Effects of Mindfulness-based interventions on physical symptoms in people with multiple sclerosis – a systematic review and meta-analysis
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Mindfulness-based interventions for physical wellbeing among people with multiple sclerosis – a systematic review and meta-analysis of randomised controlled trials

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Abstract

Background
Physical comorbidity is common among people with multiple sclerosis (PwMS). This study aims to update our previous systematic review (2014) and conduct a meta-analysis on the efficacy of Mindfulness-based interventions (MBIs) for improving physical wellbeing in PwMS.

Methods
In November 2017 we carried out systematic searches for eligible randomised controlled trials (RCTs) in seven major databases, updating our search in July 2018. We used medical subject headings and key words. Two independent reviewers used pre-defined criteria to screen, data extract, quality appraise, and analyse studies. The Cochrane Collaboration risk of bias tool was used to determine study quality. Physical wellbeing was the main outcome of interest. We used the random effects model for meta-analysis, reporting effect sizes as Standardised Mean Difference (SMD). This study is registered with PROSPERO: CRD42018093171.

Results
We identified 10 RCTs as eligible for inclusion in the systematic review (including 678 PwMS), whilst seven RCTs (606 PwMS) had data that could be used in meta-analysis. In general, comorbidity, disability, ethnicity and socio-economic status were poorly reported. MBIs included manualised and tailored interventions, treatment duration 6-9 weeks, delivered face-to-face and online in groups and also individually. The overall SMD for physical wellbeing against any comparator was 0.26 (0.08 – 0.44), I²=33%; against active comparators only SMD was 0.11 (-0.20 – 0.43), I²=56%. For fatigue SMD was 0.22 (0.05 – 0.39), I²=0%, for pain SMD was 0.16 (-0.46 – 0.79), I²=77%, for sexual satisfaction SMD was 0.66 (0.19 – 1.13), I²=0%. Three adverse events occurred across all studies.

Conclusions
MBIs effectively improve fatigue and sexual satisfaction, but not pain in PwMS. The optimal MBI for PwMS with impaired physical wellbeing remains unclear. Further research into MBI optimisation, cost- and comparative-effectiveness is required.

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**Keywords**
Multiple sclerosis
Physical wellbeing
Mindfulness
Systematic review
Meta-analysis
1.1 Background

Multiple sclerosis (MS) is a complex, poorly understood chronic inflammatory and neurodegenerative condition \(^1\). Common physical impairments include difficulties with vision, speech, swallow, bowel, bladder and sexual function, chronic pain, spasticity and limited mobility \(^1\). Comorbidity, or the presence of an additional long-term condition besides MS, is common among people with multiple sclerosis (PwMS) \(^2\). Physical comorbidities in MS are associated with more CNS lesions on Magnetic Resonance Imaging (MRI), greater levels of disability, increased hospitalisations, and higher mortality rates \(^3\). Furthermore, having additional physical conditions in MS is associated with more stress and worse quality of life (QoL); as the number of additional physical conditions increase, so does the prevalence of mental health impairment \(^2\).

Defining wellbeing is challenging \(^4\); the general consensus being that it is a multidimensional state, and recent proposals suggesting it as a useful means of 'demedicalising' the concept of 'health'. Indeed, the World Health Organization definition for health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' has been increasingly challenged lately as failing to reflect the complexity and dynamic nature of the state \(^5\). Huber et al. (2010) suggest that researchers, clinicians and policy makers should consider health as the ability to '..cope.. adapt and self-manage' a subjective 'dynamic equilibrium' or 'set-point' of one's functional capacity. In determining the effectiveness of interventions to improve physical wellbeing in the context of MS, patient reported outcome measures can be used as a proxy measure of the ability to self-manage, adapt and cope with the physical challenges associated with having the condition.

Among physical comorbidities in PwMS, hypertension, hyperlipidaemia and chronic lung disease predominate \(^6\). Specific care guidelines for managing these physical comorbidities in PwMS do not exist \(^3\). Fatigue is among the commonest symptoms reported by PwMS and chronic pain is also frequently reported \(^7\) \(^8\). The UK National Institute for Care and Clinical Excellence (NICE) recommends offering PwMS cognitive behavioural therapy (CBT), aerobic exercise, yoga, or
amantadine for fatigue, as well as avoiding stress and treating comorbid anxiety and depression. For chronic pain in PwMS, NICE recommends the application of generic treatment approaches.

Mindfulness-based interventions (MBIs) fit the UK Medical Research Council criteria for complex interventions, with multiple potential active components. Originally introduced in North America in the 1980s as a treatment for people with chronic pain, MBIs characteristically include a range of meditation practices, group exercises, psychoeducation and home practices. MBIs have been applied and researched in a range of health conditions and found to be effective treatments for anxiety, stress, recurrent depression and somatisation disorders. In a previous systematic review of the effectiveness of MBIs in PwMS in 2014, we found limited evidence to support MBIs as a potential treatment for comorbid fatigue from two randomised controlled trials (RCTs) and a controlled trial. Also in 2014, NICE highlighted MBIs as a potentially effective treatment for PwMS with fatigue. However, this assessment by NICE appears to have been based on only one high quality RCT. Since 2014, several more RCTs have been published and it is important to determine more definitively whether MBIs are effective treatments for fatigue in PwMS, as well as whether there is robust evidence for MBIs in improving other common physical comorbidities such as chronic pain or spasticity.

The aim of this review is to conduct a meta-analysis of RCTs testing the efficacy of MBIs in improving physical wellbeing in PwMS.

2.1 Methods

2.2 Protocol and registration

The protocol for this study is registered with Prospero at the Centre for Reviews and Dissemination, University of York: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=93171

In addition to this current study we also carried out a meta-analysis of MBI effects on mental wellbeing in PwMS - reported separately.
2.3 Eligibility for inclusion
We based eligibility on the Study design, Participants, Interventions, Outcomes (SPIO) model (deriving from PICOS)\(^\text{18}\). Eligible studies included: RCTs of PwMS with any MS phenotype, aged 18 years or older, any MBI that included the core practices of mindful breathing, mindful body awareness, and mindful movement, with outcomes (primary or secondary) focused on physical wellbeing.

2.4 Search strategy
We employed a search strategy from our previous systematic review for use in: Allied and Complementary Medicines Database (AMED), Cochrane Central Register of Controlled Trials, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Excerpta Medica dataBASE (EMBASE), Medical Literature Analysis and Retrieval System Online (MEDLINE), and PsycINFO. As our previous systematic review found the first study in this area was in 2000, we set our ‘years’ delimiter to 2000 – 2018. In addition, we also searched ProQuest Dissertations & Theses, reviewed key references from identified studies, searched the grey literature, and approached experts in the field. We carried out our initial search in November 2017 and repeated this in July 2018. Our search strategy as used in MEDLINE is available in Appendix A.

2.5 Study selection, storage and screening
We imported search results into COVIDENCE, a data storage package for systematic reviews. Title/abstracts were screened by two reviewers (RS, SB) for potential eligibility using keywords like ‘mindfulness’ and ‘multiple sclerosis’. Selected studies were then assessed against SPIO criteria by two reviewers (JB, RS) to assess ultimate eligibility. A senior, third party reviewer (SM) was available to arbitrate any disagreements.

2.6 Data collection/data items
Data from the final list of included studies was extracted guided by CONSORT\(^\text{19}\) and TIDieR\(^\text{20}\) checklist categories (Appendix B).
2.7 Quality appraisal
We used the Cochrane Collaboration’s tool for assessing risk of bias 21 to summarise risk for individual outcomes in selected studies, graded as high, unclear, or low risk. This assessed generation of sequence, concealment of allocation, blinding of participants, outcome assessors and personnel, incomplete outcomes, selective reporting of outcomes, and any other bias. Finally, an overall risk of bias was determined for each study based on the number of individual outcomes falling in to the high, unclear, and low risk categories:
Low = Low risk of bias for all key domains
Unclear = Low or unclear risk of bias for all key domains
High = High risk of bias for one or more key domains

2.8 Principal summary measures
The main outcome for this study was impact of MBI on physical wellbeing, with measures taken from baseline to study endpoint, where data was last reported for that outcome. For the purposes of this study, physical wellbeing is defined as the ability to ‘cope, adapt, and self-manage’ physical symptoms associated with having MS. Main outcome measures were all reported as continuous with mean, standard deviation (SD) values and the number of participants for each treatment group extracted. We calculated the unbiased standardised mean difference (SMD), a positive SMD indicating a finding in support of the intervention having a positive treatment effect. Where effect estimates were reported from adjusted regression models, we extracted these as the SMD.

2.9 Synthesis of results
Throughout this study we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 22 guidance. We used a random-effects meta-analysis regression model 23 to determine SMD, as outcome measures were known to vary widely. We report estimates with corresponding 95% confidence intervals (CI) and ‘p’ values. We used the $I^2$ statistic to determine variability between studies 24; $I^2$ representing the percentage of total variability in effect size estimates due to heterogeneity. An $I^2$ of 0% indicates that
all heterogeneity is due to sampling error, whilst an $I^2$ of 100% suggests all variability may be attributable to studies being truly heterogenous.

To assess for evidence of publication bias, we undertook Funnel plots and Egger’s Test for asymmetry. We used the ‘trim and fill’ method to determine the impact of any bias.\textsuperscript{25-28}

We carried out all statistical analyses in R version 3.4.0 and using the meta package.\textsuperscript{29}

\textbf{3.1 Results}

We identified ten RCTs as eligible for inclusion in the systematic review, with seven studies reporting endpoint data usable in meta-analysis (Figure 1). We sought additional information from several study authors; one\textsuperscript{30} replied.
Figure 1 – PRISMA flow diagram

- Records identified through database searching (n = 720)
- Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 544)

Records screened (n = 544) → Records excluded (n = 531)

Full-text articles assessed for eligibility (n = 13) → Full-text articles excluded, with reasons (n = 3; no physical wellbeing outcomes)

Studies included in qualitative synthesis (n = 10)

Studies included in quantitative synthesis (meta-analysis) (n = 7)
3.2 Systematic review

3.2.1 Study characteristics

Three studies took place in Iran 31-33, three in the UK 34-36, two in Italy 30 37, one each in the USA 38 and Switzerland 17. Four studies tested a MBI against treatment as usual 17 34-36, four versus an active comparator (three a psycho-education control 30 37 38, one pelvic floor muscle exercises 33), and in two the control condition was not clearly specified 31 32. Four study sample sizes were based on statistical power calculations 17 30 37 38. Number of study participants ranged from 24 – 150 (median 62). Eight studies reported measuring outcomes at three points in time (baseline, immediately post MBI, and at follow-up, which varied from 1 month post MBI to 1 year later) 17 30 33-38, whilst two studies took measures twice, pre and post MBI 31 32 (Table 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Powered (Y/N/unclear)</th>
<th>Comparator</th>
<th>Sample size (n)</th>
<th>Study attrition (%)</th>
<th>Outcome measures (others)</th>
<th>Data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mills &amp; Allen (2000)</td>
<td>Wales (UK)</td>
<td>Randomised controlled trial</td>
<td>N</td>
<td>Treatment as usual</td>
<td>24</td>
<td>33</td>
<td>Profile of Mood States, Standing balance, Symptom rating questionnaire</td>
<td>o Baseline  o Post MBI  o 3 months post MBI</td>
</tr>
<tr>
<td>Grossman et al. (2010)</td>
<td>Switzerland</td>
<td>Randomised controlled trial</td>
<td>Y</td>
<td>Treatment as usual</td>
<td>150</td>
<td>5</td>
<td>Center for Epidemiological Studies Depression, Spielberger Trait Anxiety Inventory, Modified Fatigue Impact Scale, Hamburg Quality of life Questionnaire in Multiple Sclerosis, Profile of health-related Quality Of Life in Chronic disorders, Goal setting, Neuropsychology assessment</td>
<td>o Baseline  o Post MBI  o 6 months post MBI</td>
</tr>
<tr>
<td>Bogosian et al. (2015)</td>
<td>England (UK)</td>
<td>Randomised controlled trial</td>
<td>N</td>
<td>Treatment as usual</td>
<td>40</td>
<td>5</td>
<td>General health questionnaire, Hospital Anxiety and Depression Scale, Multiple Sclerosis Impact Scale-29, EuroQol</td>
<td>o Baseline  o Post MBI  o 3 months post MBI</td>
</tr>
<tr>
<td>Mahdavi et al. (2016)</td>
<td>Iran</td>
<td>Randomised controlled trial</td>
<td>N</td>
<td>Indeterminate</td>
<td>24</td>
<td>0</td>
<td>Beck Anxiety Inventory, Beck Depression Inventory, Fatigue Severity Scale, Meta-Worry Questionnaire, Thought Fusion Inventory</td>
<td>o Baseline  o Post MBI</td>
</tr>
<tr>
<td>Nejati et al. (2016)</td>
<td>Iran</td>
<td>Randomised controlled trial</td>
<td>Unclear</td>
<td>Indeterminate</td>
<td>24</td>
<td>0</td>
<td>Multiple Sclerosis Quality of Life-54, Fatigue Severity Scale</td>
<td>o Baseline  o Post MBI</td>
</tr>
<tr>
<td>Simpson et al. (2017)</td>
<td>Scotland (UK)</td>
<td>Randomised controlled trial</td>
<td>N</td>
<td>Treatment as usual</td>
<td>50</td>
<td>12</td>
<td>Perceived Stress Scale, EuroQol, Multiple Sclerosis Quality of Life Inventory, Mindful Attention Awareness Scale, Self-Compassion Scale-short form, Emotional Lability Questionnaire</td>
<td>o Baseline  o Post MBI  o 3 months post MBI</td>
</tr>
<tr>
<td>Carletto et al. (2017)</td>
<td>Italy</td>
<td>Randomised controlled trial</td>
<td>Y</td>
<td>Psycho-education</td>
<td>90</td>
<td>21</td>
<td>Beck Anxiety Inventory, Beck Depression Inventory, Perceived Stress Scale, Brief Illness Perception Questionnaire, Functional Assessment of Multiple Sclerosis</td>
<td>o Baseline  o Post MBI  o 6 months post MBI</td>
</tr>
<tr>
<td>Cavalera et al. (2018)</td>
<td>Italy</td>
<td>Randomised controlled trial</td>
<td>Y</td>
<td>Psycho-education</td>
<td>139</td>
<td>39</td>
<td>Multiple Sclerosis Quality of Life-54, Hospital Anxiety and Depression Scale, Medical Outcomes Sleep Scale, Modified Fatigue Impact Scale</td>
<td>o Baseline  o Post MBI  o 6 months post MBI</td>
</tr>
<tr>
<td>Mosalanejad et al. (2018)</td>
<td>Iran</td>
<td>Randomised controlled trial</td>
<td>Unclear</td>
<td>Pelvic floor muscle exercises</td>
<td>75</td>
<td>7</td>
<td>Female Sexual Function Index</td>
<td>o Baseline  o Post MBI  o 1-month post MBI</td>
</tr>
<tr>
<td>Senders et al. (2018)</td>
<td>USA</td>
<td>Randomised controlled trial</td>
<td>Y</td>
<td>Psycho-education</td>
<td>62</td>
<td>16</td>
<td>Perceived Stress Scale, Patient-Reported Outcomes Information System, Connor-Davidson Resilience Scale, Paced Auditory Serial Attention Task</td>
<td>o Baseline  o Mid-intervention  o Post MBI  o 4 months post MBI  o 8 months post MBI  o 12 months post-MBI</td>
</tr>
</tbody>
</table>
3.2.2 Participant characteristics

There were 678 participants between the 10 RCTs included in the systematic review, versus 606 participants in the seven studies included in the meta-analysis. Participant ethnicity was described in three studies \(^{34\;36\;38}\), most were Caucasian. Between all 10 RCTs, the majority were female (76%; \(n=517\)). The extractable mean participant age was 46.0 years (not reported in \(^{31}\)). One study reported on socioeconomic status (SES) using post-code derived data \(^{36}\). Three studies described negligible data on employment status of participants \(^{35\;37}\).

Seven studies reported education status \(^{17\;30\;32\;34\;36\;38}\), most having school level education as a minimum. The majority (a minimum of 396 or 58%) had a relapsing-remitting phenotype, a minimum of 112 (17%) a secondary progressive phenotype, and a minimum of 27 (4%) a primary progressive phenotype. Degree of disability was reported in five studies \(^{17\;34\;36\;38}\), using the Expanded Disability Status Scale (EDSS) with a range of 2.3 – 6.5. Comorbidity (mental and physical) count was described in one study \(^{36}\) (mean 2.3, SD 1.7).

Four studies \(^{17\;30\;36\;38}\) described use of psychotropic and/or MS disease modifying drugs (Table 2).
## Table 2 - Participant characteristics

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>90% British Caucasian</td>
<td>Not reported</td>
<td>Not reported</td>
<td>100% British Caucasian</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>97% Caucasian</td>
</tr>
<tr>
<td><strong>Number of participants (% F)</strong></td>
<td>16 (80%)</td>
<td>150 (80%)</td>
<td>40 (55%)</td>
<td>24 (100%)</td>
<td>24 (46%)</td>
<td>50 (92%)</td>
<td>90 (71%)</td>
<td>139 (65%)</td>
<td>75 (100%)</td>
<td>67 (78%)</td>
</tr>
<tr>
<td><strong>Mean age (SD)</strong></td>
<td>49.8 (6.8)</td>
<td>47.3 (10.3)</td>
<td>52.2 (9.1)</td>
<td>NR</td>
<td>32.3 (5.1)</td>
<td>45 (10.9)</td>
<td>44.6 (9.4)</td>
<td>42.7 (8.7)</td>
<td>37.5 (6.5)</td>
<td>52.94 (11.37)</td>
</tr>
<tr>
<td><strong>Socio-economic status</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Postcode derived; controlled in analyses</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td>4 employed (25%)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>20 employed (40%)</td>
<td>59 employed (65%)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Education status (SD)</strong></td>
<td>Mean (SD) 14.1 (1.9) years of education</td>
<td>Completed high school</td>
<td>Completed high school</td>
<td>(56%) university</td>
<td>Not reported</td>
<td>11% elementary school; 52% completed high school; 38% university</td>
<td>Not reported</td>
<td>Not reported</td>
<td>60% college education at least</td>
<td></td>
</tr>
<tr>
<td><strong>Disease phenotype (%)</strong></td>
<td>Secondary progressive 16 (100%)</td>
<td>Relapsing 123 (92%)</td>
<td>Secondary progressive 23 (57.5%)</td>
<td>Primary progressive 17 (42.5%)</td>
<td>Not reported</td>
<td>Relapsing 40 (80%)</td>
<td>Secondary progressive 16 (32%)</td>
<td>Primary progressive 4 (8%)</td>
<td>Relapsing 79 (88%)</td>
<td>Secondary progressive 8 (7%)</td>
</tr>
<tr>
<td><strong>EDSS score</strong></td>
<td>Not reported</td>
<td>Mean (SD) 3.0 (1.1)</td>
<td>Mean (SD) 6.5 (1.5)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>4.4 (1.8)</td>
<td>2.3 (1.7)</td>
<td>Median 3.0</td>
<td>Not reported</td>
<td>4.6 (1.93)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Mean 2.4 (2.0); Range 0-9</td>
<td>Not reported</td>
<td>1 participant had severe depression on HADS</td>
<td>Excluded if comorbid conditions</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>On DMDs</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>26 (52%)</td>
<td>Not reported</td>
<td>104 (85%)</td>
<td>Not reported</td>
<td>34 (55%)</td>
</tr>
<tr>
<td><strong>Psychotropic medication(s)</strong></td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>No</td>
<td>Not reported</td>
<td>23 (46%)</td>
<td>Not reported</td>
<td>9 (6%)</td>
<td>Not reported</td>
<td>35 (56%)</td>
</tr>
</tbody>
</table>
3.2.3 Intervention characteristics

Mindfulness-Based Stress Reduction (MBSR) was explicitly used as the MBI in four studies \(^{17,30,36,38}\), MBSR was the loose basis in two \(^{32,37}\), two explicitly used Mindfulness-Based Cognitive Therapy (MBCT) \(^{31,34}\), one described the intervention as 'Mindfulness of Movement' \(^{35}\), and in the remaining case the foundation for the MBI was unclear \(^{33}\). Five studies reported on what course materials were provided to those taking part \(^{30,32,34-36}\). An interview was compulsory prior to taking part in three studies \(^{17,31,32}\). Two studies required evidence of impaired mental wellbeing (stress, anxiety) at baseline in order to take part \(^{34,38}\). Six studies reported on what MBI sessions comprised \(^{31,32,34,36,38}\), three provided scant information in this regard \(^{17,35,37}\), and in another this information was available in a separate publication, via the study protocol \(^{30}\).

Home practices were prescribed in six studies \(^{17,34-38}\). Teacher characteristics (training/certification/experience) were outlined in seven studies \(^{17,30,33,34,36-38}\), but details were sparse in one \(^{33}\). MBIs were delivered as groups in nine studies \(^{17,30-34,36-38}\), the remaining study delivered a one-to-one MBI \(^{35}\). An online platform was used to deliver the MBI in two studies \(^{30,34}\). Four studies reported where the MBI took place \(^{30,33,34,36}\). The majority of studies used eight MBI sessions \(^{30-34,36-38}\), there were nine in one study \(^{17}\), another used six \(^{35}\). Weekly MBI session lengths varied between 1-3 hours. There were between five to 25 participants per MBI class across the studies, sessions being administered by 1-2 MBI instructors. The core MBI components were delivered in all studies. However, in six studies the MBI was tailored for PwMS \(^{17,30,34-37}\), mostly in advance, but reflexively in one case \(^{36}\), where mindful movement was simplified to accommodate high levels of disability. Another study pre-emptively removed mindful movement following stakeholder consultation \(^{34}\). Home practice completion and/or session attendance was used to determine treatment adherence in six studies \(^{17,30,34-36,38}\). Intervention fidelity was appraised in three studies \(^{30,34,36}\), in one case by an independent observer checking session content against referenced standards \(^{34}\). The day retreat, characteristically part of week six in MBSR, was included in three studies \(^{17,37,38}\) (Table 3).
Table 3 – TIDieR checklist

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>2. Why (stated rationale/ theory/ goal)?</td>
<td>Develop moment to moment awareness of breathing, posture, movement with compassion</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Adaptation of MBSR. Focus on negative thinking, engaging low mood, changing relationship with thoughts, feelings, sensations, no longer avoiding/reacting to them automatically</td>
<td>Adaptation of MBSR. Focus on negative thinking, engaging low mood, changing relationship with thoughts, feelings, sensations, no longer avoiding/reacting to them automatically</td>
<td>Facilitate the compliance with and adaptation to medical conditions. Pay attention to being present in a non-judgmental manner</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Cultivation of mindful awareness, loving-kindness, enrichment of listening, self-compassion, sensorimotor psychotherapy principles ‘window of tolerance’</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Non-judgmental present moment awareness</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
</tr>
<tr>
<td>3. What - Materials provided to participants?</td>
<td>Written handout, audio and video aids</td>
<td>Not reported</td>
<td>Headset, webcam, compact discs for home practice</td>
<td>Not reported</td>
<td>Leaflets for each session and compact discs for home practice</td>
<td>Course manual, compact discs for home practice</td>
<td>Book - Full Catastrophe Living</td>
<td>Not reported</td>
<td>Dedicated website with online multimedia for home practices</td>
<td>Not reported</td>
</tr>
<tr>
<td>4. What - Procedures - Pre-session?</td>
<td>Had to make a commitment to regular practice</td>
<td>Personal intake interview; goal planning</td>
<td>Screened for evidence of distress on General Health Questionnaire</td>
<td>Personal intake interview</td>
<td>Personal intake interview</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Score of at least 10 on Perceived Stress Scale</td>
</tr>
<tr>
<td>4. What - Procedures - In session?</td>
<td>General description only - Body awareness, breath awareness, mindful</td>
<td>General description only - Observation of sensory, cognitive and affective experience in</td>
<td>Session content reported in paper - Raisin exercise, Mindful awareness, body scan, sitting practice, three-</td>
<td>Session outline reported in paper - Sustained attentional focus on the body and breath,</td>
<td>Session outline reported in paper - Body awareness, raisin exercise,</td>
<td>Session content reported in paper - Raisin exercise, Mindful breathing,</td>
<td>General description in trial protocol – Emphasis on sensorimotor resources: grounding, centring, self-</td>
<td>General description only - Based on original Mindfulness-based stress reduction</td>
<td>Session content reported in paper – Mindful breathing, body scan, sitting meditation, mindful</td>
<td>Session content reported in paper – Mindful breathing, body scan, mindful</td>
</tr>
</tbody>
</table>

Table 3 – TIDieR checklist

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>2. Why (stated rationale/ theory/ goal)?</td>
<td>Develop moment to moment awareness of breathing, posture, movement with compassion</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Adaptation of MBSR. Focus on negative thinking, engaging low mood, changing relationship with thoughts, feelings, sensations, no longer avoiding/reacting to them automatically</td>
<td>Adaptation of MBSR. Focus on negative thinking, engaging low mood, changing relationship with thoughts, feelings, sensations, no longer avoiding/reacting to them automatically</td>
<td>Facilitate the compliance with and adaptation to medical conditions. Pay attention to being present in a non-judgmental manner</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Cultivation of mindful awareness, loving-kindness, enrichment of listening, self-compassion, sensorimotor psychotherapy principles ‘window of tolerance’</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Non-judgmental present moment awareness</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
</tr>
<tr>
<td>3. What - Materials provided to participants?</td>
<td>Written handout, audio and video aids</td>
<td>Not reported</td>
<td>Headset, webcam, compact discs for home practice</td>
<td>Not reported</td>
<td>Leaflets for each session and compact discs for home practice</td>
<td>Course manual, compact discs for home practice</td>
<td>Book - Full Catastrophe Living</td>
<td>Not reported</td>
<td>Dedicated website with online multimedia for home practices</td>
<td>Not reported</td>
</tr>
<tr>
<td>4. What - Procedures - Pre-session?</td>
<td>Had to make a commitment to regular practice</td>
<td>Personal intake interview; goal planning</td>
<td>Screened for evidence of distress on General Health Questionnaire</td>
<td>Personal intake interview</td>
<td>Personal intake interview</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Score of at least 10 on Perceived Stress Scale</td>
</tr>
<tr>
<td>4. What - Procedures - In session?</td>
<td>General description only - Body awareness, breath awareness, mindful</td>
<td>General description only - Observation of sensory, cognitive and affective experience in</td>
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<td>General description in trial protocol – Emphasis on sensorimotor resources: grounding, centring, self-</td>
<td>General description only - Based on original Mindfulness-based stress reduction</td>
<td>Session content reported in paper – Mindful breathing, body scan, sitting meditation, mindful</td>
<td>Session content reported in paper – Mindful breathing, body scan, mindful</td>
</tr>
<tr>
<td>4. What - Procedures - Home practice?</td>
<td>Thirty minutes per day</td>
<td>Forty minutes per day</td>
<td>Ten-twenty minutes per day</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Forty-five minutes per day</td>
<td>Forty-five minutes per day</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Forty-five minutes per day</td>
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</tr>
<tr>
<td>4. What - Procedures - Post-course?</td>
<td>Not reported</td>
<td>Post course interviews for all participants</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Post course interviews for some participants</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>5. Who provided?</td>
<td>Not reported</td>
<td>Two experienced (over nine years), certified teachers</td>
<td>Study author. Had completed MBI teacher training</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Two experienced (seven and a half years), certified physician teachers</td>
<td>Trained clinical psychologists, used to working with people with multiple sclerosis</td>
<td>Expert MBSR trainer</td>
<td>Study author</td>
<td>Certified MBSR teacher with sixteen years of experience</td>
</tr>
<tr>
<td>6. How - Mode of delivery?</td>
<td>One-to-one, face-to-face, face-to-face, ten-fifteen per group</td>
<td>Group, via Skype, up to five per group</td>
<td>Group, twelve per group</td>
<td>Group, twelve per group</td>
<td>Group, face-to-face, twenty-five per group</td>
<td>Group, number per group not reported</td>
<td>Group, via Skype, average of five per group</td>
<td>Not reported</td>
<td>Group, number per group not reported</td>
<td></td>
</tr>
<tr>
<td>7. Where - Intervention location?</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Patients’ own homes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>NHS Centre for Integrative Care</td>
<td>Unclear</td>
<td>In patients own homes</td>
<td>University hospital out-patient clinic</td>
<td>Not reported</td>
</tr>
<tr>
<td>8. When and how much?</td>
<td>Six weekly sessions</td>
<td>Nine weekly two and a half hour sessions</td>
<td>Seven-hour practice day at week six</td>
<td>Eight weekly one hour sessions</td>
<td>Eight weekly two hour sessions</td>
<td>Eight weekly two and a half hour sessions</td>
<td>Eight weekly three hour sessions</td>
<td>Eight weekly sessions (? duration)</td>
<td>Eight weekly ninety minute sessions</td>
<td>Eight weekly two hour sessions</td>
</tr>
<tr>
<td>9. Tailoring?</td>
<td>Individualised application of core techniques</td>
<td>Developed with people with multiple sclerosis. MBCT manual adapted for Progressive multiple</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Developed with people with multiple sclerosis, informed MBSR optimisation</td>
<td>Protocol reports tailoring to needs of participants, but not reported in paper</td>
<td>Music meditations and acceptance of multiple sclerosis symptoms</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
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<tr>
<td></td>
<td>Not reported</td>
<td>Average thirty-two minutes home practice per day</td>
<td>Not reported</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Mindful movement removed</td>
<td>Ninety-two percent session attendance; Average twenty-nine minutes home practice per day</td>
<td>Senior clinical psychologist listened to session recordings for every session</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>for future iteration</td>
<td>Ninety-five percent completed four or more sessions. Home practice not reported</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>introduced</td>
<td>Sixty percent session attendance; Average thirty-two and a half minutes home practice per day</td>
<td>Based on National Institutes of Health (2004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Seventy-nine percent session attendance</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eighty-five percent attended six or more sessions. Median home practices thirty-eight minutes per day</td>
<td>Treatment integrity monitored, but not reported in what way</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
3.2.4 Outcome characteristics
Six studies measured the impact of MBI on fatigue, three on pain, and two on sexual satisfaction. Average home practice was reported in three studies (32, 29.2, 32.5 minutes) whilst one study reported median value/minimum-maximum range (38 minutes/day; 14 – 80). Attrition ranged from 0-39% across the ten studies.

3.3 Meta-analysis
3.3.1 Effect of MBIs on physical wellbeing measures
The effect of a MBI on physical wellbeing outcomes was measured in 10 studies; seven reported endpoint data usable in the meta-analysis. In meta-analysis the overall SMD treatment effect on physical wellbeing against any comparator was 0.26 (0.08 – 0.44; p<0.01), $I^2=33\%$ (low heterogeneity) (Figure 2); against active comparators SMD was 0.11 (-0.20 – 0.43), p<0.05, $I^2=56\%$ (medium heterogeneity) (Figure 3). Six studies evaluated MBI effect on fatigue, where the SMD against any comparator was 0.22 (0.05 – 0.39) p<0.05, $I^2=0\%$ (low heterogeneity); against active comparators only the SMD was 0.10 (-0.14 – 0.34), p=0.40, $I^2=0\%$ (low heterogeneity). Three studies evaluated MBI effect on pain, where the SMD was 0.16 (-0.46 – 0.79), p=0.61, $I^2=77\%$ (substantial heterogeneity). Two studies evaluated MBI effect on sexual satisfaction, where the SMD was 0.66 (0.19 – 1.13), p<0.01, $I^2=0\%$ (low heterogeneity).
Figure 2 Overall SMD for physical wellbeing outcomes (any comparator)

Figure 3 Overall SMD for physical wellbeing outcomes (active comparators)
3.3.2 Heterogeneity and publication bias

Using the $I^2$ statistic, heterogeneity among the studies was low (33%). The funnel plot identified no evidence of publication bias (Figure 4). The p-value from Egger’s Test of asymmetry was 0.63. The estimated number of ‘missing’ studies was seven using the trim and fill method. The pooled SMD estimate was 0.0017 (-0.20 - 0.20); p=0.99 following adjustment for those studies that were ‘missing’.

![Funnel plot with Trim and Fill](image)

3.3.3 Outcomes by intervention type

Where MBSR was used (four studies $^{17,30,36,38}$; n=401), SMD for fatigue was 0.22 (0.01 – 0.42), p=0.04, $I^2$=0%; for pain (two studies $^{36,38}$) SMD was -0.07 (-0.83 – 0.68), p=0.85, $I^2$=74%. Outcomes for MBCT came from a single pilot study $^{34}$ (n=40) versus usual care, where effect size for fatigue was 0.29 (-0.18 – 0.76), p=0.30 and the effect size for pain was 0.59 (0.14 – 1.04), p<0.05. Compared to a
psychoeducation control, a study using Body-Affective Mindfulness (n=90) had an effect size of 0.19 (-0.22 – 0.60), p=0.37 for effect on fatigue.

3.4 Study quality

Study quality was highly variable. Assessment was frequently made challenging by scanty reporting. For unclear reasons, those studies of highest quality (lowest risk of bias) originated from European countries and the United States. Eight studies outlined random sequence generation. Five studies were adjudged low risk for allocation concealment, with the remainder unclear. Blinding of assessors was outlined in six studies, as was outcome assessor blinding. Five studies were deemed low risk when assessing reporting of outcomes as incomplete. One study was assessed as at high risk for selective reporting of outcomes. In terms of overall risk of bias assessments, five studies were deemed low risk, two unclear, and three as high (Table 4). Appendix C details rationale for risk of bias assessments.
<table>
<thead>
<tr>
<th>Table 4 – Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
</tr>
<tr>
<td>Allocation concealment</td>
</tr>
<tr>
<td>Blinding of assessors</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
</tr>
<tr>
<td>Incomplete outcome data addressed</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
</tr>
<tr>
<td>Other sources of bias</td>
</tr>
<tr>
<td>Overall risk of bias</td>
</tr>
</tbody>
</table>
Figure 5 illustrates SMD for all trials able to be analysed arranged by risk of bias categories (unclear and low). No studies were deemed to have a high risk of bias. Low risk of bias (N=9) SMD was 0.27 (0.08 – 0.46); p<0.01 and unclear risk of bias (N=2) SMD was 0.31 (-0.39 – 1.01); p=0.38. Effect estimates did not vary significantly between risk of bias allocation in the overall risk of bias analysis, p=0.91.

### Figure 5 Risk of Bias Forest plot

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Study Description</th>
<th>TE</th>
<th>seTE</th>
<th>Standardised Mean Difference</th>
<th>SMD</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Bogosan:Fatigue(2015)</td>
<td>0.29</td>
<td>0.214</td>
<td>0.29 [0.18; 0.76]</td>
<td>9.5%</td>
<td></td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Bogosan:Pain(2015)</td>
<td>0.59</td>
<td>0.229</td>
<td>0.59 [0.14; 1.04]</td>
<td>10.2%</td>
<td></td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Carletti:Fatigue(2017)</td>
<td>0.19</td>
<td>0.2113</td>
<td>0.19 [-0.22; 0.60]</td>
<td>11.3%</td>
<td></td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Grossman:Fatigue(2016)</td>
<td>0.38</td>
<td>0.1884</td>
<td>0.38 [0.05; 0.71]</td>
<td>14.5%</td>
<td></td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Senders:Pain(2018)</td>
<td>-0.45</td>
<td>0.2700</td>
<td>-0.45 [-0.66; 0.08]</td>
<td>8.1%</td>
<td></td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Senders:Fatigue(2018)</td>
<td>0.21</td>
<td>0.2700</td>
<td>0.21 [-0.32; 0.74]</td>
<td>8.1%</td>
<td></td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Simpson:Fatigue(2017)</td>
<td>0.33</td>
<td>0.3200</td>
<td>0.33 [-0.30; 0.96]</td>
<td>6.3%</td>
<td></td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Simpson:Pain(2017)</td>
<td>0.32</td>
<td>0.2900</td>
<td>0.32 [-0.25; 0.89]</td>
<td>7.3%</td>
<td></td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>Simpson:Sexual Satisfaction(2017)</td>
<td>0.57</td>
<td>0.4100</td>
<td>0.57 [-0.25; 1.39]</td>
<td>4.1%</td>
<td></td>
<td>4.1%</td>
</tr>
</tbody>
</table>

Random effects model: 0.27 [0.02; 0.46] 79.5%

Test for effect in subgroup: z = 2.83 (p < 0.01)

**3.5 Meta-regression**

A meta-regression was undertaken to assess the relationship between predictors and effect estimates. We used a backward manual selection process with model covariates including: EDSS score, gender, intervention type, mean age, and risk of bias. To derive a final model, we sequentially excluded covariates based on
significance level (set for 5%). Intervention type (MBCT), mean age and risk of bias were found to be significant predictors of the effect estimate (Table 5)

Table 5 Meta-regression

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Estimates</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention type (MBCT*)</td>
<td>0.49</td>
<td>(0.03, 0.95)</td>
<td>0.04</td>
</tr>
<tr>
<td>Risk of Bias (Unclear)</td>
<td>-0.62</td>
<td>(-1.17, -0.07)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean age</td>
<td>-0.07</td>
<td>(-0.13, -0.004)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Reference for intervention type: MBSR; reference for risk of bias: Low

*MBCT – Mindfulness-based cognitive therapy; *MBSR – Mindfulness-based stress reduction

3.6 Adverse events

Two studies reported on adverse events associated with MBI exposure. In one study that used MBSR a participant reported an episode of increased spasticity during mindful body awareness. In the same study another participant described increased anxiety following the MBSR retreat. In another study using MBSR one participant with chronic pain reported increased symptoms following the raisin exercise.

4.1 Discussion

4.2 Summary of main findings

Ten RCTs that assessed the effects of an MBI on physical wellbeing outcomes in PwMS were eligible for inclusion in our systematic review; seven of these had data extractable for use in our meta-analysis. Four studies tested an MBI against an active comparator, four tested against treatment as usual, whilst the control condition was unclear in the remaining two studies. Intervention fidelity was reliably assessed in only one study. Sample sizes were mostly small, but four studies performed power calculations to inform required ‘n’ to detect meaningful effects. Follow-ups took place from immediately post-MBI to up to 1 year following course completion.
Six hundred and seventy-eight PwMS were included in these studies. Most (58%) had relapsing phenotypes. Most participants were female; mostly of Caucasian ethnicity. In general, comorbidity and disability levels were poorly reported.

Four studies used MBSR, two were loosely modeled on MBSR; two explicitly used MBCT, one ‘Mindfulness of Movement’, and in one case the basis for the MBI was unclear. Most interventions were provided as groups (n=5-25), delivering core MBI practices in and between sessions. Level of teacher training and experience were not well reported. MBI session attendance +/- home practice (treatment adherence) was described in six studies. Rates of attrition varied considerably (0-39%). Although very few adverse events were described from MBI training, few studies explicitly reported on this outcome.

Five RCTs were categorised as overall low risk of bias using the Cochrane Collaboration tool, three as high and two as unclear, signifying an overall improvement in study quality since we last assessed this in 2014.

Our meta-analysis indicates that MBIs are modestly effective treatments for fatigue in PwMS, moderately effective at improving sexual satisfaction, and are likely not effective for improving pain. No specific type of MBI was identified as optimal for treating impairment of physical wellbeing in PwMS.

4.3 Comparison with existing literature
In this study we found MBIs moderately effective for treating fatigue (SMD 0.22; 0.05 – 0.39), sexual satisfaction (SMD 0.66; 0.19 – 1.13), but likely not effective for improving pain (SMD 0.16; -0.46 – 0.79) in PwMS.

A 2018 meta-analysis of psychological interventions for treating fatigue in PwMS reported CBT to be moderately effective (SMD 0.32; 0.01 – 0.63) and MBIs to be considerably more effective (SMD 0.62; 0.12 – 1.12), but only included two of the six RCTs identified in our current review, likely reflecting an earlier search cut-off date in their study (April 2017).
No previous meta-analysis has assessed the impact of MBI training on pain in PwMS, but in chronic pain populations at large, several meta-analyses have been conducted. A 2014 meta-analysis reported moderate overall treatment effects (Cohen’s d) from MBI training (0.33; 0.03 – 0.62), a finding that diminished to a null effect when examining the effect against active comparators. A 2015 meta-analysis comprising painful musculoskeletal conditions reported small effects (Hedge’s g) versus usual care following MBI training on pain intensity (0.16; 0.03 – 0.36; the effect attenuated when compared against active comparators to 0.09; -0.13 – 0.31), moderate effects on perceived pain control (0.58; 0.23 – 0.93), but larger effects on pain acceptance versus usual care (1.58; -0.57 – 3.74). Finally, a 2017 meta-analysis found small overall effects against any comparator, SMD 0.32 (0.09 – 0.54), but included a wide variety of clinical syndromes.

No previous meta-analysis has assessed the impact of MBI training on sexual satisfaction in PwMS. However, in non-MS populations a 2017 meta-analysis assessed the impact of MBI training on female sexual function, finding moderate treatment effects (Hedge’s g) on sexual satisfaction (0.57; 0.40 – 0.74)

From our meta-analysis, MBIs appear to be a modestly effective treatment for fatigue in PwMS, may also be moderately effective in improving sexual satisfaction, but seem likely to be ineffective for improving pain in this context.

4.4 Strengths of this review
Guided by the PRISMA checklist, the TIDieR checklist and the Cochrane Collaboration tool, our multidisciplinary team of experienced reviewers used robust search, appraisal and analysis techniques for extracting and analysing data in this systematic review and meta-analysis.

4.5 Limitations of this review
Meta-analyses of RCTs by design exclude other potentially relevant data, such as that deriving from observational or qualitative research. When considering intervention feasibility, such as acceptability, accessibility and implementability,
these alternate study designs can provide important insights into how and why interventions succeed or fail in a given context. However, in this current study, the use of SPIO, the TIDieR checklist and Cochrane Collaboration tool for risk of bias, means that our evidence synthesis has covered other, related aspects of trial feasibility and execution.

4.6 Strengths and Limitations of the included studies
With all studies in our systematic review and meta-analysis being RCTs, our findings provide a robust evidence base for researchers and clinicians alike. However, it should be noted that most studies included in the meta-analysis did not undertake statistical power calculations when determining required sample size, and participant numbers were low in four studies (n=<50). Furthermore, an active comparator condition was used in only four studies. Although all types of MS phenotypes were represented in the study sample, most participants had relapsing-remitting MS. Ethnicity, SES and comorbidity were poorly covered, limiting more widespread applicability of these findings in diverse MS populations. Given the well documented high levels of physical comorbidity in PwMS, it is notable that our meta-analysis has only been able to quantify the effects of MBI training on three facets of physical wellbeing, namely fatigue, pain and sexual satisfaction. Future studies could address this evidence gap by measuring the impact of MBI training on other common physical symptoms associated with MS, for example dysarthria, dysphagia, bowel and bladder dysfunction, dynamic balance, in-coordination and spasticity. Although MBSR and MBCT both appear to be effective treatments for fatigue, it is not currently possible to recommend one approach over the other. To complicate matters, several studies tailored their MBIs with minimal/absent prior justification, making it challenging to determine why observed effects (beneficial, null or harmful) took place.

4.7 Implications for research
The quality of evidence for MBIs as effective treatments for fatigue in PwMS has strengthened considerably since our systematic review in 2014. However, adherence to CONSORT 19 reporting was poor in several studies included in the
meta-analysis, with three studies assessed overall as high risk and two as unclear according to the Cochrane Collaboration 21 tool. In addition, MBI description was often sparse in detail. Were researchers to adhere more closely to the CONSORT 19 and TIDieR 20 checklists when reporting studies of MBIs for PwMS, the knowledge base in this area could be further enhanced, helping to clarify where further research efforts should focus.

It remains unclear which type of MBI may be best for PwMS with impaired physical wellbeing. Future research could test either MBSR or MBCT against established treatments in this area; by involving people affected with the condition in this endeavor, the co-design, delivery and ongoing development of an optimised MBI course for PwMS could take place 10.

4.8 Implications for clinical practice
MBIs are modestly effective at improving fatigue in PwMS.

5.1 Conclusions
Meta-analytic evidence supports the use of MBIs in PwMS to improve fatigue. Preliminary evidence supports that MBIs may also improve sexual satisfaction in PwMS but are likely ineffective for treating pain in this population. Although the quality of study reporting has become better, room still exists for enhanced reporting in this area. No clear optimal MBI exists for improving physical wellbeing in PwMS.

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The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests
We declare no competing interests.
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