bar{x}$=9.78, SD=8.2	$\bar{x}$ number of symptoms =2.62, SD=1.94	T2=3	T1=477 T2=404	15.3%	Australia
Pakenham 2006				See Pakenham 2005				
Pakenham 2007a	81% female $\bar{x}$ age in years =49.33, SD=11.31	67% RRMS 33% CPMS	$\bar{x}$=10.56, SD=8.32	$\bar{x}$ number of symptoms =3.93, SD=2.45	T2=12	T1=388 T2=296	23.71%	Australia
Pakenham 2009				See Pakenham 2007				
Pakenham 2011	84% female $\bar{x}$ age in 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 in years =42, SD=12	Not reported	$\bar{x}$=9.3, SD=6.5	$\bar{x}$ modified AIMS score 2.63, SD=2.61	T2=4	T1=66 T2=66	0%	USA
Tepavcevic 2013	72% female $\bar{x}$ age in 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 n=109 T2 n=97	11.01%	Serbia

Note. ADL = Activities of Daily Living Self-care Scale; AIMS = Arthritis Impact Measurement Scale; CPMS = Chronic Progressive MS; EDSS = Expanded Disability Status Scale; PPMS = Primary Progressive MS; RRMS = Relapse Remitting MS; SD = Standard Deviation; SIP-P = Sickness Impact Profile Physical Domain; SPMS = Secondary Progressive MS; T# = Time point; WHOQOL-100 = The World Health Organization Quality of Life-100 Scale

Table 2. The design, significant findings and quality ratings for the included studies

First Author & Year	Distress Measures (DVs)	Psychosocial Predictors (IVs)	MS & Demographic Variables (IVs)	Prospective Analysis	Variables Included in the Prospective Models	Distress Outcomes (significant findings <0.05)	Statistical Findings	NOS Rating
Aikens 1997	▪ Depression: BDI	▪ Life stress: LES ▪ Coping style: WOCQ-R	▪ Disability: EDSS ▪ Cognitive status: QMSE	▪ Hierarchical linear regression models for T1 to T2, & T2 to T3 predicting BDI ▪ Controlled for EDSS and QMSE ▪ No control of T1 DV	▪T1 to T2, DV BDI ▪Step 1) EDSS & QMSE, Step 2) Life Stress, Step 3) Escape Avoidance & Positive Reappraisal ▪T2 to T3, DV BDI ▪Step 1) EDSS & QMSE, Step 2) Life Stress, Step 3) Escape Avoidance & Positive Reappraisal	▪T1 to T2: T1 life Stress significantly predictive T2 BDI ▪T2 to T3: As above, but also 'Escape Avoidance' Coping Style significant	▪ T1 to T2: T1 Life Stress β=0.53, ΔR^2=0.20, 53% T2 BDI variance ▪ T2 to T3: T2 Life Stress β=0.54, ΔR^2=0.19; T2 Coping 'Escape Avoidance' β=0.64, ΔR^2=0.16, 62% T3 BDI variance	S=1 C=1 O=3 Total=5
Barnwell 1982	▪ Depression: BDI ▪ Self-esteem: CSEI ▪ Performance measures: P Mood ▪ P Social	▪ Self-efficacy measures: SE Mood & SE Social	▪ Disability: SIP-P ▪ Disease history variables ▪ Age, SES, Marital Status & Gender	▪ Hierarchical linear regression predicting T2 DVs ▪ Controlled for demographics & disease history variables forced simultaneous into the models at step 1 ▪ Controlled for T1 DVs	▪DV T2 P Mood ▪Step 1) T1 P Mood, Step 2) SE Mood ▪DV T2 P Social ▪Step 1) T1 P Social, Step 2) SE Social, Step 3) SIP-P	▪T1 SE Mood explained additional variance in T2 P Mood ▪T1 SE Social activities explained additional variance in T2 self-esteem	▪ T1 SE Mood β=0.72, ΔR^2=0.04, 53% T2 P Mood variance ▪ T1 SE Social β =0.5, ΔR^2=0.04, 62% T2 Self-esteem variance	S=1 C=2 O=3 Total =6
Johansson 2016	▪ Depression: BDI & BDI Mood Cluster	▪ Coping capacity: SOC ▪ Perceived impact of MS: MSIS 29 ▪ Social/Lifestyle Activities: FAI	▪ Disability: EDSS ▪ Fatigue: FSS ▪ Disease course ▪ Cognitive status: SDMT ▪ Gender, Age, Work Status	▪ GEE models predicting ORs for DVs ▪ Psychosocial IVs: SOC, MSIS 29 & FAI ▪ Interaction variable: Time	▪IVs: Weak Coping Capacity, Reduced Frequency of Life Style Activities, Not Working, & Perceived Impact of MS (High & Low) ▪Interaction Variable: Time (T2 & T3)	▪Significant interaction 'Time × High Perceived Impact of MS' ▪Significant IVs: Weak Coping Capacity, Reduced Social/Lifestyle Activities & High Perceived Impact of MS	▪ High Perceived Psychological Impact of MS predicting BDI: ORs ranged from 3.34 (95% CI 1.02–10.99) - 5.78 (95% CI 1.61–20.83) 12 & 24 months ▪ Weak Coping Capacity OR predicting BDI & Mood: ORs ranged from 4.9 (95% CI 2.57–9.35) - 6.06 (95% CI 3.05–12.05) ▪ Reduced Social/Lifestyle Activities predicting BDI & Mood: ORs ranged from 2.2 (95% CI 1.28–3.77) - 2.29 (95% CI 1.25–4.22)	S=2 C=2 O=3 Total =7
Kneebone 2015	▪ Depression: CES	▪ Attributional style: ASQ-S ▪ Life stress: RLCQ	▪ Disability: FASQ-R ▪ Time Since Exacerbation (TSE)	▪ Simultaneous linear regression predicting T2 & T3 CES ▪ Controlled for disability ▪ Interaction 'Negative Life Events × Negative Attributional Style' ▪ Controlled for T1 DV	▪DV: T2 & T3 CES ▪IVs: T1 FASQ-R, T1 ASQ-S, TSE ▪Interactions: TSE × Attributions (Global & Stability), & RLCQ × Attributions (Global & Stability)	▪T1 Negative Attributional Style predictive of Depression at T2 & T3, however, not after controlling for T1 DV ▪Significant interaction 'Recent Life Changes × Negative Global Attributions'	▪ Recent Life Changes × Negative Global Attributions β=0.0005	S=2 C=2 O=2 Total=6

First Author & Year	Distress Measures (DVs)	Psychosocial Predictors (IVs)	MS & Demographic Variables (IVs)	Prospective Analysis	Variables Included in the Prospective Models	Distress Outcomes (significant findings <0.05)	Statistical Findings	NOS Rating
Madan 2014	▪ Depression & anxiety: BSI ▪ Positive affect: BABS ▪ Positive states of mind: PSMS	▪ Dispositional hope: THS ▪ MS related stress: Single item question	▪ Disability: ADL ▪ Cognitive status: MPAI ▪ Number of Symptoms ▪ Disease course ▪ Demographics: Age & Partner Status	▪ Hierarchical linear regression predicting T2 adjustment DVs ▪ Interaction 'Hope × Stress' ▪ T2 Hope and Stress used to predict T2 DVs ▪ Controlled for T1 DVs	▪ Separate models for DVs ▪ Step 1) T1 DV, Step 2) Demographics, Step 3) Illness Variables (Disease Course, Number of Symptoms, MPAI, ADL), Step 4) T2 Stress, Step 5) T2 Hope, Step 6) Hope × Stress	▪ T2 Stress explained additional variance in T2 Depression & Anxiety ▪ T2 Hope explained additional variance in T2 Depression ▪ T2 Stress & Hope predictive of BABS & PSMS ▪ Significant interaction 'Hope × Stress'	▪ T2 Stress β=0.20, ΔR^2=0.03, 46% T2 Anxiety variance ▪ T2 Stress β=0.18, ΔR^2=0.03; T2 Hope β=-0.18, ΔR^2= 0.03, 53% T2 Depression variance ▪ Significant interaction 'Hope × Stress' accounted for additional 1% variance after controlling for baseline adjustment DVs	S=2 C=2 O=2 Total=6
McCabe 2004	▪ Depression & anxiety: PMS-S ▪ Self-esteem: WHOQOL-100	▪ Coping style: WOCQ-R ▪ Work capacity & social relationships: WHOQOL-100	▪ Health: WHOQOL 100 (mobility, energy & fatigue, pain & discomfort)	▪ Hierarchical linear regression predicting T2 adjustment DVs ▪ Controlled for health variables ▪ Controlled for T1 DVs	▪ DVs: T2 Anxiety, Depression, Confusion & Self-esteem ▪ Step 1) T1 DVs, Step 2) Health, social relationships & work capacity , Step 3) T1 Coping variables (Problem-focused, Detachment, Wishful Thinking, Seek Social Support & Positive Focus)	▪ No significant findings after controlling for baseline levels of DVs		S=1 C=2 O=2 Total =5
McCabe 2005	▪ Depression & anxiety: PMS-S ▪ Self-esteem: WHOQOL-100	▪ Coping style: WOCQ-R	▪ Recent exacerbation: Self report item	▪ Hierarchical linear regression predicting DVs separately for exacerbation vs. no exacerbation groups ▪ Controlled for T1 DVs	▪ DVs: T2 & T3 DVs ▪ Step 1) T1 DVs, Step 2) T1 Coping Variables (Problem-focused, Detachment, Wishful Thinking, Seek Social Support & Positive Focus)	▪ Exacerbation group: Coping variables did not explain additional variance in T2 Mood or Self-esteem ▪ No exacerbation group: As above		S=1 C=1 O=2 Total=4
Pakenham 1999	▪ Depression: BDI ▪ Global distress: BSI	▪ Stressful life events: SRS ▪ Coping: WCC ▪ Cognitive appraisal: Stanton & Snider (1993) ▪ Social support: SSS	▪ Disability: SIP ▪ Disease severity: EDSS ▪ Duration of MS ▪ Age	▪ Hierarchical linear regression predicting T2 DVs ▪ Interaction analysis 'Threat Appraisal × Coping' ▪ Controlled T1 DVs	▪ DVs: BDI & BAI ▪ Step 1) T1 DVs, Step 2) Age, Step 3) SRS, Step 4) Illness Variables (Duration of MS, EDSS & SIP), Step 5) T1 SSS, Step 6) T1 Appraisal Variables (Threat & Challenge), Step 6) T1 Coping Variables (Emotion-focused vs. Problem-focused)	▪ T1 'Emotion-focused' Coping explained additional variance in T2 BSI ▪ Model 2: T1 Social Support & 'Emotion-focused' Coping explained additional variance in T2 BDI ▪ Both models controlled for T1 DVs	▪ T1 'Emotion-focused' Coping β=0.23, ΔR^2= 0.04, 59% T2 BSI variance ▪ T1 Social Support β=-0.18, ΔR^2= 0.03, T1 Coping 'Emotion-focused' β=0.28, ΔR^2= 0.07, 56% T2 BDI variance	S=2 C=2 O=2 Total=6

First Author & Year	Distress Measures (DVs)	Psychosocial Predictors (IVs)	MS & Demographic Variables (IVs)	Prospective Analysis	Variables Included in the Prospective Models	Distress Outcomes (significant findings <0.05)	Statistical Findings	NOS Rating
Pakenham 2005a	▪ Global distress: BSI ▪ Positive & negative affect: BABS	▪ Benefit finding: BF ▪ MS related stress: Single item question	▪ Cognitive status: MPAI ▪ Number of MS problems ▪ Number of Symptoms ▪ Disease Course ▪ Demographics: Age & Marital Status	▪ Hierarchical linear regression predicting T2 DVs ▪ Explored 'Stress × Benefit Finding' interaction ▪ Controlled for demographics & illness variables ▪ No control of baseline DVs	▪DVs: BSI & BABS (Positive & Negative Affect) ▪Step 1) Demographics, Step 2) Illness Variables, Step 3) Number of Problems, Step 4) Stress Appraisal (MS related stress), Step 5) BF (Family Relations & Personal Growth), Step 6) Stress × BF (Family Relations)	▪Stress Appraisal & 'Stress × Benefit Finding' interaction explained additional variance in T2 Global Distress ▪Stress Appraisal & Benefit Finding 'Family Relations' explained additional variance in T2 Negative Affect ▪Stress Appraisal & Benefit Finding explained additional variance in T2 Positive Affect	▪ T1 Stress Appraisal β=0.44, ΔR^2=0.18, 'Stress × Benefit Finding Family Relations' β =-0.15, ΔR^2=0.02, 32% T2 Global Distress variance ▪ T1 Stress Appraisal β=0.35, ΔR^2= 0.11, T1 Benefit Finding 'Family Relations' β=0.1, ΔR^2=0.02, 25% T2 Negative Affect variance ▪ T1 Stress Appraisal β =-0.18, ΔR^2= 0.03, T1 Benefit Finding 'Family Relations' β =0.15, 'Personal Growth' β =0.15, ΔR^2=0.06, 14% T2 Positive Affect variance	S=2 C=1 O=3 Total =6
Pakenham 2006	▪ Depression & Anxiety: SCL 90 ▪ Positive affect: BABS	▪ Coping: CMSS ▪ Stress appraisal: Single item question	▪ Cognitive status: MPAI ▪ Time since diagnosis ▪ Disease course ▪ Number of symptoms ▪ Number of problems	▪ Hierarchical linear regression predicting T2 DVs ▪ Controlled for demographics & illness variables ▪ No control of baseline DVs	▪DVs: T2 Depression, Anxiety & Positive Affect ▪Step 1) T1 Demographics (Age, Gender & Marital Status, Step 2) Illness Variables, Step 3) T1 Number of Problems, Step 4) Stress Appraisal, Step 5) Coping Variables	▪T1 Stress Appraisal & Coping 'Acceptance' explained additional variance in T2 Depression ▪T1 Stress Appraisal, Coping 'Avoidance' & 'Acceptance' explained additional variance in T2 Anxiety ▪T1 Coping 'Emotional Release' explained additional variance in T2 Positive Affect	▪ T1 Stress Appraisal β=0.42, ΔR^2= 0.15, Coping 'Acceptance' β=-0.2, ΔR^2= 0.06, 27% T2 Depression variance ▪ T1 Appraisal β=0.3, ΔR^2=0.08, Coping 'Avoidance' β=0.14. Coping 'Acceptance' β=-0.13, 22% T2 Anxiety variance ▪ T1 Coping 'Emotional Release' β=0.18, ΔR^2= 0.09, 16% T2 Positive Affect variance	S=2 C=1 O=3 Total=6
Pakenham 2007a	▪ Depression & Anxiety: SCL 90 ▪ Positive states of mind: PSMS	▪ Sense making: SMS	▪ Cognitive status: MPAI ▪ Disability: ADL (self-care) ▪ Time since diagnosis ▪ Demographics: Age & Religious / Spiritual	▪ Hierarchical linear regression predicting T2 DVs ▪ Controlled for demographics & illness variables ▪ Controlled for T1 DVs	▪DVs: Depression, Anxiety & Positive States of Mind ▪Step 1) T1 DVs, Step 2) Demographics & Disease Variables, Step 3) SMS Factors	▪T2 Sense Making 'Changed Values & Priorities' (CVP) & 'Acceptance' explained additional variance in T2 Anxiety ▪T2 Sense making 'Redefined Life Purpose' (RLP), 'CVP' & 'Acceptance' explained additional variance in T2 Depression ▪Sense making 'RLP', 'CVP', 'Acceptance' & 'Luck' explained additional variance in T2 PSMS	▪ T2 Sense Making 'CVP' β=0.18, 'Acceptance' β=-0.27, ΔR^2=0.09, 50% T2 Anxiety variance ▪ T2 Sense Making 'RLP' β=-0.25, 'CVP' β=0.11, Acceptance β=-0.14, ΔR^2= 0.07, 53% T2 Depression variance ▪ T2 Sense Making 'RLP' β=0.25, 'CVP' β=-0.13, 'Acceptance' β=0.12, 'Luck' β=-0.1, ΔR^2= 0.08, 51% T2 PSMS variance	S=2 C=2 O=2 Total=6

First Author & Year	Distress Measures (DVs)	Psychosocial Predictors (IVs)	MS & Demographic Variables (IVs)	Prospective Analysis	Variables Included in the Prospective Models	Distress Outcomes (significant findings <0.05)	Statistical Findings	NOS Rating
Pakenham 2009	▪ Depression & Anxiety: SCL 90 ▪ Positive affect: BABS ▪ Positive States of Mind: PSMS	▪ Benefit finding: BFMS	▪ Cognitive status: MPAI ▪ Disability: ADL (self-care) ▪ Time since diagnosis ▪ Demographics: Age & Religious / Spiritual ▪ Social Desirability: MCSDS	▪ Hierarchical linear regression predicting T2 DVs ▪ Controlled for age & time since diagnosis ▪ Controlled for T1 DVs	▪ DVs: T2 Depression, Anxiety, Positive Affect & Positive States of Mind ▪ Step 1) T1 DVs, Step 2) Age, T1 Religious / Spiritual Beliefs, Time Since Diagnosis & T2 MCSDS, Step 3) BFMS factors	▪ T1 BFMS 'Lifestyle Gains' explained additional variance in T2 Depression variance ▪ As above for T2 Anxiety ▪ T1 BFMS 'New Opportunities' explained additional variance in T2 Positive Affect ▪ T1 BFMS 'Compassion/Empathy' & 'New Opportunities' explained additional variance in T2 PSMS	▪ T1 BFMS 'Lifestyle Gains' β=-0.18, ΔR^2=0.03, 48% variance in T2 Depression variance ▪ T1 BFMS 'Lifestyle Gains' β=-0.19, ΔR^2=0.04, 45% T2 Anxiety variance ▪ T1 BFMS 'New Opportunities' β=0.26, ΔR^2= 0.04, 40% T2 Positive Affect variance ▪ T1 BFMS 'Compassion/Empathy' β=-0.15, 'New Opportunities' β=0.16, ΔR^2=0.04, 35% T2 PSMS variance	S=2 C=2 O=2 Total=6
Pakenham 2011	▪ Distress: DASS 21 ▪ Positive affect: BABS	▪ Acceptance: MSAQ	▪ Disability: ADL ▪ Cognitive status: MPAI ▪ Demographics: Employment, Marital Status, Gender	▪ Hierarchical linear regression predicting T2 DVs ▪ Controls for T1 DVs ▪ Measured Acceptance at T2 ▪ Controlled for illness variables & demographics	▪ DVs: Distress & Positive Affect ▪ Step 1) T1 DVs, Step 2) Employment, Marital Status, Gender, ADL & MPAI, Step 3) Acceptance (Action & Willingness)	▪ T2 Acceptance 'Action' explained additional variance in T2 Depression ▪ T2 Acceptance 'Action' & 'Willingness' explained additional variance in T2 Positive Affect	▪ T2 Acceptance 'Action' β=-0.23, ΔR^2=0.04, 50% T2 Depression variance ▪ T2 Acceptance 'Action' β=0.38, 'Willingness' β=0.2, ΔR^2=0.12, 49% T2 Positive Affect variance	S=2 C=2 O=3 Total=7
Schiaffino 1998	▪ Depression: CES-D	▪ Illness representations: IMIQ	▪ Illness severity: AIMS ▪ Demographics: Age, Education & Income	▪ Hierarchical linear regression predicting T2 CES-D ▪ Separate models for each IMIQ Factor (Cure, Responsibility, Consequences & Variability) ▪ Controlled for illness severity ▪ Controlled for T1 DV	▪ DV: Depression ▪ Step 1) Age, Education & Income, Step 2) T1 CES-D, Step 3) T2 Illness Severity, Step 4) IMIQ Factors, Step 5) Severity × IMIQ Factors	▪ T1 Representations 'Variability' predicted additional variance in T2 Depression	▪ T1 Representations 'Variability'β =0.25, ΔR^2= 0.05, 60% T2 Depression variance	S=2 C=2 O=3 Total=7
Tepavcevic 2013	▪ Depression: HDRS	▪ Quality of life: MSQOL 54 (Mental Health & Social Function subscales	▪ Disability: EDSS ▪ Fatigue: FSS ▪ Demographics: Age & Gender	▪ Simultaneous linear regression predicting change in Depression (T2 minus T1) ▪ Separate models for Mental Health & Social Function subscales ▪ Controlled for T1 depression ▪ Controlled for illness & demographics variables	▪ DV: HDRS score change during the follow-up ▪ IVs: T1 MSQOL-54 subscale (Mental Health or Social Function), T1 HDRS, T1 EDSS, T1 FSS & demographics (Age & Gender)	▪ T1 Quality of Life 'Mental Health' predictive of change in Depression ▪ T1 Quality of Life 'Social Functioning' predictive of Depression ▪ Does not report R^2	▪ T1 Quality of Life 'Mental Health' β=0.19 predicting change in Depression ▪ T1 Quality of Life 'Social Functioning' β=-0.23 predicting change in Depression	S=2 C=0 O=3 Total =5

Note.

ADL = Activities of Daily Living Self-care Scale
AIMS = Arthritis Impact Measurement Scale
AQQ = Acceptance & Action Questionnaire
ASQ-S = Attributional Style Questionnaire Survey
BABS = Bradburn Affect Balance Scale
BDI = Beck Depression Inventory
BF = Benefit Finding
BFMS = Benefit Finding in MS
BSI = Brief Symptom Inventory
C = Comparability domain of the Newcastle-Ottawa Scale
CES-D = Center for Epidemiological Studies Depression Scale
CMSS = Coping with MS Scale
CPMS = Chronic Progressive MS
CSEI = Coopersmith Self-esteem Inventory
CVP = Changed Values & Priorities
DASS 21 = Depression Anxiety and Stress Scale
EDSS = Expanded Disability Status Scale
FAI = Frenchay Activities Index
FAQ-R = Functional Assessment Screening Questionnaire-Revised
FASQ-R = Functional Assessment Screening Questionnaire Revised
FSS = Fatigue Severity Scale
GEE = Generalised Estimating Equations
HDRS = Hamilton Depression Rating Scale
IES = Impact of Events Scale
IMIQ = Implicit Models of Illness Questionnaire
IPQ = Inter-Quartile Range
LES = Life Experiences Survey
MCSDS = Marlowe-Crown Social Desirability Scale
MPAI = Mayo-Portland Adaptability Inventory
MSAQ = MS Acceptance Questionnaire
MSIS = Multiple Sclerosis Impact Scale 29
MSQOL 54 = MS Quality of Life
O = Outcome domain of the Newcastle-Ottawa Scale
OR = Odds Ratio
P Mood = Performance at Mood Control
P Social = Performance at Social Activity
PAIS = Psychological Adjustment to Illness Scale
PMS-S = Profile of Mood States Short Form
PPMS = Primary Progressive MS
PSMS = Positive States of Mind Scale
PwMS = People with MS
QMSE = Quantitative Mental Status Examination
RLCQ = Recent Life Changes Questionnaire
RLP = Redefined Life Purpose
RRMS = Relapse Remitting MS
S = Selection domain of the Newcastle-Ottawa Scale
SCL 90 = Symptom Checklist 90
SD = Standard Deviation
SDAS = Spanier Dyadic Adjustment Scale
SDMT = Symbol Digit Modalities Test
SE Mood = Self efficacy for mood control
SE Social = Self efficacy for social activities
SES = Socioeconomic Status
SHSS = Subjective Health Status Scale
SIP-P = Sickness Impact Profile Physical Domain
SLS = Satisfaction with Life Scale
SMS = Sense Making Scale
SOC = Sense of Coherence Scale
SPMS = Secondary Progressive MS#
SRS = Social Readjustment Scale
SSS = Social Support Scale
T# = Time-point
THS = Trait Hope Scale
WCC = Ways of Coping Checklist
WHOQOL-100 = The World Health Organization Quality of Life-100
WOCQ-R = Ways of Coping Questionnaire

3.1 Overview of the Included Studies

Eight studies were conducted in Australia (10 papers), two in the United States, and one in each of the remaining countries, Sweden, Serbia and the United Kingdom (refer to Table 1). The majority of studies (n = 14) used self-report questionnaires. Ten studies used a mixture of distress measures, and the remaining studies used a single distress outcome, which was depression (refer to Table 1). General distress was measured in three studies, depression in 12, and anxiety in six (refer to Table 1). Several other outcomes including self-esteem, positive and negative affect, and mood control, were also assessed (refer to Table 1). One study used clinician-rated interview to measure severity of assessment of depression (i.e., Hamilton Depression Rating Scale) (refer to Table 1). A range of psychosocial conceptual areas were investigated in the studies. Table 3 details these and the psychosocial predictors, distress outcomes and first authors of the studies. All studies administered at least one validated measure of stress and coping, cognitive appraisals of illness, social and lifestyle factors, positive psychology, self-efficacy, attributional styles and quality of life.

3.1.1 Sample Characteristics

All studies had a majority of female participants (refer to Table 1). Across the studies, rates of attrition ranged from 0 to 24% over the total duration of prospective data collection (i.e., baseline to final follow-up) (refer to Table 1). Mean sample ages ranged from 35 to 49 years and the mean time since diagnosis ranged from 4 to 16 years. Two studies did not report time since diagnosis (refer to Table 1). The clinical course of MS was reported in nine studies (refer to table 1). RRMS was the most prevalent clinical course of MS, followed by chronic progressive types (i.e., SPMS / PPMS) (refer to table 1). The level of disease severity was assessed using a range of measures (refer to Table 1). Methods consisted of participants reporting the number of symptoms experienced at the time of the study, administering a modified version of an instrument designed for a comparable disease (Schiaffino, Shawaryn, & Blum, 1998), measures of daily living and self-care (i.e., ADL), mobility subscales (i.e., WHOQOL-100) and specific disability scales (i.e., EDSS) (refer to Table 1). Of the four studies that provided EDSS scores, three reported mean scores between 2.2 (i.e., mild) to 5.12 (i.e., moderate). One study (Johansson, Gottberg, Kierkegaard, & Ytterberg, 2016) specified the number of participants classified within each level of disease severity using cut-off scores.

3.1.2 Prospective Methodology and Statistical Analyses

The duration of follow-up ranged from 2 months to 3 years (refer to Table 1). Four studies used three time-points and the remaining 11 studies used two time-points (refer to table 1). Time between baseline and follow-up ranged from 2 months to 3 years (refer to table 1). One study used a 3 year follow-up (Tepavcevic et al., 2013). Thirteen studies analysed prospective data using hierarchical linear regression, accounting for significant covariates (e.g., disease variables and demographics) identified through preliminary bivariate analyses (refer to table 1). Ten studies controlled for baseline levels of distress, however, of these only eight studies used multilevel modelling in which the unique contribution of the predictor variables to subsequent distress could be extracted (refer to Table 2).

3.1.3 Quality of the Studies

Three studies were of superior methodological quality according to the modified NOS quality assessment used in this review (Johansson et al., 2016; Pakenham & Fleming, 2011; Schiaffino et al., 1998). These studies recruited samples that were adequately reflective an average community sample of PwMS, adopted approaches that allowed for the statistical control of covariates, and reported less than 20% attrition over the course of prospective data collection. Eight studies also received high quality ratings for these reasons, but were not equally robust as they reported higher rates of attrition (Kneebone et al., 2015; Madan & Pakenham, 2014; Pakenham, 1999, 2007a; Pakenham & Cox, 2009), employed a short duration of follow-up (Barnwell & Kavanagh, 1982), and lacked the statistical control of baseline levels of the dependent variables (Pakenham, 2005a, 2006). Four studies received lower ratings than the aforementioned studies due to incomplete reporting of the sample characteristics, lacking statistical controls (Aikens et al., 1997; McCabe, 2005; McCabe & Di Battista, 2004), and applying exclusion criteria that limited the representativeness of the sample recruited (Tepavcevic et al., 2013).

3.2 Psychosocial Predictors

The results of the studies are summarised in the following sections, organised into the conceptual areas. Studies predicted a range of distress outcomes including, depression, anxiety, global distress, mood control, positive and negative affect, positive states of mind, and self-esteem (refer to Table 3).

Table 3. The distress outcomes, psychosocial predictors and main conceptual areas explored in the included studies

Distress outcomes	Main conceptual areas studied	Range of psychosocial predictors	First author & year of the relevant studies
Depression	Attributional style; Cognitive appraisals of illness; Positive Psychology; Social & lifestyle factors; Stress & coping; Quality of life	Acceptance; Attributional styles; Benefit finding; Cognitive appraisals; Coping capacity; Coping styles; Dispositional hope; Illness appraisals; Life stress; MS related stress; Self-efficacy; Sense making; Perceived impact of MS; Quality of life; Social & lifestyle activities; Social relationships; Social support; Stress appraisal; Stressful life events; Work capacity	Aikens 1997; Barnwell 1982; Johansson 2016; Kneebone 2015; Madan 2014; McCabe 2004; McCabe 2005; Pakenham 1999; Pakenham 2006; Pakenham 2007a; Pakenham 2009; Pakenham 2011; Schiaffino 1998; Tepavcevic 2013
Anxiety	Cognitive appraisals of illness; Positive psychology; Social & lifestyle factors; Stress & coping	Benefit finding; Coping style; Disposition hope; MS related stress; Sense making; Social relationships; Stress appraisal; Work capacity	Madan 2014; McCabe 2004; McCabe 2005; Pakenham 2006; Pakenham 2007a; Pakenham 2009;
Global distress	Cognitive appraisals of illness; Positive psychology; Social & lifestyle factors; Stress & coping	Benefit finding; Cognitive appraisal; Coping style; Social support; Stressful life events; MS related stress	Pakenham 1999; Pakenham 2005a
Mood control	Self-efficacy	Self-efficacy for mood control & social activities;	Barnwell 1982
Positive & negative affect	Positive psychology; Stress & coping	Acceptance; Benefit finding; Coping styles; Dispositional hope; MS related stress	Madan 2014; Pakenham 2005a; Pakenham 2006; Pakenham 2009; Pakenham 2011;
Positive states of mind	Cognitive appraisals of illness; Positive psychology; Stress & coping	Dispositional hope; MS related stress; Sense making; Benefit finding	Madan 2014; Pakenham 2007a; Pakenham 2009
Self esteem	Self-efficacy; Social & lifestyle factors; Stress & coping	Coping style; Self-efficacy for mood control & social activities; Social relationships; Work capacity	Barnwell 1982; McCabe 2004; McCabe 2005

Note. Some of the studies assessed multiple distress outcomes and explored several psychosocial predictors within each conceptual area. However, the differed in terms of the selection of each given predictor and outcome (refer to Table 2).

3.2.1 Stress and coping

Five primary studies assessed stress. Four studies found that higher stress was a significant predictor of a range of distress outcomes. Specifically, higher MS related stress predicted higher levels of general distress, depression and anxiety, after three (Pakenham, 2005a, 2006) and 12 months follow-up (Madan & Pakenham, 2014). However, in these studies stress was measured with a single item in which participants rated how stressful their main MS problem had been in the month prior to the survey (Madan & Pakenham, 2014; Pakenham, 2005a, 2006). The broader concept of life stress was significant predictor of depression in one study (Aikens, Fischer, Namey, & Rudick, 1997), while

two other studies found non-significant results for life stress (Kneebone, Guerrier, Dunmore, Jones, & Fife-Schaw, 2015; Pakenham, 1999).

In the seven studies that tested the effects of coping on distress, four studies found coping styles were significant predictors of subsequent distress (Aikens et al., 1997; Pakenham, 1999, 2006; Pakenham & Fleming, 2011). Emotion-focused and avoidant coping styles, predicted higher general distress, anxiety and depression after 3, 6 and 12 months (Aikens et al., 1997; Pakenham, 1999, 2006). Acceptance coping styles predicted lower levels of anxiety and depression, and conversely higher levels of positive affect in two of the studies, employing 3 and 12 month follow-up tranches (Pakenham, 2006; Pakenham & Fleming, 2011). Finally, a weak coping capacity predicted depression caseness after two years (Johansson et al., 2016).

3.2.2 Cognitive appraisals of illness

In two of the three studies assessing cognitive appraisals of illness, two identified significant predictors of distress. Schiaffino et al. (1998) found that appraisals of high illness variability predicted higher levels of depression at 4 months follow-up, after controlling for baseline depression, age, education, income and disease severity (Schiaffino et al., 1998). In the other study, sense making appraisals predicted depression, anxiety and positive states of mind when baseline levels of the dependent variables were statistically controlled (Pakenham, 2007a). However, sense-making appraisals assessed at follow-up were used as predictors, therefore this aspect of the analysis was cross-sectional (Pakenham, 2007a). The final study assessing cognitive appraisals of illness, specifically cognitions related to threat, challenge and controllability, found non-significant results (Pakenham, 1999). The author reported a potential issue with the sensitivity of the appraisals measure used (Pakenham, 1999).

3.2.3 Social and lifestyle factors

Two of the three studies assessing the impact of social and lifestyle factors found significant results (Johansson et al., 2016; Pakenham, 1999). Higher levels of social support predicted lower levels of depression at follow-up (Pakenham, 1999), and reduced social and lifestyle activities

predicted depression caseness at 12 and 24 months follow-up (Johansson et al., 2016). These studies used different statistical approaches to control for baseline levels of the distress outcomes and a range of other covariates (i.e., Generalised Estimation Equation modelling [GEE] and linear regression). Capacity to work and engagement in social relationships was non-significant in a study assessing these variables influence on levels of depression, anxiety and self-esteem over an 18 month period (McCabe & Di Battista, 2004).

3.2.4 Positive psychology

In the three studies measuring dispositional hope and benefit finding, higher levels of disposition hope was a predictor of lower levels of distress (Madan & Pakenham, 2014), and benefit finding variables explained additional variance in distress after 3 and 12 months follow-up (Pakenham, 2005a; Pakenham & Cox, 2009). However, one of these studies did not control for baseline levels of distress (Pakenham, 2005a). The other more robust study, also validated a measure of benefit finding specifically for PwMS (Pakenham & Cox, 2009). Results showed higher lifestyle gains was the strongest predictor of lower levels of subsequent depression and anxiety, after controlling for baseline distress and illness covariates (Pakenham & Cox, 2009).

3.2.5 Self-efficacy

One study tested whether self-efficacy for mood control and social activities predicted mood control performance and self-esteem after 2 months (Barnwell & Kavanagh, 1997). Greater self-efficacy for mood control was a significant predictor of higher mood control performance, and self-efficacy for social activities was a predictor of increased levels of self-esteem (Barnwell & Kavanagh, 1997). In this study, while self-esteem was measured with a validated scale (Coopersmith, 1984), the measures of self-efficacy and subsequent performance were adapted versions of a scale designed to assess outcomes of cognitive-behavioural therapy (Kavanagh & Wilson, 1989). The study controlled for baseline levels of illness history, demographic variables and baseline levels of depression.

3.2.6 Attributional style

In the single study that assessed attributional styles (Kneebone et al., 2015), after accounting for baseline levels of depression, negative attributional styles did not account for additional variance in depression at 12 and 24 months follow-up. However, an interaction between recent life changes and negative global attributions was predictive of subsequent depression, although the effect size was very small (Kneebone et al., 2015).

3.2.7 Quality of life

Quality of life variables were investigated in two studies (Johansson et al., 2016; Tepavcevic et al., 2013). Using GEE modelling, one study found that participants with high perceived impact of MS were at greater risk for depression caseness at 12 and 24 months follow-up (Johansson et al., 2016). Employing a comparable measure (WHOQOL-100), Tepavcevic et al. (2013) tested whether mental health and social functioning QoL composite scores predicted depression over 3 year period. Lower social activity QoL predicted a deterioration in mood, while higher mental health QoL was protective of depression (Tepavcevic et al., 2013).

4. Discussion

This review summarised prospective research investigating psychosocial factors involved in distress in PwMS. The aim was to identify psychosocial variables that predicted distress outcomes over time. The search identified 15 empirical papers reporting 13 primary prospective studies testing several broad categories of psychosocial variable. Studies controlled for a variety of different demographic and clinical variables. Of the psychosocial variables investigated, stress and coping variables emerged as the most consistent predictors of subsequent distress in PwMS, although not all of the studies controlled for baseline levels of distress (Aikens et al., 1997; Pakenham, 2005a, 2006). Furthermore, there was also variation in the demographic and clinical covariates accounted for.

4.1 Stress-coping and Cognitive Appraisals

The findings of the review largely supported the stress-coping model (Lazarus & Folkman, 1984), which asserts that distress is mediated by illness appraisals, coping strategies/responses and coping resources (Pakenham, 1999). Four studies reported high-perceived stress in relation to MS, or life stress more broadly, predicted higher distress over time (Aikens et al., 1997; Madan & Pakenham, 2014; Pakenham, 2005a, 2006). However, only one study accounted for baseline distress (Madan & Pakenham, 2014).

There was also some support for the influence of coping variables, predicted by the stress-coping model (Lazarus & Folkman, 1984). Three studies found negative coping styles such as emotion-focused and escape-avoidance, predicted higher subsequent distress (Aikens et al., 1997; Pakenham, 1999, 2006). Negative coping styles share relevance with concepts from other theoretical models of emotional distress yet to be explored in PwMS. For example, according to the Self-Regulatory Executive Function (S-REF) model (Wells & Matthews, 1994, 1996), avoidance and the suppression of difficult internal experiences (i.e., thoughts and feelings) are viewed as a coping responses that backfire. While limited to a single study, the review also identified support for positive coping styles, in this case acceptance coping, which predicted lower depression and higher positive affect (Pakenham & Fleming, 2011). The concept of acceptance is also one of six core processes used to

promote psychological flexibility and well-being in Acceptance and Commitment Therapy (ACT) (Hayes, Follette & Lineham, 2004).

Evidence in relation to the appraisals aspect of the stress coping-model (Lazarus & Folkman, 1984), conceptualised as threat and challenge cognitions in response to illness events, were not supported (Pakenham, 1999). However, it is possible that the higher representation of people with chronic progressive MS may have obscured the significance of these variables. Greater support was found for appraisals predicted by the common-sense model (Leventhal et al., 1997; Leventhal, Nerenz, & Steel, 1984), which extends the stress-coping model to include illness-specific beliefs/appraisals. In keeping with the notion that a more cyclical illness increases distress (Dennison et al., 2009), one study found appraisals of high variability (i.e., cyclical timeline) were predictive of elevated distress (Schiaffino et al., 1998). Also, another study assessing appraisals relating to whether an individual has reached a stage of illness acceptance, and redefined life goals, found that these variables predicted lower distress (Pakenham, 2007a). Overall these findings support the notion that a more variable disease course may predispose PwMS to higher distress, possibly by interrupting the process of adjustment due to the higher levels of stress often experienced during acute episodes of neurological disability.

4.2 Social and Lifestyle Factors

In two studies higher levels of social support and engagement in leisure and lifestyle activities were protective of depression (Johansson et al., 2016; Pakenham, 1999). Social support can facilitate role transitions and identity change as a chronic health condition progresses, support the mastery of new skills needed to cope effectively with changing abilities, and provide a person with a sense of belonging to bolster self-esteem (Cobb, 1976; Costa, Sá, & Calheiros, 2012). A single study found less engagement in social relationships and reduced work capacity did not predict distress, however, in this study levels of distress were relatively stable over time, limiting the potential for the study to identify predictors using regression analyses (McCabe & Di Battista, 2004).

4.3 Positive Psychology

Three studies investigated variables that are thought to enhance optimism (Madan & Pakenham, 2014; Pakenham, 2005a; Pakenham & Cox, 2009), two of which were of high methodological quality (Madan & Pakenham, 2014; Pakenham & Cox, 2009). One study explored dispositional hope, specifically testing a cognitive-motivational theory of hope (Snyder, Lehman, Kluck, & Monsson, 2006). This theory suggests that hope-related agency, which concerns both a person's ability to generate viable avenues to achieve goals and sense of determination to continue goal pursuit, will ultimately influence emotional distress (Snyder et al., 2004). Consistent with this theory, Madan and Pakenham (2014) found that higher levels of hope predicted lower distress and higher positive states of mind. Furthermore, a protective effect on levels of distress emerged under high stress conditions (Madan & Pakenham, 2014), possibly due to high stress being appraised as a challenge in participants with high levels of dispositional hope.

One study assessed whether benefit finding factors predicted distress in PwMS (Pakenham & Cox, 2009). Benefit finding is defined as the identification of benefits when faced with adversity (Pakenham & Cox, 2009; Tennen & Affleck, 2002), and is a process of meaning making when redefining one's assumptions about the self and world in the face of significant life events such as illness (Janoff-Bulman & Yopyk, 2004). Pakenham and Cox (2009) developed and validated measure of benefit finding for PwMS, and found that lifestyle gains was a predictor of lower depression and anxiety, while new opportunities and levels of compassion/empathy predicted positive affect and positive states of mind. This study controlled for time since diagnosis, spiritual beliefs and age (Pakenham & Cox, 2009). These findings may lend credence to therapeutic approaches that serve to address self-criticism and shame by applying the compassion model within psychotherapy, as is the case in Compassion-Focused Therapy (CFT) (Gilbert, 2009).

4.4 Self-Efficacy and Attributional Style

One study assessed whether self-efficacy predicted distress in PwMS (Barnwell & Kavanagh, 1997). Self-efficacy refers to appraisals in relation to the perceived capability to control future performance (Bandura, 1977). Therefore self-efficacy overlaps with the notion of hope-related

agency, however, the difference in this study was the focus on perceived self-efficacy specifically related to the goal of mood control and engagement in social activities, both of which predicted subsequent mood control performance and self-esteem (Barnwell & Kavanagh, 1997).

A single study evaluated attributional styles and depression, which are inferred by hopelessness theory of depression (Abramson, Metalsky, & Alloy, 1989). Global and stable attributional styles (i.e., attributing negative events as externally caused) were not predictive of subsequent depression when accounting for baseline levels of depression. However, when global attributions and life events were combined, the interaction was a significant predictor of depression a year later (Kneebone et al., 2015).

4.5 Quality of Life

Two studies assessed whether QoL variables predicted depression over time (Johansson et al., 2016; Tepavcevic et al., 2013). One study found that perceived impact of MS on everyday life predicted subsequent depression using a MS-specific measure of QoL (MSIS-29) (Johansson et al., 2016). Another study used mental health and social functioning indices within a health-related QoL measure (WHOQOL-100) and found both indices were predictors of depression (Tepavcevic et al., 2013). However, many of the mental health QoL items within the WHOQOL-100 overlap with those that purport to measure depression, limiting the specificity of QoL as a predictor. It is often the case that the best predictor of subsequent distress will be baseline levels, which can be seen across all the reviewed studies that measured distress at baseline (refer to Table 1).

4.6 Limitations of the Review

While this review provided the first synthesis of psychosocial variables that predicted distress over time in PwMS, there are several limitations. Since the review focused exclusively on prospective designs, only a small number of studies were included in the final synthesis of evidence, limiting the conclusions that could be made. There was also considerable variation in the methodology across the studies, such as the range and nature of the covariates controlled for, the robustness of the measures assessing the predictors, the duration of prospective data collection and rates of attrition. Furthermore, the majority of 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).

4.7 Clinical Implications

Findings of the review broadly supported the importance of stress and coping variables in predicting distress in PwMS. Perceptions of stress, whether concerning life events or stress in response to MS symptoms, could be tackled by interventions aiming to help PwMS recognise and reattribute unhelpful stress-related cognitions, teach stress-management techniques and adopt more adaptive coping strategies as opposed to emotion-focused responses (e.g., avoidance and denial). CBT interventions of this kind delivered to PwMS have received support (Thomas, Thomas, Hiller, Galvin, & Barker, 2006). Cognitions relating to the perceived variability of MS and appraisals of acceptance, may also present an avenue for intervention. For example, interventions that enhance the perceived predictability of MS, such as self-monitoring strategies, may reduce illness uncertainty, while acceptance-based approaches such as ACT (Hayes et al., 2004) and Mindfulness-Based Cognitive Therapy (MBCT) (Segal, Williams, & Teasdale, 2002) may promote more adaptive coping responses (Nordin & Rorsman, 2012). Other third wave models such as CFT (Gilbert, 2009) may also be beneficial in PwMS given the findings related to the protective effects of compassion/empathy (Pakenham & Cox, 2009). With respect to social support and engagement in social and lifestyle activities (Johansson et al., 2016; Pakenham, 1999), interventions that enable PwMS to explore new avenues of socialisation and support seem warranted in light of the protective effects on distress. Nevertheless, to date intervention studies have centred on CBT with a variety of treatment elements not routinely addressing social factors (Fiest et al., 2016).

4.8 Future Research

Much of the consistent evidence in this review conformed to the traditional CBT paradigm (Beck, 1976). Many other more contemporary psychological models have yet to be investigated in PwMS. For example, Acceptance and Commitment Therapy (ACT) (Hayes et al., 2004), which is based on Relational Frame Theory (RFT) (Hayes, Barnes-Holmes, & Roche, 2001), has been

successfully implemented to treat distress in a range of chronic health conditions (Graham, Gouick, Krahe, & Gillanders, 2016; McCracken, Eccleston, & Vowles, 2005). In addition, the core assumptions of Self-Regulatory Executive Function (S-REF) (Wells & Matthews, 1994, 1996) model have been tested in a variety of chronic health conditions, including cancer (Cook et al., 2015), chronic fatigue syndrome (Maher-Edwards, Fernie, Murphy, Wells, & Spada, 2011), Parkinson's disease (Allott, Wells, Morrison, & Walker, 2005; Brown & Fernie, 2015) and epilepsy (Fisher, Cook, & Noble, 2016). Therefore future research should pursue emerging areas and investigate the processes underpinning distress in PwMS.

As noted in the limitations of this review, future methodological approaches must account for the issues of measurement error, and where possible Structural Equation Modelling (SEM) should be used (Westfall & Yarkoni, 2016). To achieve adequate sample sizes for SEM, multicentre research may be needed. Where research cannot achieve adequate samples, parsimonious and theory-driven studies should be conducted to develop hypothesises for larger scale studies.

4.9 Conclusion

Evidence summarised in this review provides support for the role of stress and coping, illness appraisals and social factors in maintaining distress in PwMS. This follows the current dominance of the stress-coping model and common-sense model in clinical health populations (Lazarus & Folkman, 1984; Leventhal et al., 1997; Leventhal et al., 1984). The paucity of evidence underscores the need for longitudinal studies with designs capable of uncovering psychological processes contributing to the persistence of distress. This should include studies that test emerging areas within clinical health, such as RFT and S-REF models, which have so far advanced further in mental health research (Normann, van Emmerik, & Morina, 2014; Smout, Hayes, Atkins, Klausen, & Duguid, 2012).

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Chapter two

The Role of Metacognition in Emotional Distress in People with Multiple Sclerosis

Phillip E. Heffer-Rahn[a*]

Supervisors: Peter L. Fisher[a] & Peter Salmon[ab]

[a]*Institute of Psychology, Health and Society, University of Liverpool, UK*

[b]*The Royal Liverpool and Broadgreen University Hospitals NHS Trust, UK*

[*]Corresponding author at: Phillip Heffer-Rahn, Institute of Psychology, Health and Society, University of Liverpool, Whelan Building, Brownlow Hill, Liverpool UK.

E-mail address: prahn@liverpool.ac.uk

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Abstract

Aim: Multiple sclerosis (MS) is a chronic demyelinating disease that poses significant life challenges. Depression and anxiety often occur in people with MS (PwMS). An information processing model of psychopathology, the Self-Regulatory Executive Function (S-REF) model specifies that maladaptive metacognitive beliefs play a fundamental role in the development and maintenance of emotional distress. The model also asserts that a style of thinking known as the cognitive attentional syndrome (CAS), which consists of worry and rumination, focusing on sources of threat, and unhelpful coping responses, is common across all psychological conditions. This study investigated for the first time whether metacognitive beliefs explained additional variance in emotional distress in PwMS, after accounting for demographic, clinical, and illness appraisal variables. **Method**: One hundred and thirty two participants with MS completed self-report questionnaires measuring distress, fatigue, pain, metacognitive beliefs, illness appraisals and the CAS. Hierarchical regression modelling was used to test whether metacognitive beliefs accounted for distress. Mediational modelling was also run to examine whether the CAS mediated the association between metacognitive beliefs and distress. **Results:** Metacognitive beliefs about the uncontrollable and harmful nature of worry made a unique contribution to distress, over and above demographic and clinical variables, and illness appraisals. Levels of fatigue and illness appraisals in relation to treatment control also made significant and independent contributions to distress in PwMS. The CAS fully mediated the relationship between positive metacognitive beliefs and distress, and partially mediated the relationship between negative metacognitive beliefs and distress. **Conclusions:** This is the first study to demonstrate that metacognitive beliefs contribute to emotional distress in PwMS, and the CAS mediates this relationship. These variables may provide modifiable targets for psychological intervention.

Keywords: Multiple Sclerosis, depression, anxiety, distress, metacognition, fatigue, pain, mediation

1 Introduction

Multiple sclerosis (MS) is a chronic and progressive inflammatory disease of the central nervous system, which affects around 2.5 million people worldwide [1, 2]. MS manifests in a variety of disabling symptoms, including motor and sensory disabilities, cognitive impairment, sexual dysfunction, pain, fatigue, and bladder and bowel disturbances [1, 3-7]. The often variable and unpredictable nature of the clinical symptoms can be frightening for people with MS (PwMS) [2]. Around 80-90% of PwMS have an episodic form of the illness in which neurological symptoms flare up for periods lasting days, weeks, or months, and only partially resolve (i.e., relapse-remitting MS; RRMS) [2]. After 10 years approximately a half of those with RRMS experience the onset of a progressive form of the illness in which there is a gradual progression of neurological impairment (i.e., secondary-progressive MS; SPMS) [2]. The rarer forms of the illness are known as primary-progressive MS (PPMS), wherein there is a gradual deterioration from onset, and progressive-relapsing MS (PRMS), in which a gradual deterioration from onset is accompanied by episodic exacerbations without remission [2]. Along with physical, sensory and cognitive symptoms, there are profound psychosocial challenges [7]. The onset for many, occurs around early-to-mid adulthood [1], and there is frequent disruption to employment, family life, social roles, and leisure activities [7]. Emotional distress adds further disruption to the lives of PwMS [8]. Approximately a third of PwMS meet the diagnostic threshold for anxiety, and around half for depression [9], although some studies suggest the prevalence of anxiety is higher than depression [8, 10-12].

Acknowledging the significant psychosocial impact of MS, clinical guidance recommends cognitive-behavioural therapy (CBT) to treat distress in chronic physical health conditions [13]. While CBT has been shown to reduce distress in PwMS [14], effect sizes have been modest [15]. The limited efficacy of CBT could be due to the difficulties modifying negative cognitions. Research suggests PwMS often make realistic and accurate appraisals of their illness (e.g., “MS has major consequences on my life” and “MS is a serious condition”) [16], which is unsurprising given the challenging nature of the condition. A potentially more effective approach would be to address

modifiable factors that maintain heightened distress. For example, persistent worry has been shown to be higher in PwMS compared to the healthy controls and is associated with higher levels of depression, fatigue and sleep disturbance [17].

The transdiagnostic Self-Regulatory Executive Function (S-REF) model [18, 19] is an information processing model of emotional disorder that may be applicable to PwMS experiencing emotional distress. According to the S-REF model, it is not the content of negative thoughts or negative appraisals related to MS that prolong distress *per se*, but metacognitive beliefs that drive a deleterious style of thinking and responding to those thoughts, known as the cognitive-attentional syndrome (CAS) [20]. The CAS consists of engaging in worry/rumination (i.e., perseverative thinking), focusing attention on sources of threat (e.g., focusing attention on bodily sensations such as pain), and coping responses that backfire (e.g., avoidance of seeking medical advice, drinking too much alcohol). According to the S-REF model, all aspects of the CAS are activated and maintained by metacognitive beliefs [18]. Positive metacognitive beliefs (PMCBS) encourage the selection of worry/rumination as a coping response (e.g., "Worrying about how my MS will progress keeps me prepared") with a heightened focus on threat monitoring (e.g., paying close attention to physical sensations). Negative metacognitive beliefs (NMCBS) further fuel distress because worry/rumination is appraised as uncontrollable and dangerous ("I have no control over my worry about my illness; I am losing my mind"), whilst also giving rise to unhelpful patterns of cognitive self-regulation (e.g., thought suppression, avoidance).

Although the utility of the S-REF model has been tested in several chronic health populations [21-24], so far the model is untested in PwMS. Given that metacognitive therapy (MCT) [25] is an effective intervention for a range of anxiety and affective disorders [26], with techniques that target and modify metacognitive beliefs and interrupt the CAS [25], it raises the possibility that similar approaches may be applicable in chronic health populations such as PwMS. However, before MCT can be developed for PwMS, the predictions of the S-REF model must be empirically investigated whilst also considering how the predictions fit within current psychological understandings of the condition.

A prominent psychological model in chronic health is the common-sense model (CSM) [27, 28]. The CSM affirms that a person's appraisals about their illness (i.e., thoughts and ideas about their illness) mediate their coping responses, and in turn influence levels of emotional distress. For example, a person that believes they have little personal control over their illness may not see the benefit in adaptive coping behaviours such as seeking advice and guidance when symptoms flare up. Consistent with the CSM, the S-REF model also predicts that negative illness appraisals will be associated with distress, framing these as negative intrusive thoughts related to the illness, and as the focus of worry/rumination (e.g., "Nothing I do will affect my MS"). However, the S-REF goes further to predict that metacognitive beliefs (e.g., "Worrying about my symptoms helps me solve problems") will explain additional variance in distress over and above illness appraisals. This is because according to the model, it is not necessarily the content of thoughts or illness-specific appraisals that are fundamental to emotional distress, but the psychological factors involved in the control and regulation of cognition. From this perspective, the CAS should mediate the relationship between metacognitive beliefs and distress, given PMCBS gives rise to worry/rumination and heightened focus on threat monitoring, whilst NMCBS lead to further emotional distress due to negative appraisals of worry and unhelpful cognitive self-regulation strategies (e.g., thought suppression).

Metacognitive beliefs and processes are associated with emotional distress in other neurological populations [23, 24], therefore this study tested the predictions of the S-REF model in PwMS, whilst controlling for demographic and clinical variables, and illness appraisals [18, 19, 27, 28]. Specifically, this study makes the following predictions; 1) metacognitive beliefs will be positively associated with distress, 2) metacognitive beliefs will explain significant variance in distress after controlling for established covariates (i.e., demographic and clinical variables, and illness appraisals), and 3) the CAS will fully mediate the relationship between PMCBS and distress, and partially mediate the relationship between NCMBS and distress, whilst controlling for covariates (i.e., education, pain, fatigue and treatment control illness appraisals).

2 Method

2.1 Design

This study reports data collected from an online cross-sectional survey. The study approved by the University of Liverpool Ethics Committee (Reference: IPHS-1516-30, see Appendix H).

2.2 Participants and Procedure

One hundred and thirty-two participants were recruited consecutively via an advert placed on the MS Society, MS Trust and National MS Society websites. PwMS were invited to complete an anonymous survey asking them about their beliefs about worry, perceptions of their illness and experiences of fatigue, pain, and depression and anxiety. They were informed before taking part that if they completed the survey they could enter a prize draw for a chance to win one of three £50 retail vouchers. Inclusion criteria were; 1) current diagnosis of MS, 2) aged 18 and over, and 3) the ability to understand written English. Data was obtained by self-report questionnaires using an online survey platform (Qualtrics).

2.3 Measures

2.3.1 Dependent variable

Hospital Anxiety and Depression Scale (HADS) [29] was used to measure distress (see Appendix I). The HADS has been used widely in physical health populations [30] and has also been validated for use in PwMS [31, 32]. In the present study, a cut-off score of 11 or more for both the anxiety and depression subscales was used to define caseness of depression and anxiety [29]. The scale consists of 14 items, which are statements about symptoms of depression or anxiety (e.g., “I feel tense and wound up), scored on a 4-point scale (e.g., 0 = *not at all* to 3 = *most of the time*; 0 = *definitely as much* to 3 = *hardly at all*). The total distress score showed adequate levels of internal consistency in this sample ($\alpha = 0.85$).

2.3.2 Independent variables

Demographic and clinical data was collected in the survey (see Appendix J). This included; gender, age, years in full-time education, ethnicity, employment status, duration of MS, clinical course, and history of treatment for depression and anxiety (i.e., current and past treatment for depression or anxiety).

The Fatigue Severity Scale (FSS) [33] was used to assess severity of fatigue (see Appendix K). FSS contains nine items, which are questions about how fatigue interferes with a range of activities (e.g., "Fatigue interferes with my work, family, or social life; Exercise brings on my fatigue"), each scored on a 7-point scale (1 = *strongly disagree* to 7 = *strongly agree*). In this study, a mean score was used as an index for fatigue (i.e., total score/number of items). However, to designate severe levels of fatigue, a cut-off total score of 36 and over was used [33]. The FSS was designed and validated for use in MS and shows good psychometric properties [33]. The scale showed high internal consistency in this sample ($\alpha = 0.94$).

Pain was measured with a visual analogue scale, a unidimensional measure used extensively in adult physical health populations [34] (see Appendix L). Participants were asked to select a level of pain intensity on a visual continuum ranging from 0-100 (100 = unbearable pain). A higher score indicated greater pain.

The Illness Perception Questionnaire-Revised (IPQ-R) [35] was used to measure cognitive appraisals of MS (see Appendix M). The IPQ-R has been demonstrated to be a valid and reliable measure in MS samples [35, 36]. This study used the core section of the questionnaire, which consists of 38 items assessing beliefs and emotional responses to MS (e.g., "Nothing I do will affect my MS; There is very little that can be done to improve my MS"). Participants responded to each item using a 5-point scale (1 = *strongly disagree* to 5 = *strongly agree*). The IPQ-R has seven subscales; timeline (acute vs. chronic), consequences (effects and outcome), personal control, treatment control, coherence, timeline cyclical, and emotional representations. In the present study, as the scale was used

to assess cognitive appraisals of MS, the emotional representation subscale was not used. The six subscales utilised showed acceptable-to-good levels of reliability in this sample ($\alpha = 0.73$ to $\alpha = 0.86$).

The Metacognitions Questionnaire-30 (MCQ) [37] was used to assess metacognitions (see Appendix N). The MCQ-30 consists of five subscales; positive beliefs about worry (PMCBS), negative beliefs about the uncontrollability and dangerous nature of worry (NMCBS), cognitive confidence (CC), need to control thoughts (NC), and cognitive self-consciousness (CSC). The MCQ-30 has been used in other neurological populations, for example Parkinson's disease [23]. The scale consists of 30 items (e.g., "My worrying is dangerous for me; Worrying helps me avoid problems in the future"), scored on a 4-point scale (1 = *do not agree* to 5 = *agree very much*). Total subscales scores range from 6-24. Higher scores on the subscales indicate greater prominence of metacognitive beliefs. Subscales in this sample showed good levels of internal consistency (i.e., ranged from $\alpha = 0.8$ to $\alpha = 0.93$).

2.3.3 Mediator variable

Cognitive Attentional Syndrome-10 (CAS-10) [25]. The CAS-10 is a 10 item self-report questionnaire that assesses metacognitive beliefs and processes (see Appendix O). Items 7-10 duplicates assessment of metacognitive beliefs and are disregarded here. Items 1- 6 assess the extent to which individuals have been using the main aspects of the CAS; perseverative thinking in the form of worry/rumination (e.g., "How much time in the last week have you been dwelling on your problems?"), threat monitoring (e.g., "How much time in the past week have you been focusing your attention on things you find threatening?"), and unhelpful coping responses (e.g., "How much time in the past week have you tried to not think certain thoughts?") [25]. Participants responded to each item with the degree to which they had engaged in the particular style of thinking or coping, on a continuous scale. For this study, an index score was calculated by dividing the total score by the number of items summed for the index. Items measuring metacognitive beliefs were discarded. The CAS index score showed good levels of internal consistency in this sample (CAS $\alpha = 0.82$).

2.4 Statistical Analysis

Intercorrelations between the primary predictor variables (i.e., distress, pain, fatigue, illness appraisals, metacognitive beliefs, and the CAS) were tested with parametric and non-parametric methods. Due to the large number of correlations undertaken, a significance level of 0.01 was adopted to reduce Type 1 error. Correlations were also scrutinised against a more stringent Bonferroni corrected alpha level ($p < 0.004$). In the main analysis, hierarchical regression was used to test whether metacognitions explained additional variance in distress in PwMS, after controlling for demographics and clinical variables, and illness appraisals. Statistical power was calculate using a-priori calculation for hierarchical regression with a medium effect size of 0.15, power of 0.8 and significance level of 0.05. Based on linear regression testing F_{change}, a minimum sample of 129 was estimated. Multicollinearity was inspected by examining the variable inflation factor (VIP) and tolerance for all variables entered in the regression (cut offs; VIP < 10, tolerance > 0.2) [38]. The order of the variables and method of entry into the regression equation was based on methodological and logical precedence. Step 1 controlled for demographic variables which were forced into the equation (age, gender, education, and employment status); Step 2 controlled for clinical variables using forced-entry (pain and fatigue); Step 3 controlled for cognitive appraisals of illness (IPQ-R subscales) using stepwise selection to determine model entry; and Step 4 tested the independent contribution of metacognitive beliefs (MCQ-30 subscales) after controlling for the aforementioned variables also using stepwise variable selection.

To test the hypothesised relationships between metacognitive beliefs, the CAS and distress, two mediational analyses were performed; Model 1, x = PMCBS, m = CAS, y = distress, and Model 2, x = NMCBS, m = CAS, y = distress. Both mediation models controlled variables that made significant independent contributions in the hierarchical regression (education, pain, fatigue and treatment control). Three criteria for carrying out mediation analyses were satisfied in this study [39]; 1) all variables entered into the mediational model were significantly correlated, 2) the design of the model was based on a hypothesised temporal precedence of metacognitive beliefs preceding distress [22, 40], and 3) the relationship between metacognitive beliefs and distress was reduced or eliminated

when accounting for variance in the CAS. All analyses were carried out using SPSS version 20.0.0 Hayes [41]. The PROCESS macro for SPSS was used to run the mediational analyses. Bootstrapping with 5,000 samples was used in line with recommendations [42]. Bias-corrected and accelerated confidence intervals are reported in the mediation analysis.

3 Results

3.1 Sample Characteristics

Table 1 provides a summary of the sample characteristics. Of the 132 participants that completed the survey, 100 (75.8%) reported having RRMS. A large proportion of the sample had received or were in receipt of treatment for anxiety or depression (84.8%). Sixty nine participants (52.3%) scored above 11 for anxiety and 45 for depression (34.1%). There were 45 (34.1%) participants that met caseness for both anxiety and depression using a cut-off score of 11+. One hundred and thirteen (85.6%) participants reported severe levels of fatigue [33]. One hundred and twenty five (94.7%) identified themselves as White, which is a moderately higher composition of Caucasian people compared to African or Asian as found in epidemiological studies of PwMS [43].

Table 1
Sample characteristics (N = 132)

Variable	N (%) or Mean (SD)
Demographic Variables:	
Gender	
Female	111 (84.1%)
Male	21 (15.9%)
Age in years	M = 43.3 (SD = 11.94)
Years full-time education	M = 14.43 (SD = 3.2)
Ethnicity	
White	125 (94.7%)
African	1 (0.8%)
Caribbean	2 (1.5%)
Asian	1 (0.8%)
Mixed ethnicity	1 (0.8%)
Other	2 (1.5%)
Number employed	65 (49.2%)
Clinical Variables:	
Duration of MS in years	M = 7.31 (SD = 7.5)
Disease course	
RRMS	100 (75.8%)
SPMS	15 (11.4%)
PPMS	8 (6.1%)
PRMS	2 (1.5%)
Unknown	7 (5.3%)
Received treatment for depression / anxiety	81 (61.4%)
Past treatment for depression / anxiety	100 (75.8%)
HADS caseness for depression	
Non-cases (score range 0-7)	50 (37.9%)
Doubtful cases (score range 8-10)	37 (28%)
Cases (score 11+)	45 (34.1%)
HADS caseness for anxiety	
Non-cases (score range 0-7)	27 (20.5%)
Doubtful cases (score range 8-10)	36 (27.3%)
Cases (score 11+)	69 (52.3%)
HADS comorbid depression & anxiety	45 (34.1%)
Fatigue	M = 5.71 (SD = 1.4)
Pain	M = 3.98 (SD = 3.1)

Note. RRMS = relapse remitting MS; SPMS = secondary progressive MS; PPMS = primary progressive MS; PRMS = progressive lapsing MS. Caseness for depression and anxiety was defined by a score of 11 or more on both HADS subscales [29]. A mean score from the FSS was used in the present study (i.e., total score/number of items). Pain was scored on a VAS ranging from 0 *no pain* – 10 *unbearable pain.*

3.2 Correlations and Descriptive Statistics

Intercorrelations and descriptive statistics for the independent and dependent variables (i.e., IPQ-R, MCQ-30 subscales and the CAS) are presented in Table 2. Three illness appraisal subscales were significantly associated with distress (i.e., positive correlation for consequences, and negative

correlations for personal and treatment control, $r = 0.3$ to 0.35, $p < 0.01$). Of the metacognition subscales, four were positively associated with distress (PMCBS, NMCBS, CC, and NC, $r = 0.37$ to 0.49, $p < 0.01$), confirming the first prediction of this study. It was particularly noteworthy that there was an absence of significant correlations between positive and negative metacognitive beliefs and all illness appraisal subscales, demonstrating the specificity of PMCBS and NMCBS, whereas the CAS correlated with both of these sets of variables ($r = 0.2$ to 0.59, $p < 0.01$), apart from 'timeline' illness appraisals ($r = 0.05$, $p > 0.01$).

Table 2
Intercorrelations between the study primary predictor variables and descriptive statistics

		2	3	4	5	6	7	8	9	10	11	12	13	M	SD
1	HADS	.18	.30**	-.24**	-.35**	-.15	.22	.22*	.49**	.45**	.37**	0.1	.67**	19.46	6.92
2	T		.26**	-.25**	-.46**	.06	.04	-.05	.02	.24**	.01	-.09	.05	26.74	3.9
3	C			-.08	-.37**	-.08	.18	-.05	.10	.31**	.10	.20	.28**	24.64	4.18
4	PC				.49**	.12	.03	.06	.03	-.10	.01	.23**	-.20*	19.35	5.17
5	TC					.01	.04	.07	-.11	-.33**	-.09	.08	-.26**	13.79	4
6	IC						-.29**	-.09	-.05	-.18	-.16	.04	-.23**	16.46	5.42
7	TLC							.06	.11	.29**	.19	.07	.23**	14.16	3.66
8	PMCBS								.45**	.09	.59**	.31**	.26**	10.84	4.38
9	NMCBS									.28**	.61**	.42**	.59**	14.61	4.49
10	CC										.28**	.10	.35**	15.08	5.52
11	NC											.43**	.41**	11.89	4.33
12	CSC												.27**	16.24	4.46
13	CAS													4.15	2.01

Note. M = Mean; SD = Standard deviation; HADS = Distress; *IPQ-R Subscales*: T = Timeline; C = Consequences; PC = Personal Control; TC = Treatment Control; IC = Illness Coherence; TLC = Timeline Cyclical. *MCQ-30 Subscales*: PMCBS = Positive Metacognitive Beliefs; NMCBS = Negative Metacognitive Beliefs; CC = Cognitive Confidence; NC = Need to Control; CSC = Cognitive Self-consciousness; CAS = Cognitive Attentional Syndrome Index; * $p < 0.01$; ** Bonferroni corrected $p < 0.004$

3.3 The Unique Contribution of Metacognitive Beliefs to Distress

Table 3 shows the results from the hierarchical regression predicting distress, whilst controlling for demographic and clinical variables (age, gender, employment, pain and fatigue), and illness appraisals. According to a-priori power calculation the hierarchical regression was adequately powered with the sample size employed. Demographic variables entered at Step 1 were non-significant ($F = 1.89$, $df = 4,127$, $p = 0.12$). Levels of pain and fatigue entered at Step 2 were

significant (F_{change} = 20.64, *df* = 2,125, $p < 0.001$), accounting for an additional 23% of the variance in distress. At step 3, using stepwise selection of the illness appraisal variables, treatment control appraisals entered the model and accounted for a further 4% of the variance in distress (F_{change} = 7.37, *df* = 1,124, $p < 0.01$). In the final step of the model, Step 4, in which metacognition variables entered the model using stepwise entry, NMCBS made a significant and unique contribution to distress, accounting for an additional 18% of the variance (F_{change} = 45.74, *df* = 1,123, $p < 0.001$). This result therefore confirmed the second prediction of the study. Overall the final model explained 48% of the variance in distress. Whilst the demographic variables entered as a single block of variables was non-significant, years in full time education did make a significant and independent contribution to the model (r = -0.20, $p < 0.05$). The largest significant and independent contributions were for NMCBS (β = 0.45, $p < 0.001$) and levels of fatigue (β = 0.38, $p < 0.001$).

Table 3
Summary of the hierarchical regression predicting distress

	Stepwise Statistics			**Final Statistics**		
Step	**Variable**	**ΔR^2**	**Sig.**	***β***	***T***	**Sig.**
1 Enter	Age	0.056	0.115	-0.076	-0.820	0.414
	Gender			0.011	0.121	0.904
	Education			-0.202	-2.260	**0.026**
	Employment			-0.125	-1.342	0.182
2 Enter	Pain	0.234	**0.000**	0.263	2.988	**0.003**
	Fatigue			0.371	4.178	**0.000**
3 Stepwise	TC	0.040	**0.008**	-0.169	-2.454	**0.016**
4 Stepwise	NMCBS	0.182	**0.000**	0.454	6.763	**0.000**

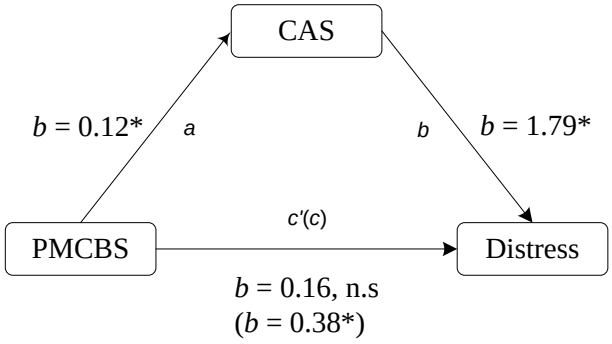
Note. TC = Treatment Control; NMCB = Negative Metacognitive Beliefs; Significant results highlighted in bold.

3.4 Mediation of the Association between Metacognitive Beliefs and Distress by the CAS

Results of the mediational analyses are presented in Figures 1 and 2. In both mediational models education, pain, fatigue and treatment control appraisals were controlled for as covariates. Bootstrapping techniques were performed with 5,000 samples and the analysis had satisfactory statistical power (bias-corrected and accelerated confidence intervals are reported). In the first model,

there was a significant indirect effect between PMCBS and distress (*ab* = 0.22, BCa 95% CIs = 0.08 to 0.39), mediated by the CAS. The results indicated full mediation, as the direct effect between PMCBS and distress was non-significant when accounting for the CAS. Similarly, the CAS significantly mediated the relationship between NMCBS and distress (*ab* = 0.35, BCa 95% CIs = 0.22 to 0.52), however, the direct effect remained significant when including the CAS in the model, indicating partial mediation (*b* = 0.38, *p* < 0.01).

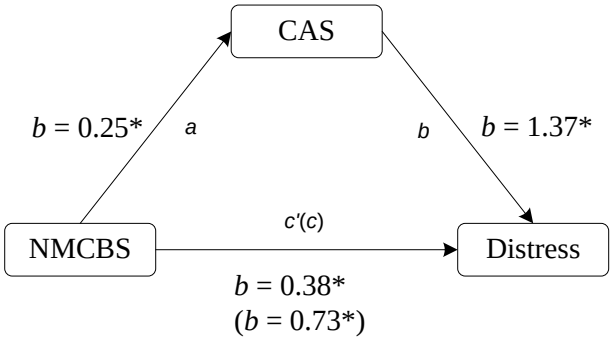
Figure 1. Mediation of PMCBS and distress via the CAS.



Indirect effect = 0.22, BCa 95% CIs = 0.08 to 0.39

Notes. PMCBS = positive metacognitive beliefs about worry; CAS = cognitive attentional syndrome; n.s = non-significant; * *p* < 0.01; Model covariates; education, pain, fatigue and treatment control. Bootstrapping with 5,000 samples was used.

Figure 2. Mediation of NMCBS and distress via the CAS.



Indirect effect = 0.35, BCa 95% CIs = 0.22 to 0.52

Notes. NMCBSs = negative metacognitive beliefs about worry; CAS = cognitive attentional syndrome; n.s = non-significant; * $p < 0.01$; Model covariates; education, pain, fatigue and treatment control. Bootstrapping with 5,000 samples was used.

4 Discussion

This study investigated the role of metacognitive beliefs in distress in PwMS, specifically testing the predictions of the S-REF model for the first time in this population. In this sample, four types of metacognitive beliefs were positively associated with distress confirming the first prediction of the study. In addition, the second prediction asserting that metacognitive beliefs would make a unique contribution to distress, over and above covariates was also confirmed with NMCBS accounting for additional variance in distress after controlling levels of fatigue and pain, and illness appraisals. In the mediational analysis, the relationship between PMCBS and distress was fully mediated by the CAS, while the CAS partially mediated the association between NMCBS and distress, in line with the final prediction of the study.

4.1 Metacognitive Beliefs and Distress

Findings were consistent with the results from previous studies testing the role of metacognitive beliefs in emotional distress in other chronic health populations [23, 44]. However, while positive and significant correlations were evident between metacognitive beliefs and distress which confirms the first prediction of the study, only NMCBS made an independent and significant contribution in the regression model, with fatigue being the next largest contributor. This pattern of results therefore only provides partial support for the second prediction of the study. It does however suggest that NMCBS about the uncontrollability and dangerous nature of worry (e.g., “Once I start worrying, I cannot stop; I am damaging my mind with worry”) and levels of fatigue, are important factors involved in heightened distress in PwMS. The negative finding for PMCBS was noteworthy, given these metacognitive beliefs (e.g., “Worrying helps me avoid problems in the future”) have been implicated in previous research employing comparable methodology [44]. However, here we used a total distress score, where previous research has modelled depression and anxiety separately [44]. This difference may have be due to the MCQ-30 lacking sensitivity to PMCBS about rumination, which is often a more prominent feature in depression [45]. Although comorbid depression and anxiety were high in

this sample, there were participants that met the caseness threshold for depression and not anxiety, potentially reducing the sensitivity of the MCQ-30 to PMCBS in the depressed participants.

4.2 Illness Appraisals and Distress

The results demonstrated that illness appraisals about the consequences (e.g., “My MS has major consequences on my life”), and personal and treatment control over the illness (e.g., “My actions will have no effect on the outcome of my illness; There is very little that can be done to affect the outcome of my MS”) were predictive of distress in this sample, consistent with previous studies testing the assertions of the common-sense model in this population [16, 46]. However, after controlling for demographic and clinical variables, only treatment control appraisals made a significant and independent contribution to distress, explaining a small proportion of the overall variance. Given previous studies have not controlled for levels of pain and fatigue [16, 46], it is possible that these variables play an important role in influencing the nature and conviction of illness appraisals. Indeed, previous research has identified links between fatigue and illness appraisals [36, 47]. It is also possible that different illness appraisals are differentially associated with depression and anxiety, which has been found when levels of depression and anxiety have been modelled separately [16].

4.3 Metacognitive Beliefs and the CAS

According to the S-REF model, PMCBS do not cause distress *per se*, but do so by promoting the selection of worry/rumination as a coping response (e.g., “Worrying helps me cope”) and increasing focus on sources of threat, whilst NMCBS lead to negative appraisals of worry/rumination (e.g., “My worrying could make me go mad” and “When I start worrying, I cannot stop”) and unhelpful self-regulation strategies (e.g., avoidance and thought suppression). The results of the mediational analysis supported these hypothesises, with a full mediation effect of the CAS between PMCBS and distress, and a partial mediation effect of the CAS between NMCBS and distress. These findings cross-validate previous studies employing comparable mediational models [44, 48].

4.4 Study Limitations

Research investigating the hypothesised relationships between psychosocial factors and emotional distress is challenging area, due to issues with construct specificity, measurement error, and confounding effects. Steps were taken in this study to inspect the measures in terms of their prior validation and to examine the distinctiveness of the items. Confounding effects of variables clinical variables (e.g., pain and fatigue) were also statistical controlled for.

While this study provides the first evidence implicating the deleterious role of metacognitive beliefs in PwMS, a number of limitations should be noted. Firstly, relationships between the outcome and predictors could theoretically be reversed, in which distress causes the predictor variables rather than the assumed direction of causality. Nevertheless, the predictions were based on previous longitudinal research [22, 40]. Secondly, although the study controlled for established clinical variables (i.e., pain and fatigue), there are other potentially important variables that warrant measurement, such as disease severity [49-53]. Thirdly, the representativeness of the sample may have been limited, given most of the sample were female, and predominantly White, exceeding estimates from epidemiological research [43].

4.5 Implications and Conclusions

The findings largely support the relevance of the S-REF model in the maintenance of distress in PwMS, specifically the deleterious role of negative beliefs about the uncontrollability and harmful nature of worry. Psychological interventions with PwMS may be more effective when they target and modify metacognitive beliefs and the CAS (e.g., tackling worry/rumination, attentional focus, and unhelpful coping responses such as avoidance). Such an approach diverges from traditional cognitive-behavioural therapy, which would lend greater credence to the specific cognitive content, both in relation to the distressing aspects of the illness (e.g., “I could have another relapse any day now”), and negative illness appraisals (e.g., “My illness has major consequences on my life”) that are often appropriate and realistic in PwMS [16].

Several models of therapy may effectively address NMCBs in PwMS. In Metacognitive Therapy [25] behavioural experiments are used to demonstrate the ability to disengage from the process of worry (e.g., worry postponement) and to highlight the safety of thoughts when observed without conceptual processing (i.e., detachment of self from thoughts). Similarly, in Acceptance and Commitment Therapy [54] metaphors and mindfulness skills are used to promote cognitive flexibility, to undermine experiential control (i.e., pushing against thoughts or mentally avoiding them), to weaken cognitive fusion (e.g., to move the client from what their mind says to attend to the present moment), and to develop the observer self. Therefore ACT in a sense tackles NMCBs by defusing the client from what their mind is saying about losing control of one's thoughts, to a state of awareness without an evaluation of content or meaning. A somewhat different approach can be found in Compassion-Focused Therapy (CFT) [55], which applies functional analysis with specific reference to exploring the nature of a perceived threat. In the case of NMCBs, the threat could the potential of damaging one's mind through excessive worry (i.e., self-criticism in relation to losing control, e.g., "I cannot stop worrying about my MS, I should be able to cope"). CFT promotes a compassionate self-view to reduce self-criticism in order to strengthen an adaptive way of processing of difficult emotions.

To take forward the findings of this study, longitudinal research is necessary to investigate whether metacognitive beliefs measured at baseline predict distress over time, whilst controlling for baseline levels of distress, clinical and demographic variables, and illness appraisals. To support the translation of these empirical findings to clinical practice, psychological interventions that target and modify NMCBS in PwMS should be investigated in trials testing their efficacy against traditional cognitive-behavioural approaches.

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Appendices

Appendix A. Author guidelines for the British Journal of Health Psychology.

Appendix C. Statement of Contribution

What is already known on this subject?

Multiple sclerosis (MS) is a common demyelinating disease that significantly impacts on the quality of life. The prevalence of depression and anxiety is higher in people with MS than the general population. Research has identified of a range psychosocial correlates of emotional distress in MS.

What does this study add?

Prospective psychosocial studies of MS has been an emerging area of research in the last decade. No systematic reviews have been published that identify psychosocial predictors of emotional distress over time in MS. The review summarises prospective evidence for psychosocial predictors, engendering novel avenues of research in MS.

Appendix D. Database search strategy

Boolean operator	Search terms	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

Appendix E. Study data to assess inclusion

First Author & Date	Sample	MS Sample Size	Distress Outcomes	Psychosocial Variables	Validated Measures	Reason for Exclusion
Aikens 1997	PwMS	T1 = 27 T2 = 22 T3 = 22	▪ Depression	▪ Life stress ▪ Coping style	Yes	Included
Barnwell 1982	PwMS	T1 = 75 T2 = 71	▪ Depression ▪ Self-esteem ▪ Performance	▪ Self-efficacy	Yes	Included
Brooks 1982	PwMS	T1 = 103 T2 =103	▪ Self-concept	▪ Locus of control	No	Excluded: Measures not validated and inadequately described
Devins 1993	PwMS	T1 = 146	▪ Depression ▪ Affect ▪ Mood states ▪ Mood Symptoms	▪ Illness intrusiveness ▪ Personal control	Yes	Excluded: No longitudinal analysis due to stability in primary outcomes
Janssens 2006	PwMS Partners	T1 = 120 T2 = 98 T3 = 97 T4 = 88	▪ Depression & anxiety ▪ Disease-related distress		Yes	Excluded: Study focused on describing the course of distress rather than identifying predictors
Johansson 2016	PwMS	T1 =199 T1 = 185 T3 = 185	▪ Depression	▪ Coping capacity ▪ Perceived impact of MS ▪ Social/Lifestyle Activities	Yes	Included
Koch 2015	PwMS	T1 = 1376 T2 = 984 T3 = 967 T4 = 457 T5 = 258	▪ Depression		Yes	Excluded: No psychosocial predictors. Study focused on clinical predictors
Kneebone 2015	PwMS	T1 = 495 T2 = 396 T3 = 386	▪ Depression	▪ Attributional style ▪ Life stress	Yes	Included
Madan 2014	PwMS	T1 = 388 T2 = 296	▪ Depression & anxiety ▪ Positive affect ▪ Positive states of mind	▪ Dispositional hope ▪ MS related stress	Yes	Included
McCabe 2004	PwMS	T1 = 251 T2 = 251	▪ Depression & anxiety ▪ Self-esteem	▪ Coping style ▪ Work capacity & social relationships	Yes	Included
McCabe 2005	PwMS	T1 = 243 T2 = 243 T3 = 243	▪ Depression & anxiety ▪ Self-esteem	▪ Coping style	Yes	Included
Pakenham 1999	PwMS	T1 = 122 T2 = 96	▪ Depression ▪ Global distress	▪ Stressful life events ▪ Coping ▪ Cognitive appraisal ▪ Social support	Yes	Included
Pakenham 2005	PwMS	T1 = 477 T2 = 404	▪ Global distress ▪ Positive & negative affect	▪ Benefit finding ▪ MS related stress	Yes	Included
Pakenham 2005b	PwMS Carers	T1 = 222 T2 = 155	▪ Global distress ▪ Positive & negative affect ▪ Dyadic adjustment	▪ Benefit finding	Yes	Excluded: Study focused on carer adjustment
Pakenham 2006	PwMS	T1 = 477 T2 = 404	▪ Depression & Anxiety ▪ Positive affect	▪ Coping ▪ Stress appraisal	Yes	Included
Pakenham 2007	PwMS	T1 = 388 T2 = 296	▪ Depression & Anxiety ▪ Positive states of mind	▪ Sense making		Included
Pakenham 2007b	PwMS	T1 = 502 T2 = 404		▪ Benefit finding	Yes	Excluded: Content analysis study of Benefit finding
Pakenham 2009	PwMS	T1 = 388 T2 = 296	▪ Depression & Anxiety	▪ Benefit finding	Yes	Included

			▪ Positive affect ▪ Positive States of Mind			
Pakenham 2011	PwMS	T1 = 145 T2 = 128	▪ Distress ▪ Positive affect	▪ Acceptance: MSAQ	Yes	Included
Schiaffino 1998	PwMS PwRA	T1 = 66 T2 = 66	▪ Depression	▪ Illness representations	Yes	Included
Tepavcevic 2013	PwMS	T1 = 109 T2 = 97	▪ Depression	▪ Quality of life	Yes	Included

Notes. PwMS = people with multiple sclerosis; T* = time point ; PwRA = separate group of people with Rheumatoid Arthritis

Appendix F. Data Extraction Form

<table>
<tr><td colspan="3">First author:</td><td colspan="3">Year of study:</td></tr>
<tr><td colspan="6">Citation:</td></tr>
<tr><td colspan="6">Study Eligibility</td></tr>
<tr><td rowspan="4">Type of Study</td><td colspan="2">☐ Cohort study</td><td>Location of study:</td><td>Total duration of FU:</td><td>Number of time-points:</td></tr>
<tr><td colspan="2"></td><td></td><td></td><td></td></tr>
<tr><td colspan="5">Inclusion criteria
1) Peer-reviewed empirical study collecting prospective data
2) Tested psychosocial predictors of subsequent distress
3) Results focused on people with multiple sclerosis
4) Used validated outcome measures
5) Published in English language</td></tr>
<tr><td colspan="5">Study aims:</td></tr>
<tr><td rowspan="4">Sample Characteristics</td><td>Sample size per time-point:</td><td>Demographic information reported:</td><td>Disease course / MS types:</td><td>Time since diagnosis:</td><td>Level of disability & measure(s) used:</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="3">Are participants defined as a group having specific social or cultural characteristics?</td><td colspan="2">Yes ☐ No ☐ Unclear ☐</td></tr>
<tr><td colspan="3"></td><td colspan="2">Details:</td></tr>
<tr><td colspan="6">Outcomes and Predictors</td></tr>
<tr><td rowspan="3">Distress Measures</td><td colspan="5">Distress outcomes and measures used:</td></tr>
<tr><td colspan="3">Do the outcome measures meet this criteria for inclusion?</td><td colspan="2">Yes ☐ No ☐ Unclear ☐</td></tr>
<tr><td colspan="5">Details:</td></tr>
<tr><td rowspan="3">Psychosocial Predictors</td><td colspan="5">Psychosocial variables and measures used:</td></tr>
<tr><td colspan="3">Do the measures meet this criteria for inclusion?</td><td colspan="2">Yes ☐ No ☐ Unclear ☐</td></tr>
<tr><td colspan="5">Details:</td></tr>
<tr><td colspan="6">Statistical Analysis and Covariates</td></tr>
<tr><td>Statistical Analysis</td><td colspan="5">Description of analysis:</td></tr>
<tr><td>Demographic Variables</td><td colspan="5">Demographic variables:</td></tr>
</table>

Clinical Variables	Clinical variables and measures:	
	Does the study design meet the criteria for inclusion?	Yes ☐ No ☐ Unclear ☐
	Details:	

Psychosocial Predictor Findings		
Variables included in the analysis:	Distress outcomes:	Statistical results:

Appendix G. Modified version of the Newcastle-Ottawa Quality scale for assessing bias in cohort studies

SELECTION (maximum of 1 star for each numbered item)
1) Representativeness of the exposed cohort
   a) Truly representative of the average Multiple Sclerosis in the community ⋆
   b) Somewhat representative of the average Multiple Sclerosis in the community (i.e., the majority of sample consists of people with relapse-remitting MS) ⋆
   c) Selected group of users, e.g., specific disease course group
   d) No description of the disease course of the cohort
2) Selection of the non-exposed cohort (*Note*. Not applicable - review concerned with studies employing multilevel modelling with continuous scales of measurement)
   a) Drawn from the same community as the exposed cohort ⋆
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure (i.e., psychosocial measure)
   a) Secure record ⋆
   b) Validated psychosocial measure ⋆
   c) Written self-report
   d) No description
4) Demonstration that outcome of interest was not present at start of study (*Note*. Not applicable - outcome of interest measured on a continuous scale)
   a) Yes ⋆
   b) No

COMPARABILITY (maximum of 2 stars)
1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for baseline levels of the dependent variable(s) ⋆
   b) Study controls for any additional factors; demographics or illness variables (e.g., illness severity, pain, fatigue, etc) ⋆

OUTCOME (maximum of 1 star for each numbered item)
1) Assessment of outcome
   a) Independent blind assessment or validated measure of distress ⋆
   b) Record linkage ⋆
   c) Self-report
   d) No description
2) Was follow-up long enough for a change in distress to occur?
   a) Yes (≥3 months) ⋆
   b) No
3) Adequacy of follow up of cohorts
   a) Complete follow up (all subjects included in baseline assessment followed-up successfully) ⋆
   b) Subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % of baseline sample successfully followed up, or description provided of those lost) ⋆
   c) Follow up rate < 80% of baseline sample and no description of those lost
   d) No statement

Appendix H. Ethical Approval Email

Appendix I. Hospital Anxiety and Depression Scale

Appendix J. Demographic and clinical data.

Please answer the following demographic questions

Gender

- Male
- Female

How old are you? Please give your answer in years and months

What is your ethnic group?

- White
- Mixed/multiple ethnic groups
- Asian
- African
- Caribbean
- Other ethnic group

How many years have you attended full time education?(e.g. The statutory school age in England, Wales and Scotland is from 5 years to 16 years, so this equates to 11 years full time education)

Are you currently employed, in voluntary work, or a full time carer?

- Employed
- Voluntary work
- Full time carer
- Unemployed
- None of the above

Please answer the following questions about your multiple sclerosis and well-being

How long have you had your diagnosis of multiple sclerosis? Please give your answer in years and months

Do you know the type of MS you have?

- Relapse Remitting
- Secondary Progressive
- Primary Progressive
- Progressive Relapsing
- Don't know

Are you currently receiving treatment for depression or anxiety?

- Yes
- No

Have you in the past received treatment for depression or anxiety?

- ❍ Yes
- ❍ No

Appendix K. Fatigue Severity Scale

Appendix L. Pain Visual Analogue Scale

Appendix M. Illness Perception Questionnaire – Revised

Appendix N. Metacognitions Questionnaire-30

A**ppendix O.** Cognitive Attentional Syndrome-10

Appendix P. Study Advert

Appendix Q. Participant Information Sheet

Appendix R. Participant Consent Form