Emotional outcomes in clinically isolated syndrome and early phase multiple sclerosis: a systematic review and meta-analysis

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurological disease of the central nervous system. It is one of the most common causes of neurological disability in adults as its peak onset is in people aged between 20 and 40 years, with an increased prevalence in women [1]. Diagnosis is based on the clinical and neuroradiological (i.e., magnetic resonance imaging – MRI) evidence of disease dissemination in space and time, and on the exclusion of alternative diagnoses [2]. The diagnostic criteria have changed over time to improve specificity and sensitivity and to allow an earlier diagnosis [3]. People presenting with a first neurological event highly suggestive of MS, but who do not meet the full criteria for a diagnosis of MS, are classified as having a clinically isolated syndrome (CIS) [4]. CIS is defined as a monophasic neurologic event (usually an optic neuritis or a focal myelitis) lasting for at least 24 hours caused by inflammation and demyelination within the central nervous system [5]. The symptoms usually develop within hours or days and they must be associated to objective neurological signs found in MRI or spinal fluid examination [5].

Previous systematic reviews have recognized depressive and anxiety symptoms in MS without the distinction of the disease duration [6,7], but similar systematic reviews on emotional

outcomes have not yet been performed in CIS. The prevalence of depressive symptoms in MS is extremely variable, ranging from 5 to 60% [8] with four times higher risk of depression compared to the general population [9]. Despite this, emotional outcomes are often underestimated in clinical practice, as formal psychological evaluations are infrequent and symptoms undertreated [8,10–12]. Physical symptoms and non-specific symptoms such as fatigue and cognitive problems, which are common both to MS and affective disorders, also hinder the identification of depression and anxiety [6]. Also, symptomatic treatments in MS tend to focus more often on the physical rather than emotional outcomes [6].

Previous studies have reported that the prevalence of depressive symptoms may be lower in the relapsing remitting course of MS than in the progressive course, and in the secondary course more than in the primary progressive courses [13]. However, some evidence suggests otherwise as depression was found to relate only partially to higher disability [14], and some studies observed an inverse correlation between depressive symptoms and disease duration [15,16]. Therefore, the direction of causation is not yet clear. A higher prevalence of anxiety has been reported in the initial phases of the disease, which is explained by the need to adapt to a chronic and unpredictable disease [17]. Recent systematic reviews have highlighted the prevalence of depression (31%) and anxiety (22%) [7] and the relationship between anxiety symptoms and increased disability and low quality of life in people with MS [18]. However, both reviews focused on MS without the distinction of the disease duration. Early phase MS represents a critical period during which the person assigns meaning to the disease, with consequences on treatment decisions and symptom adaptations [19]. The first years after the MS diagnosis may represent an important time-frame, in which helping people to build an active disease

adjustment could improve disease and treatment decision-making, adherence to treatments, and could prevent development of psychiatric disorders [20].

Depression in MS is not only a strong predictor for reduced health-related quality of life (HRQoL) independent of disability [21], but is also highly correlated with suicidality symptoms [22]. People with MS are 1.8–7.5 times more likely to die by suicide compared to the general population, and the risk is particularly high in the first year after the diagnosis, stressing the importance of identifying depressive symptoms in the early years of MS [23]. For HRQoL in MS, quality of life is reduced mainly due to the impact of physical disability on daily life functioning [24]. People with MS have reported a greater decline in perceived physical health than in mental health functioning in 10-year general-population studies [25,26]. Perceived emotional outcomes of HRQoL instruments, such as emotional well-being, have shown improvement in 10-year follow-up studies although no change has been found in overall mental health [26,27]. However, there is not yet been extensive review evaluation of emotional HRQoL in CIS and in early phase MS.

To our knowledge, no systematic review has been conducted on the prevalence and relationships of depressive and anxiety symptoms and disorders in CIS and in early phase MS. Based on clinical evidence, we conducted a systematic review in CIS and early phase MS with the following aims:

1) To quantify the prevalence of depression and anxiety,
2) To estimate the pooled mean symptoms scores of depression and anxiety,

3) To estimate the associations between pooled mean symptoms scores of depression and anxiety and study characteristics,
4) To determine the strength of any association of emotional HRQoL with depressive and anxiety symptoms,
5) To determine the prevalence of suicide risk and suicidality symptoms and their relation with depressive and anxiety symptoms.

2. Method

2.1. Search strategy

A systematic literature search was conducted using four databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Comprehensive Biomedical Literature Database (EMBASE), Archive of Biomedical and Life Sciences Journal Literature (PubMed), and the Behavioral and Social Science Research (PsycInfo). The first search was performed for studies published until 3rd April 2017. An updated search was conducted using the same databases for studies between 1st April 2017 until 1st October 2018. A combined flow chart of study selection is presented in Figure 1. The protocol for this systematic review has been registered on the Prospective Register of Systematic Reviews (PROSPERO) and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=68909.

Inclusion criteria were designed by members of the research team and were checked with the patient advisory board in the European research consortium: Remote Assessment of Disease and Relapse – Central Nervous System (RADAR-CNS) which included people with direct experience of MS. Inclusion criteria were adults (18 years of age or older) with CIS and adults with a maximum of 5 years since the diagnosis of MS (hereafter, early phase MS). As there is no clear international consensus for the classification of "early phase MS", we decided to

include patients with MS who received a diagnosis within five years before the study assessment. This choice was based on a comprehensive search of the definition of the early phase of MS from previous studies which resulted in a heterogeneous range from zero [28] to six [29] years since diagnosis. Depending on the year of the study, diagnosis of MS was defined either by McDonald or Poser criteria [2,30–32].

Studies were also required to report outcomes of depression, anxiety, life satisfaction, suicide risk/suicidality symptoms, or HRQoL in CIS or in early phase MS. Only studies published in English were included in the review. Study samples consisting of only adolescents (under 18 years) and studies including other or similar diagnoses without a separate analysis of people with MS or CIS were excluded. The corresponding authors of the studies were contacted for further information if these criteria were inadequately reported. Previous systematic reviews, interventional and qualitative studies, and study protocols were also excluded.

Two researchers (A.R. and S.S.) performed the searches in the selected databases in collaboration with the research team. In addition to this, a patient advisory board of people with experience of living with MS were consulted about the most important questions to ask and outcomes of interest (see supplementary file). The final search terms included various medical subject headings (MeSH) or keyword headings describing emotional effects (e.g., depression, anxiety, stress, distress, mood, stressor) and terms related to MS and CIS. Additionally, to capture the terminology related to the diagnosis time of MS, we used time-related terms such as “first stage”, “onset”, “early phase”, and “recently diagnosed”. The original search strategy is available in Appendix 1.

2.2. Data extraction

Three reviewers (A.R. and M.R./G.L.) independently screened the studies in line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [33,34]. An updated search was conducted also by three reviewers (A.R. and F.M./S.S.). After the screening of the studies based on their title and abstract, relevant studies were independently

evaluated for full-text assessment. In case of a disagreement, a fourth assessor evaluated the studies. If needed, the corresponding authors of the included studies were contacted for further information.

2.3. Methodological quality of the studies

Methodological quality of the included observational studies was assessed independently by two pairs of reviewers (M.R./G.L. and V.B./C.B.) using the 14-item Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [35–37]. An item was scored positive (Yes) if the criterion was fulfilled, negative (No), or other (Other) if inadequately reported or not applicable. The total score of a study reflected the total sum of positive scores. The maximum score was 14 points. Overall quality rating per study was assessed either good, fair, or poor where good indicates the least risk of bias (≥ 10 points), a "fair" study indicates some bias not sufficient to have a major impact to its results (6–9 points), and "poor" indicates a significant risk of bias (≤ 5 points) [35].

2.4. Statistical synthesis

Study and participant characteristics were extracted and a descriptive analysis was performed on all outcomes. Agreement level between the reviewers was assessed using Cohen's Kappa [38]. Pooled prevalence estimates and mean values for depression and anxiety were calculated via pairwise meta-analysis for CIS and MS groups separately. For both prevalence and pooled mean meta-analyses, heterogeneity was assessed using I^2, with values of 25%, 50% and 75% representing low, moderate and high heterogeneity respectively [39], and meta-analyses were only conducted if a minimum of 2 papers could contribute to the analysis.

Depression and anxiety prevalence data were collected into categories of "mild", "moderate" and "severe" symptoms, combining different questionnaires with thresholds relating to these definitions. To incorporate as much data as possible, additional categories of "any depression" and "any anxiety" were created, to reflect all the studies, which reported cases of depression

according to one threshold as opposed to levels of severity. Due to anticipated high levels of heterogeneity, random-effects meta-analyses with 95% confidence intervals (CIs) were conducted with each screening tool at each threshold, using the "*metaprop*" command for Stata (version 14.0), with *ftt* subcommand [40]. Missing prevalence data were requested from the authors of the primary research, and not included if data were unavailable.

Pooled mean and standard error (SE) scores for depression, anxiety and HRQoL were meta-analysed taking into account the random-effects for anticipated heterogeneity using the "*metan*" package for Stata (version 14.0) [41]. This process was conducted for depression and anxiety separately. Missing SE data were imputed from all other available information, including SD data. If no SD data were available, missing data were imputed by calculating the mean SD from data available in other studies reporting outcomes from the same questionnaires. Studies with missing mean data were excluded from the meta-analyses.

Meta-regression was used to investigate the relationship between study-level characteristics and pooled mean depression, anxiety, and to explain the possible heterogeneity. A priori decisions were made to investigate the study-level characteristics: sample mean age; the proportion of female gender; sample size; time since experiencing symptoms; time since diagnosis; disease severity; publication year; proportion of the sample still in employment; and overall study quality. All characteristics were treated as continuous variables and analysed individually as univariate meta-regression models. The results of the meta-regression show the relationship between these study characteristics and variability in meta-analysis outcomes, with the beta indicating the increase or decrease in pooled mean score associated with a 1-unit change in these study-level characteristics. Results are also reported with SE, 95% CI, and adjusted-R^2.

3. Results

The literature search identified 1841 studies after removing duplicate studies. Screening of 374 full-text studies retrieved 51 studies that fulfilled the inclusion criteria. Within those 51 studies,

39 studies focused on early phase MS, 10 studies on CIS, and two studies on both disease conditions. A flow chart of the screening process is presented in Figure 1, and individual study information is reported in Appendixes 2 to 4. Agreement level between the reviewers yielded a value of 0.71 indicating substantial agreement (0.61–0.80) in the title screening, a value of 0.50 indicating a moderate agreement (0.41–0.60) in the abstract screening, and 0.84 indicating excellent agreement (0.81–0.99) in the full-text screening. The update search yielded 0.88 in the title screening, 0.81 in the abstract screening, and 0.83 in the full-text screening.

3.1. Description of the participants

The selected studies included a total of 3,498 participants, of which 2,896 were people with early phase MS and 602 with CIS.

Early phase MS. Participants with early phase MS had the mean (SD) age of 36.3 (4.2, range 29.9–52.0) years and sixty-seven percent of them were female. Mean (SD) disease duration was 16.8 (10.5, range 2.0–49.5) months from the onset of diagnosis, and 95% had relapsing-remitting MS. Disease severity were reported in 21 (51%) studies with a median (interquartile range) of 1.8 (1.6–2.4) in the Expanded Disability Status Scale (EDSS) and one study reporting the median (range) of 2.0 (0–6) in the Patient Determined Disease Steps (PDDS). Only 19 (46%) studies reported any medication related to MS, and of those studies, 83% (N = 1162) of participants with early phase MS used a disease-modifying treatment (DMT) or other symptomatic treatments related to MS. Only four studies reported antidepressant (N = 26), anxiety (N = 6), or combination of different psychiatric medication (N = 79) [17,42–44].

CIS. The mean (SD) age was 34.9 (2.9) years and average (SD) disease duration was 12.3 (8.6) months. Fifty percent of CIS diagnosed participants were female. Disease severity was assessed by EDSS in eight (67%) studies with median (interquartile range) disease severity of 1.1 (1.0–1.7), respectively. Five studies reported medication, and of those studies, fifteen percent of people with CIS used DMT. Only one study reported the use of antidepressant (N = 16) [44].

3.2. Methodological quality and the risk of bias

The overall methodological quality of the studies was fair (Table 4). Most of the studies were characterized by good data presentation and validated measures for the assessment of emotional outcomes. The major issue in the quality of studies was the small sample sizes, which limited the precision of the findings. Other common limitations included failure to report the timing of study period and clear description of eligible population, which increased the risk of possible selection bias. In addition, the majority of the studies did not report the blindness status of the assessors.

3.3. The prevalence of depression and anxiety

Early phase MS. Prevalence of depression in MS was reported in 18 out of 34 studies (53%) that investigated depression (Appendix 2). Prevalence estimates varied from 0% to 82% [17,28,51–58,42,44–50]. Table 1 shows the results of the prevalence meta-analyses, with the most robust analyses (with four or more studies) also shown as a forest plot in Figure 2. Pooled prevalence estimates for depression ranged between 0% and 37%, with severe depression (representing the BDI with a threshold of > 29 and the Montgomery-Åsberg Depression Rating Scale (MADRS) with a threshold of > 34) and the Diagnostic and Statistical Manual (DSM) diagnostic criteria for MDD yielding the lowest and highest point prevalence estimates, respectively.

Prevalence of anxiety was reported in 9 out of 16 studies (Appendix 2) [17,44,46,47,49,55,57–59]. Cut-off points of anxiety prevalence estimates varied across studies and the prevalence estimates ranged from 8% to 64%. The most commonly used tool to identify possible anxiety symptoms was the HADS-A (Table 1); this was used in five included studies (N = 589) using a threshold of > 7 and 1 study with a threshold of > 8. Results of this meta-analysis indicate a prevalence of 49%. No other anxiety measures were used often enough to provide meta-analysed prevalence estimates.

CIS. Only four out of 10 CIS studies reported prevalence estimates of depressive symptoms that ranged from 22% to 30% (Appendix 3) [44,60–62]. Only two studies reported the prevalence estimates of anxiety symptoms with HADS-A values of 36% (N = 124) and 100% (N = 56) [44,62]. Both prevalence estimates indicated that mild depressive and anxiety symptoms are present among people with CIS.

3.4. Depressive and anxiety symptom burden

Early phase MS. Data were available from four measures assessing depressive symptoms – the Beck Depression Inventory (BDI), the depression scale of Hospital Anxiety Depression Scale (HADS-D), Hamilton Depression Scale (HAM-D), and the Symptom Checklist-90 item (SCL-90). Depressive symptoms varied from a normal state to moderate (Table 2). Meta-regression results of 12 studies with 530 participants showed no association between study-level characteristics for BDI outcomes (Table 3). However, meta-regression of seven studies with 696 participants observed a significant relationship between sample size (β = 0.01; 95% CI: 0.00 to 0.02; $p = 0.03$) and study quality (β = 0.38; 95% CI: 0.05 to 0.71; $p = 0.03$) and overall pooled mean HADS-D outcome (4.55; 95% CI: 3.41 to 5.69; $p < .0001$; $I^2 = 93.2$). This indicates that a one-unit increase in sample size and study quality is associated with a 0.01 and 0.38 increase in mean depression scores, respectively.

Mean anxiety data were available for four different anxiety measures - the Beck Anxiety Inventory (BAI), State Trait Anxiety Inventory (STAI), the anxiety symptom scale of HADS (HADS-A), and SCL-90. Anxiety symptoms varied from a normal state to mild (Table 2). HADS-A data of seven studies with 696 participants were sufficient for meta-regression (Table 3). Results of this analysis showed a significant relationship between sample size (β = 0.04; 95% CI: 0.02 to 0.06; $p < .01$) and pooled mean HADS-A outcomes (6.31; 95% CI: 5.79 to 6.83; $p < .0001$; $I^2 = 61.2$). This indicates that a one-unit increase in sample size is associated with a 0.04 increase in mean HADS-A score.

CIS. Eleven CIS studies used five different instruments to assess depressive symptoms (Appendix 3) [44,60,69,61–68]. The most frequently used questionnaire was BDI, which allowed for a meta-analysis of four studies (Table 2). Overall pooled mean depression was 7.1 (95% CI: 5.55 to 8.65; $p < .001$), which indicated that the mean score for BDI was below recognized thresholds for depression.

Anxiety in CIS was investigated in three prospective cohort [60,62,67] and three cross-sectional [44,63,64] studies (Appendix 3). Not enough data were reported in these studies to combine them meaningfully in meta-analysis. The most commonly used measurement was the HADS-A questionnaire in three studies [44,62,64], but only one of these studies reported the anxiety data that indicated a normal state in anxiety symptoms among 38 participants with CIS [64]. Mild anxiety symptoms were reported in two studies using the STAI instrument [60,67] and in one study using the BAI instrument [63].

3.5. Emotional HRQoL and its association with emotional outcomes

Early phase MS. Thirteen studies used an outcome of HRQoL (Appendix 4) [43,44,75,76,46,54,67,70–74]. Five different HRQoL instruments were identified, with most studies using the 54-item Multiple Sclerosis Quality of Life (MSQOL-54) questionnaire [43,54,67,70,74]. Total mental health summary scores of MSQOL-54 ranged from 53.4 to 69.6 points out of 100 [43,54,67,70]. Second most used HRQoL questionnaire was the 36-Item Short Form Survey (SF-36) [46,71,75,76], but only one reported mean mental health composite score of 56.8 out of 100 [76]. Four studies reported that emotional HRQoL emotional were correlated or associated with depression outcomes regardless of the HRQoL measurement (Appendix 4) [46,73,74,77]. Only one study reported a difference between early phase MS and healthy participants, and indicated that the SF-36 mental health composite score and domain of mental health were reduced in people with early phase MS compared with healthy participants [75]. Follow-up studies did not find a change in emotional HRQoL in early phase MS, when MSQOL-54 was observed after 30 months [67] and SF-36 after 12 months [46].

CIS. Four studies investigated HRQoL with three different measurements – the Functional Assessment of Multiple Sclerosis (FAMS), MSQOL-54, and the French version of MSQOL-54 (SEP-54) (Appendix 4) [44,66,67,78]. One study found a correlation between the FAMS total score and the Multiple Sclerosis Neuropsychological Questionnaire, and one study with a 30-month follow-up revealed no change in total mental health composite score in MSQOL-54 [67].

3.6. Suicide risk and/or suicidality symptoms

Three studies reported a subgroup analysis of suicide risks within five years from the MS diagnosis [23,79,80]. Comparing to later phases of MS, Brønnum-Hansen et al. [2005] observed an increased risk of 3.2 (standard mortality ratio) for suicide within the first year after diagnosis [23]. Fredrikson et al., [2003] and Stenager et al. [1992] found suicide was the most common cause of death, comprising 58% of all mortality in 5 years following diagnosis [79]. Our search results did not find CIS studies investigating suicide or suicidality symptoms.

4. Discussion

The purpose of this systematic review and meta-analysis was to investigate emotional outcomes in people with CIS and early phase MS. The two main findings are that mild-to-moderate depressive and anxiety symptoms are common in CIS and early phase MS, and that low emotional health-related quality of life linked to depression and an increased suicide risk were observed in early phase MS. Meta-regression analyses revealed an increase in mean HADS-D and HADS-A associated with larger sample size, and higher HADS-D mean with increased study quality. Our findings are comparable with previous studies that focused on later phases of MS [7–9,18,81], which also confirmed a higher prevalence of emotional distress in MS compared to the general population [8,9,81].

Early phase MS. Our meta-analysis of three studies with 114 participants indicated a prevalence of 37% for major depressive disorder according to DSM criteria and we identified

a decrease in prevalence according to depression severity, identified through combining cases identified with different questionnaire thresholds representing “mild”, “moderate” and “severe” depression. Given that the criteria for a diagnosis of DSM major depressive disorder are more strict, it is surprising that we found a higher prevalence of major depressive disorder than of a broader array of depressive symptoms as measured with a questionnaire. However, the small number of included studies in the meta-analysis indicates that these results should be interpreted with caution and more research is required to provide more robust data for meta-analysis. Although the number of studies in these meta-analyses were low, these findings indicate that depressive symptoms are common in the early years of MS. Our results for depressive symptoms are in line with the previous studies that investigated longer disease duration of MS. A systematic review of 58 studies estimated the prevalence of depression to be 31%, but with high level of heterogeneity [7].

Similar findings were also observed on anxiety symptoms in early phase MS. Anxiety prevalence estimates were observed with a range of 8% to 64% and our meta-analysis indicated that 35% of 589 participants experienced anxiety symptoms (HADS-A). These findings support previous studies that reported anxiety in 19% to 36% of the patients with a longer disease duration of MS (i.e., 14–19 years), suggesting that anxiety is present and common in MS [21,82,83]. Compared to previous studies, our findings might indicate that anxiety symptoms are similar or even slightly higher in early phase MS compared to later phase of MS. The high prevalence of anxiety may reflect the population under investigation. There is some evidence to suggest that shorter disease duration is associated with increased anxiety, with the recency of diagnosis and adjustments to illness potentially having immediate implications for anxiety symptoms [18,84]. Future research could test this hypothesis more robustly to examine longitudinal change in anxiety symptoms as disease duration increases. This is particularly important as a previous study has found that anxiety disorders are overlooked and under-treated in MS [21]. Adequate treatment of anxiety symptoms may help the patients in the process of disease acceptance and diminish the risk of developing a depression.

To investigate heterogeneity in our findings, our meta-regression from seven studies with 696 participants revealed that an increase in mean HADS-D and HADS-A was associated with larger sample size, and higher HADS-D mean was associated with increased study quality. These findings indicate that studies with higher sample sizes might capture depression and anxiety symptoms more accurately, and findings captured with HADS-D might be influenced by the study quality. However, our results did not indicate associations with disease duration or EDSS, which supports previous findings [83]. This might indicate that depressive and anxiety symptoms might be persisting, or persons with MS are experiencing these symptoms at different times. The lack of studies prevented us from investigating the influence of disease-modified treatments, which might have an effect on emotional outcomes in early phase MS.

Emotional health-related quality of life was mainly investigated as a predictor in the early phases of MS rather than as an outcome of observational studies. We observed several limitations such as the low number of studies, lack of reporting values on quality of life, and wide variety of measurements used. The individual quality of life varied across included studies. In sum, quality of life measurements did not indicate emotional burden, and follow-up studies did not find a change in mental health, when MSQOL-54 was observed after 30 months [67] and SF-36 after 12 months [46]. However, four studies reported that the emotional quality of life was correlated or associated with either depression, disease severity, or other emotional-related outcomes regardless of the quality of life measurement [46,73,74,77]. This might indicate that people with early phase MS experiencing depression or other emotional challenges also reported decline in emotional quality of life. This also supports the evidence from previous MS reviews, who focused on longer disease duration [24,85]. Only three studies investigated suicide risk within five years of the MS diagnosis, indicating an increased risk of suicide in the early years of MS when it was compared to the later phases of MS [23,79,80]. Previous studies have reported a higher suicide risk within MS population comparing to healthy population [86,87]. Our conclusion on health-related quality of life and suicide risk/suicidality symptoms indicates that these phenomena have been investigated quite poorly in the first five years of MS onset.

CIS. In our descriptive analysis findings, the prevalence of depressive symptoms ranged from 22% to 30% [44,60–62] and in anxiety from 36% to even 100% [44,62]. Our meta-analysis included four studies using BDI indicated minimal depressive symptoms in persons with CIS (N=92). Although the number of included studies and study samples were low, these findings suggest that both depression and anxiety are similarly present both in CIS. Previous individual studies have found conflicting evidence, either indicating that emotional disturbances such as depressive symptoms are present among people with CIS [60], or that there is no indication of differences on depression and anxiety between CIS and healthy controls [63].

Emotional health-related quality of life in CIS were in the same direction as in early phase MS, but the lack of included studies and variety of used measurements prohibited firm conclusions on the possible impact of emotional quality of life in CIS. Only one 30-month follow-up study revealed no change in total mental health composite score in MSQOL-54 over time [67]. One aim of this review was to evaluate the suicide risk and suicidality symptoms in CIS, but our search did not identify any studies investigating outcomes of these in CIS. Because of the lack of evidence, there is no clear understanding of the emotion-related quality of life or suicide risk and suicidality symptoms in people with CIS, how it might change over time, or influence other physical and psychological outcomes.

Study strengths and limitations

The major strength of this review is the focus on emotional outcomes in CIS and early phase MS. To our knowledge, this is the first systematic review to investigate these outcomes in both conditions. One strength of this study is also to involve people with a direct experience of MS in the research process to share their view of the findings. Comments of the patient advisory board was asked in every stages of the review study. Our results offers important insight into emotional burden in both conditions, and will hopefully guide future studies to focus on psychological aspects of CIS and early phase MS, in order to understand the emotional impact of these conditions on daily life functioning. We need more observational studies to gather evidence-based knowledge on emotional effects for both conditions, which might guide clinicians to take into account the emotional burden in their clinical decision-making process.

This review also has some limitations. The major issue in the quality of studies was the small sample sizes, which limited the precision of the findings. Other common limitations included a failure to report the timing of study and a clear description of the eligible population, both of which will increase the risk of selection bias. Another key limitation, which has been reported in other depression prevalence meta-analyses in physical disease [88], is the wide range of questionnaires and thresholds used to identify the presence of depression and anxiety. A total of 12 depression questionnaires and 7 anxiety questionnaires were used with a range of different, often seemingly arbitrary thresholds, were used to identify cases. This makes pooling data into meaningful categories for comparison with the general population or other disease groups challenging, and one clear direction for future research would be to attempt to standardise how mental disorders are reported to allow cross-study comparisons. Clinical and statistical findings were heterogeneous with more studies sensitivity and subgroup analyses might identify factors to explain this heterogeneity. One additional limitation as a study selection bias may also be that our search strategy was not extended to grey-literature sources. Despite these limitations, we believe that our review gives important insight in the emotional effects of CIS and early phase MS, which hopefully will raise the awareness to investigate these effects more in the future.

Recommendations for future research

Depression in MS might be caused by a reaction to the presence of the disease and the consequent implications on daily life or a biological damage of the central nervous system that impact on the normal functioning of affectivity and emotion regulation. Our findings support the need of an appropriate psychological evaluation after the diagnosis, as depression may develop already in the early phases, confirming that mood disorders are partially related to disability. The major challenge to understand the prevalence estimates of depression is the variability in the instruments used to measure depression, and the wide range of thresholds used to define cases. This is one of the major limitations highlighted also by the recent American Academy of Neurology (AAN) guidelines [6]. Only 52% of included studies

reported cut-off threshold points of depression, which demonstrates a lack of reporting depression in early phase MS. We recommend for the future studies to report depression prevalence estimates using measures with validated thresholds.

To confirm our findings in our review, we recommend more longitudinal observational studies to monitor depressive and anxiety symptoms, health-related quality of life, and suicidal ideas and behaviours in both conditions, especially to the time point once the diagnosis of MS is defined. Insight into the emotional disturbances in the transition phase of CIS and MS may be informative to help people with their possible emotional burden in an uncertain time after diagnosis. Finally, we recommend future studies to involve people with a direct experience of MS in the research process.

5. Conclusion

This systematic review suggests that mild-to-moderate depressive and anxiety symptoms might be present in CIS and in early phase MS. Future research on both clinical populations are needed, especially longitudinal monitoring of emotional outcomes.

References

[1] National Multiple Sclerosis Society, About MS: what we know about MS, (2012).

[2] A.J. Thompson, B.L. Banwell, F. Barkhof, W.M. Carroll, T. Coetzee, Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria, Lancet Neurol. (2018). doi:10.1016/s1474-4422(17)30470-2.

[3] R. Milo, A. Miller, Revised diagnostic criteria of multiple sclerosis, Autoimmun. Rev. (2014). doi:10.1016/j.autrev.2014.01.012.

[4] C.M. Dalton, P.A. Brex, K.A. Miszkiel, S.J. Hickman, D.G. MacManus, G.T. Plant, A.J. Thompson, D.H. Miller, Application of the new Mcdonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis, Ann. Neurol. (2002). doi:10.1002/ana.10240.

[5] J.F. Marcus, E.L. Waubant, Updates on Clinically Isolated Syndrome and Diagnostic

Criteria for Multiple Sclerosis, The Neurohospitalist. (2013). doi:10.1177/1941874412457183.

[6] S.L. Minden, A. Feinstein, R.C. Kalb, D. Miller, D.C. Mohr, S.B. Patten, C. Bever, R.B. Schiffer, G.S. Gronseth, P. Narayanaswami, Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS Report of the Guideline Development Subcommittee of the American Academy of Neurology, Neurology. (2014). doi:10.1212/WNL.0000000000000013.

[7] R.E. Boeschoten, A.M.J. Braamse, A.T.F. Beekman, P. Cuijpers, P. van Oppen, J. Dekker, B.M.J. Uitdehaag, Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis, J. Neurol. Sci. 372 (2017) 331–341. doi:10.1016/j.jns.2016.11.067.

[8] C. Solaro, G. Gamberini, F.G. Masuccio, Depression in Multiple Sclerosis: Epidemiology, Aetiology, Diagnosis and Treatment, CNS Drugs. (2018). doi:10.1007/s40263-018-0489-5.

[9] J.L. Ayuso-Mateos, J.L. Vázques-Barquero, C. Dowrick, V. Lehtinen, O.S. Dalgard, P. Casey, C. Wilkinson, L. Lasa, H. Page, G. Dunn, G. Wilkinson, J. Ballesteros, G. Birkbeck, T. Børve, M. Costello, P. Cuijpers, I. Davies, J.F. Diez-Manrique, N. Fenlon, M. Finne, F. Ford, L. Gaite, A. Gomez del Barrio, C. Hayes, A. Herrán, A. Horgan, T. Koffert, N. Jones, M. Lehtilä, C. McDonough, E. Michalak, C. Murphy, A. Nevra, T. Nummelin, B. Sohlman, Depressive disorders in Europe: Prevalence figures from the ODIN study, Br. J. Psychiatry. (2001). doi:10.1192/bjp.179.4.308.

[10] D. Hind, J. Cotter, A. Thake, M. Bradburn, C. Cooper, C. Isaac, A. House, Cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: A systematic review and meta-analysis, BMC Psychiatry. (2014). doi:10.1186/1471-244X-14-5.

[11] D.C. Mohr, S.L. Hart, I. Fonareva, E.S. Tasch, Treatment of depression for patients with multiple sclerosis in neurology clinics., Mult. Scler. (2006). doi:10.1191/135248506ms1265oa.

[12] K. Cetin, K.L. Johnson, D.M. Ehde, C.M. Kuehn, D. Amtmann, G.H. Kraft, Antidepressant use in multiple sclerosis: epidemiologic study of a large community

sample., Mult. Scler. (2007). doi:10.1177/1352458507077864.

[13] C. Solaro, E. Trabucco, A. Signori, V. Martinelli, M. Radaelli, D. Centonze, S. Rossi, M.G. Grasso, A. Clemenzi, S. Bonavita, A. D'Ambrosio, F. Patti, E. D'Amico, G. Cruccu, A. Truini, Depressive symptoms correlate with disability and disease course in multiple sclerosis patients: An Italian multi-center study using the Beck Depression Inventory, PLoS One. (2016). doi:10.1371/journal.pone.0160261.

[14] M.W. Koch, S. Patten, S. Berzins, S. Zhornitsky, J. Greenfield, W. Wall, L.M. Metz, Depression in multiple sclerosis: A long-term longitudinal study., Mult. Scler. (2014). doi:10.1177/1352458514536086.

[15] A.M. Bamer, K. Cetin, K.L. Johnson, L.E. Gibbons, D.M. Ehde, Validation study of prevalence and correlates of depressive symptomatology in multiple sclerosis, Gen. Hosp. Psychiatry. (2008). doi:10.1016/j.genhosppsych.2008.04.006.

[16] L. Chwastiak, D.M. Ehde, L.E. Gibbons, M. Sullivan, J.D. Bowen, G.H. Kraft, Depressive symptoms and severity of illness in multiple sclerosis: Epidemiologic study of a large community sample, Am. J. Psychiatry. (2002). doi:10.1176/appi.ajp.159.11.1862.

[17] A. Giordano, F. Granella, A. Lugaresi, V. Martinelli, M. Trojano, P. Confalonieri, D. Radice, A. Solari, Anxiety and depression in multiple sclerosis patients around diagnosis, J. Neurol. Sci. (2011). doi:10.1016/j.jns.2011.05.008.

[18] E. Butler, F. Matcham, T. Chalder, A systematic review of anxiety amongst people with Multiple Sclerosis, Mult. Scler. Relat. Disord. (2016). doi:10.1016/j.msard.2016.10.003.

[19] L. Dennison, L. Yardley, A. Devereux, R. Moss-Morris, Experiences of adjusting to early stage multiple sclerosis, J. Health Psychol. (2011). doi:10.1177/1359105310384299.

[20] J.R. Miller, The importance of early diagnosis of multiple sclerosis., J. Manag. Care Pharm. (2004).

[21] M. Korostil, A. Feinstein, Anxiety disorders and their clinical correlates in multiple sclerosis patients., Mult. Scler. (2007). doi:10.1177/1352458506071161.

[22] A.J. Carson, S. Best, C. Warlow, M. Sharpe, Suicidal ideation among outpatients at

general neurology clinics: prospective study, BMJ. (2000). doi:10.1136/bmj.320.7245.1311.

[23] H. Brønnum-Hansen, E. Stenager, E.N. Stenager, N. Koch-Henriksen, Suicide among Danes with multiple sclerosis, J. Neurol. Neurosurg. Psychiatry. (2005). doi:10.1136/jnnp.2004.056747.

[24] A.J. Mitchell, A.J. Mitchell, J. Benito-León, J. Benito-León, J.-M.M. González, J.-M.M. González, J. Rivera-Navarro, J. Rivera-Navarro, Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing., Lancet Neurol. 4 (2005) 556–66. doi:10.1016/S1474-4422(05)70166-6.

[25] A. Rintala, A. Hakkinen, J. Paltamaa, Ten-year follow-up of health-related quality of life among ambulatory persons with multiple sclerosis at baseline, Qual. Life Res. 25 (2016) 3119–3127. doi:http://dx.doi.org/10.1007/s11136-016-1347-x.

[26] A. Giordano, G. Ferrari, D. Radice, G. Randi, L. Bisanti, A. Solari, Self-assessed health status changes in a community cohort of people with multiple sclerosis: 11years of follow-up, Eur. J. Neurol. 20 (2013) 681–688. doi:10.1111/ene.12028.

[27] A. Rintala, A. Häkkinen, J. Paltamaa, Ten-year follow-up of health-related quality of life among ambulatory persons with multiple sclerosis at baseline, Qual. Life Res. 25 (2016). doi:10.1007/s11136-016-1347-x.

[28] M. Sullivan, B. Weinshenker, S. Mikail, K. Edgley, Depression before and after diagnosis of multiple sclerosis, Mult. Scler. J. 1 (1995) 104–108.

[29] M. Müller, R. Esser, K. Kötter, J. Voss, A. Müller, P. Stellmes, Third ventricular enlargement in early stages of multiple sclerosis is a predictor of motor and neuropsychological deficits: A cross-sectional study, BMJ Open. (2013). doi:10.1136/bmjopen-2013-003582.

[30] C.H. Polman, S.C. Reingold, B. Banwell, M. Clanet, J.A. Cohen, M. Filippi, K. Fujihara, E. Havrdova, M. Hutchinson, L. Kappos, F.D. Lublin, X. Montalban, P. O'Connor, M. Sandberg-Wollheim, A.J. Thompson, E. Waubant, B. Weinshenker, J.S. Wolinsky, Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria, Ann. Neurol. (2011). doi:10.1002/ana.22366.

[31] C.M. Poser, D.W. Paty, L. Scheinberg, W.I. McDonald, F.A. Davis, G.C. Ebers, K.P.

Johnson, W.A. Sibley, D.H. Silberberg, W.W. Tourtellotte, New diagnostic criteria for multiple sclerosis: Guidelines for research protocols, Ann. Neurol. (1983). doi:10.1002/ana.410130302.

[32] T. Fangerau, S. Schimrigk, M. Haupts, M. Kaeder, G. Ahle, N. Brune, K. Klinkenberg, S. Kotterba, M. Möhring, E. Sindern, Diagnosis of multiple sclerosis: Comparison of the Poser criteria and the new McDonald criteria, Acta Neurol. Scand. (2004). doi:10.1111/j.1600-0404.2004.00246.x.

[33] D. Moher, L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, D.G. Altman, A. Booth, A.W. Chan, S. Chang, T. Clifford, K. Dickersin, M. Egger, P.C. Gøtzsche, J.M. Grimshaw, T. Groves, M. Helfand, J. Higgins, T. Lasserson, J. Lau, K. Lohr, J. McGowan, C. Mulrow, M. Norton, M. Page, M. Sampson, H. Schünemann, I. Simera, W. Summerskill, J. Tetzlaff, T.A. Trikalinos, D. Tovey, L. Turner, E. Whitlock, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, Syst. Rev. (2015). doi:10.1186/2046-4053-4-1.

[34] L. Shamseer, D. Moher, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, D.G. Altman, A. Booth, A.W. Chan, S. Chang, T. Clifford, K. Dickersin, M. Egger, P.C. Gøtzsche, J.M. Grimshaw, T. Groves, M. Helfand, J. Higgins, T. Lasserson, J. Lau, K. Lohr, J. McGowan, C. Mulrow, M. Norton, M. Page, M. Sampson, H. Schünemann, I. Simera, W. Summerskill, J. Tetzlaff, T.A. Trikalinos, D. Tovey, L. Turner, E. Whitlock, Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation, BMJ. (2015). doi:10.1136/bmj.g7647.

[35] National Heart Lung and Blood Institute, Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, (2018). https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

[36] D. Mangin, G. Stephen, V. Bismah, C. Risdon, Making patient values visible in healthcare: A systematic review of tools to assess patient treatment priorities and preferences in the context of multimorbidity, BMJ Open. (2016). doi:10.1136/bmjopen-2015-010903.

[37] J. Wardling, A. Steel, Systematic reviews in integrative medicine: a clinician's guide to publication, Adv. Integr. Med. 2 (2015) 103–109.

[38] A.J. Viera, J.M. Garrett, Understanding interobserver agreement: The kappa statistic, Fam. Med. 37 (2005) 360–363. doi:Vol. 37, No. 5.

[39] J.P.T. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ Br. Med. J. (2003). doi:10.1136/bmj.327.7414.557.

[40] V.N. Nyaga, M. Arbyn, M. Aerts, Metaprop: A Stata command to perform meta-analysis of binomial data, Arch. Public Heal. (2014). doi:10.1186/2049-3258-72-39.

[41] R. Harris, M. Bradburn, J. Deeks, R. Harbord, D. Altman, T. Steichen, J. Sterne, METAN: Stata module for fixed and random effects meta-analysis, (2010). https://econpapers.repec.org/software/bocbocode/s456798.htm.

[42] A. Jønsson, J. Andresen, L. Storr, T. Tscherning, P. Soelberg Sørensen, M. Ravnborg, Cognitive impairment in newly diagnosed multiple sclerosis patients: A 4-year follow-up study, J. Neurol. Sci. (2006). doi:10.1016/j.jns.2005.09.016.

[43] A.H. Jun-O'Connell, A. Butala, I.B. Morales, N. Henninger, K.M. Deligiannidis, N. Byatt, C. Ionete, The Prevalence of Bipolar Disorders and Association With Quality of Life in a Cohort of Patients With Multiple Sclerosis, J. Neuropsychiatry Clin. Neurosci. 29 (2017) 45–51. doi:10.1176/appi.neuropsych.15120403.

[44] S. Simioni, C. Ruffieux, J. Kleeberg, L. Bruggimann, J.M. Annoni, M. Schluep, Preserved decision making ability in early multiple sclerosis, J. Neurol. (2008). doi:10.1007/s00415-008-0025-5.

[45] M.P. Amato, G. Ponziani, G. Pracucci, L. Bracco, G. Siracusa, L. Amaducci, Cognitive Impairment in Early-Onset Multiple Sclerosis: Pattern, Predictors, and Impact on Everyday Life in a 4-year Follow-Up, Arch. Neurol. (1995). doi:10.1001/archneur.1995.00540260072019.

[46] E. Montanari, M. Rottoli, D. Maimone, P. Confalonieri, K. Plewnia, M. Frigo, A. Francia, A. Pala, N.A. Losignore, P. Ragonese, A. Veneziano, A 12-month prospective, observational study evaluating the impact of disease-modifying treatment on emotional burden in recently-diagnosed multiple sclerosis patients: The POSIDONIA study, J. Neurol. Sci. (2016). doi:10.1016/j.jns.2016.02.047.

[47] T. Moreau, N. Schmidt, O. Joyeux, C. Bungener, V. Souvignet, Coping strategy and anxiety evolution in multiple sclerosis patients initiating interferon-beta treatment, Eur. Neurol. (2009). doi:10.1159/000222777.

[48] M.C. Bonnet, M.S.A. Deloire, E. Salort, V. Dousset, K.G. Petry, B. Brochet, Evidence of cognitive compensation associated with educational level in early relapsing-remitting multiple sclerosis, J. Neurol. Sci. (2006). doi:10.1016/j.jns.2006.08.002.

[49] A.B. de Lima, R.A. Paes, R.M.P. Alvarenga, Personality factors in recently diagnosed multiple sclerosis patients: a preliminary investigation with the NEO-FFI scale, Arq. Neuropsiquiatr. (2015). doi:10.1590/0004-282X20140234.

[50] E. Hankomäki, J. Multanen, E. Kinnunen, P. Hämäläinen, The progress of cognitive decline in newly diagnosed MS patients, Acta Neurol. Scand. (2014). doi:10.1111/ane.12161.

[51] S. Kern, T. Schultheiß, H. Schneider, W. Schrempf, H. Reichmann, T. Ziemssen, Circadian cortisol, depressive symptoms and neurological impairment in early multiple sclerosis, Psychoneuroendocrinology. (2011). doi:10.1016/j.psyneuen.2011.04.004.

[52] M. Kraemer, M. Herold, J. Uekermann, B. Kis, J. Wiltfang, I. Daum, I. Dziobek, P. Berlit, R.R. Diehl, M. Abdel-Hamid, Theory of mind and empathy in patients at an early stage of relapsing remitting multiple sclerosis, Clin. Neurol. Neurosurg. (2013). doi:10.1016/j.clineuro.2012.10.027.

[53] E. Millefiorini, A. Padovani, C. Pozzilli, C. Loriedo, S. Bastianello, C. Buttinelli, V. Di Piero, C. Fieschi, Depression in the early phase of MS: influence of functional disability, cognitive impairment and brain abnormalities, Acta Neurol Scand. (1992).

[54] M.F. Possa, E. Minacapelli, S. Canale, G. Comi, V. Martinelli, M. Falautano, The first year after diagnosis: psychological impact on people with multiple sclerosis, Psychol. Heal. Med. (2017). doi:10.1080/13548506.2016.1274043.

[55] T.A.M. Siepman, A.C.J.W. Janssens, I. De Koning, C.H. Polman, J.B. Boringa, R.Q. Hintzen, The role of disability and depression in cognitive functioning within 2 years after multiple sclerosis diagnosis, J. Neurol. (2008). doi:10.1007/s00415-008-0814-x.

[56] M.J.L. Sullivan, S. Mikail, B. Weinshenker, Coping with a diagnosis of multiple sclerosis., Can. J. Behav. Sci. / Rev. Can. Des Sci. Du Comport. 29 (1997) 249–256.

doi:10.1037/0008-400X.29.4.249.

[57] S. Tan-Kristanto, L.A. Kiropoulos, Resilience, self-efficacy, coping styles and depressive and anxiety symptoms in those newly diagnosed with multiple sclerosis, Psychol. Health Med. (2015). doi:10.1080/13548506.2014.999810.

[58] M. Vitkova, Z. Gdovinova, J. Rosenberger, J. Szilasiova, I. Nagyová, P. Mikula, M. Krokavcova, J.W. Groothoff, J.P. Van Dijk, Factors associated with poor sleep quality in patients with multiple sclerosis differ by disease duration, Disabil. Health J. 7 (2014) 466–471. doi:10.1016/j.dhjo.2014.05.004.

[59] A.C.J.W. Janssens, D. Buljevac, P.A. van Doorn, F.G.A. van der Meché, C.H. Polman, J. Passchier, R.Q. Hintzen, Prediction of anxiety and distress following diagnosis of multiple sclerosis: a two-year longitudinal study., Mult. Scler. (2006). doi:10.1177/1352458506070935.

[60] S. Di Legge, M.C. Piattella, C. Pozzilli, P. Pantano, F. Caramia, I.F. Pestalozza, A. Paolillo, G.L. Lenzi, Longitudinal evaluation of depression and anxiety in patients with clinically isolated syndrome at high risk of developing early multiple sclerosis., Mult. Scler. (2003). doi:10.1191/1352458503ms921oa.

[61] P. Iaffaldano, R.G. Viterbo, B. Goretti, E. Portaccio, M.P. Amato, M. Trojano, Emotional and neutral verbal memory impairment in Multiple Sclerosis, J. Neurol. Sci. (2014). doi:10.1016/j.jns.2014.03.038.

[62] T.F. Runia, N. Jafari, D.A.M. Siepman, R.Q. Hintzen, Fatigue at time of CIS is an independent predictor of a subsequent diagnosis of multiple sclerosis, J. Neurol. Neurosurg. Psychiatry. (2015). doi:10.1136/jnnp-2014-308374.

[63] C.F. Anhoque, S.C. Domingues, T. Carvalho, A.L. Teixeira, R.B. Domingues, Anxiety and depressive symptoms in clinically isolated syndrome and multiple sclerosis, Arq Neuropsiquiatr. 69 (2011) 882–886. http://www.ncbi.nlm.nih.gov/pubmed/22297872.

[64] C. Fazekas, M. Khalil, C. Enzinger, F. Matzer, S. Fuchs, F. Fazekas, No impact of adult attachment and temperament on clinical variability in patients with clinically isolated syndrome and early multiple sclerosis, Clin. Neurol. Neurosurg. (2013). doi:10.1016/j.clineuro.2012.05.022.

[65] A. Labiano-Fontcuberta, M.L. Martinez-Gines, Y. Aladro, L. Ayuso, A.J. Mitchell, V.

Puertas-Martin, M. Cerezo, Y. Higueras, J. Benito-Leon, A comparison study of cognitive deficits in radiologically and clinically isolated syndromes, Mult. Scler. J. (2016). doi:10.1177/1352458515591072.

[66] D.W. Langdon, R.H.B. Benedict, E.M. Wicklein, K. Beckmann, S. Fredrikson, Reports of patients and relatives from the cognicis study about cognition in clinically isolated syndrome: What are our patients telling us?, Eur. Neurol. (2013). doi:10.1159/000345698.

[67] K. Mattarozzi, L. Vignatelli, E. Baldin, A. Lugaresi, E. Pietrolongo, M.R. Tola, L. Motti, W. Neri, S. Calzoni, F. Granella, M. Galeotti, M. Santangelo, S. Malagu', L. Fiorani, A. Guareschi, C. Scandellari, R. D'Alessandro, Effect of the disclosure of MS diagnosis on anxiety, mood and quality of life of patients: A prospective study, Int. J. Clin. Pract. (2012). doi:10.1111/j.1742-1241.2012.02912.x.

[68] T. Štecková, P. Hluštík, V. Sládková, F. Odstrčil, J. Mareš, P. Kaňovský, Thalamic atrophy and cognitive impairment in clinically isolated syndrome and multiple sclerosis, J. Neurol. Sci. (2014). doi:10.1016/j.jns.2014.04.026.

[69] V. Planche, A. Ruet, P. Coupé, D. Lamargue-Hamel, M. Deloire, B. Pereira, J. V. Manjon, F. Munsch, N. Moscufo, D.S. Meier, C.R. Guttmann, V. Dousset, B. Brochet, T. Tourdias, Hippocampal microstructural damage correlates with memory impairment in clinically isolated syndrome suggestive of multiple sclerosis, Mult. Scler. J. (2017). doi:10.1177/1352458516675750.

[70] E.J. Abdullah, H.E. Badr, Assessing the quality of life in patients with multiple sclerosis in Kuwait: a cross sectional study, Psychol. Heal. Med. 23 (2018) 391–399. doi:10.1080/13548506.2017.1366660.

[71] V. de Groot, H. Beckerman, J.W. Twisk, B.M. Uitdehaag, R.Q. Hintzen, A. Minneboo, G.J. Lankhorst, C.H. Polman, L.M. Bouter, Vitality, perceived social support and disease activity determine the performance of social roles in recently diagnosed multiple sclerosis: A longitudinal analysis, J. Rehabil. Med. (2008). doi:10.2340/16501977-0145.

[72] E. Calandri, F. Graziano, M. Borghi, S. Bonino, Coping strategies and adjustment to multiple sclerosis among recently diagnosed patients: The mediating role of sense of

coherence, Clin. Rehabil. (2017). doi:10.1177/0269215517695374.

[73] M.S. a Deloire, M.C. Bonnet, E. Salort, Y. Arimone, M. Boudineau, K.G. Petry, B. Brochet, How to detect cognitive dysfunction at early stages of multiple sclerosis?, Mult. Scler. (2006). doi:10.1191/1352458506ms1289oa.

[74] S. Heiskanen, B. Vickrey, A.-M. Pietilä, Health-related quality of life and its promotion among multiple sclerosis patients in Finland, Int. J. Nurs. Pract. (2011). doi:10.1111/j.1440-172X.2009.01804.x.

[75] A. Ruet, M. Deloire, D. Hamel, J.C. Ouallet, K. Petry, B. Brochet, Cognitive impairment, health-related quality of life and vocational status at early stages of multiple sclerosis: A 7-year longitudinal study, J. Neurol. (2013). doi:10.1007/s00415-012-6705-1.

[76] M. Vitkova, J. Rosenberger, M. Krokavcova, J. Szilasiova, Z. Gdovinova, J.W. Groothoff, J.P. Van Dijk, Health-related quality of life in multiple sclerosis patients with bladder, bowel and sexual dysfunction, Disabil. Rehabil. 36 (2014) 987–992. doi:10.3109/09638288.2013.825332.

[77] S. Kern, W. Schrempf, H. Schneider, T. Schultheiss, H. Reichmann, T. Ziemssen, Neurological disability, psychological distress, and health-related quality of life in MS patients within the first three years after diagnosis., Mult. Scler. (2009). doi:10.1177/1352458509103300.

[78] M. Cohen, B. Brochet, P. Clavelou, E. Le Page, P. Vermersch, A. Tourbah, T. Moreau, H. Joly, C. Sakarovitch, C. Lebrun, Cognition and quality of life in clinically isolated syndrome patients starting a disease modifying therapy in the QUALICIS study may not predict treatment response at one year, J. Neurol. Sci. (2017). doi:10.1016/j.jns.2017.09.030.

[79] S. Fredrikson, Q. Cheng, G.-X. Jiang, D. Wasserman, Elevated suicide risk among patients with multiple sclerosis in Sweden., Neuroepidemiology. (2003). doi:68746.

[80] E.N. Stenager, E. Stenager, N. Koch-Henriksen, H. Bronnum-Hansen, K. Hyllested, K. Jensen, U. Bille-Brahe, Suicide and multiple sclerosis: An epidemiological investigation, J. Neurol. Neurosurg. Psychiatry. (1992). doi:10.1136/jnnp.55.7.542.

[81] R. Viner, K.M. Fiest, A.G.M. Bulloch, J.V.A. Williams, D.H. Lavorato, S. Berzins, N.

Jetté, L.M. Metz, S.B. Patten, Point prevalence and correlates of depression in a national community sample with multiple sclerosis, Gen. Hosp. Psychiatry. (2014). doi:10.1016/j.genhosppsych.2013.12.011.

[82] R.A. Marrie, S. Reingold, J. Cohen, O. Stuve, M. Trojano, P.S. Sorensen, G. Cutter, N. Reider, The incidence and prevalence of psychiatric disorders in multiple sclerosis: A systematic review, Mult. Scler. J. (2015). doi:10.1177/1352458514564487.

[83] A.G. Beiske, E. Svensson, I. Sandanger, B. Czujko, E.D. Pedersen, J.H. Aarseth, K.M. Myhr, Depression and anxiety amongst multiple sclerosis patients, Eur. J. Neurol. (2008). doi:10.1111/j.1468-1331.2007.02041.x.

[84] T. Olivares, Y. Perez, M. Bncort, A. Nieto, J. Barroso, M. Gonzalez-Platas, M. Hernandez, Anxiety and Depression in MS: Short-term evolution and relationship with cognitive and clinical variables, Mult. Scler. 18 (2012) 182–182.

[85] J. Benito-León, J. Manuel Morales, J. Rivera-Navarro, A.J. Mitchell, A review about the impact of multiple sclerosis on health-related quality of life, Disabil. Rehabil. 25 (2003) 1291–1303. doi:10.1080/09638280310001608591.

[86] M. Pompili, A. Forte, M. Palermo, H. Stefani, D.A. Lamis, G. Serafini, M. Amore, P. Girardi, Suicide risk in multiple sclerosis: A systematic review of current literature, J. Psychosom. Res. (2012). doi:10.1016/j.jpsychores.2012.09.011.

[87] A. Scalfari, V. Knappertz, G. Cutter, D.S. Goodin, R. Ashton, G.C. Ebers, Mortality in patients with multiple sclerosis, Neurology. (2013). doi:10.1212/WNL.0b013e31829a3388.

[88] F. Matcham, L. Rayner, S. Steer, M. Hotopf, The prevalence of depression in rheumatoid arthritis: A systematic review and meta-analysis, Rheumatol. (United Kingdom). (2013). doi:10.1093/rheumatology/ket169.

Figure 1. Flow chart.

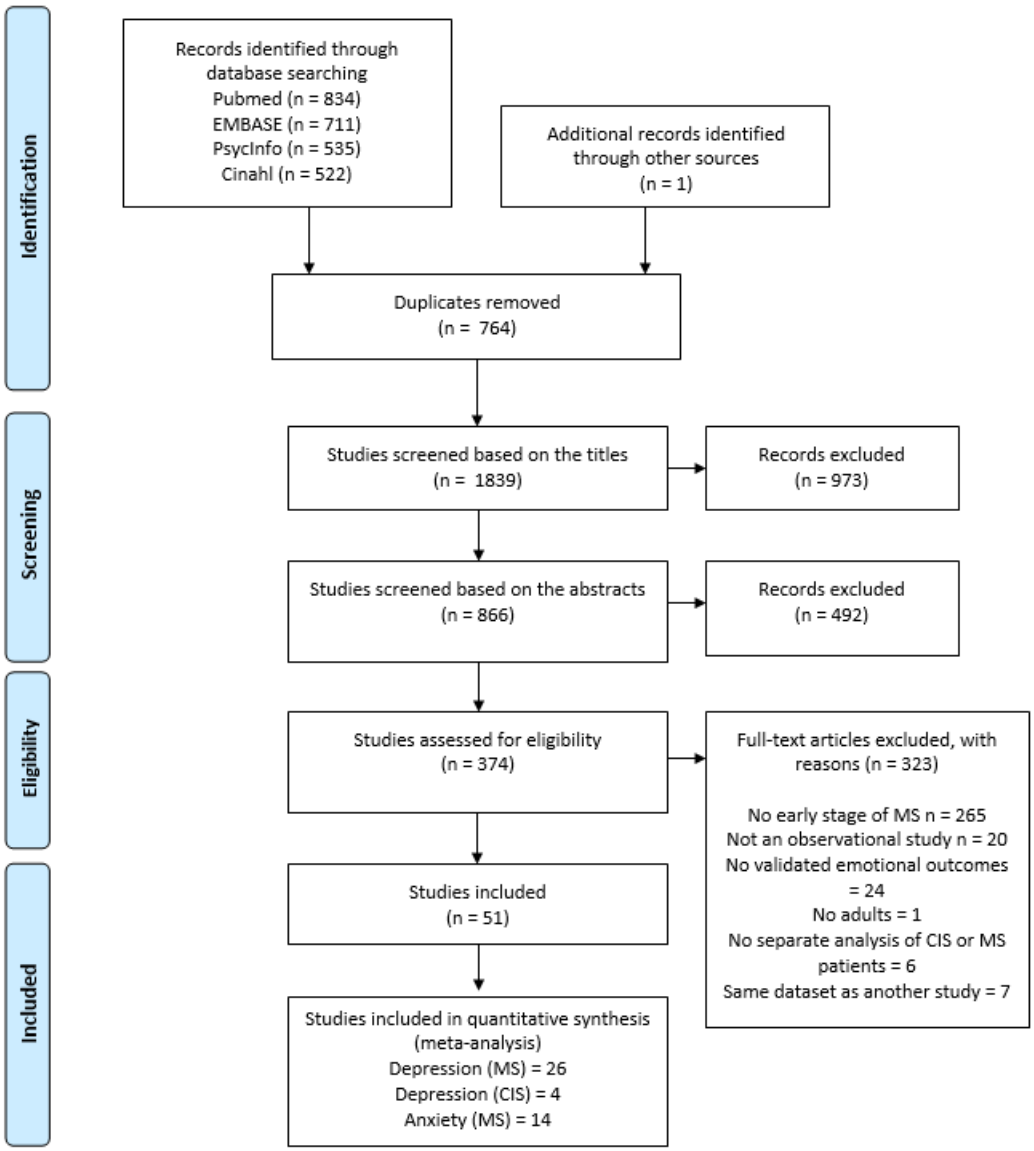

Figure 2. Pooled prevalence meta-analysis of depression in early phase multiple sclerosis.

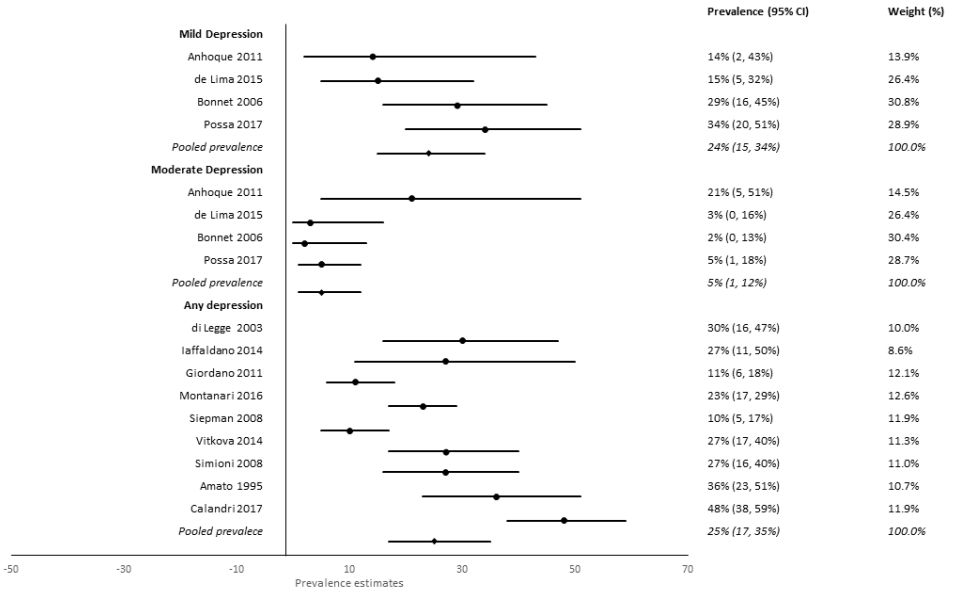

Table 1. Prevalence meta-analysis in early phase multiple sclerosis.

Questionnaire	Measures (thresholds; N of papers)	Total N papers	Total Sample	Prevalence (%)	95% CI	p	% I2 (Tau 2)
DEPRESSION							
Mild depression[1]	BDI (10-18; 2) MADRS (7-19; 2)	4	127	24	15.0, 34.0	<0.001	30.3 (0.0)
Moderate depression[2]	BDI (19-29; 2) MADRS (20-34; 2)	4	127	5	1.0, 12.0	<0.001	35.6 (0.0)
Severe depression[3]	BDI (>29; 2) MADRS (>34; 1)	3	89	0	0.0, 2.0	1.00	0.0 (0.0)
Any depression[4]	BDI (>8; 1) BDI (>9; 1) HADS (>7; 4) HADS (>8; 1) HAMD (>13; 1) CESD (>10; 1)	9	752	25	17.0, 35.0	<0.001	86.7 (0.1)
DSM	MDD	3	114	37	28.0, 46.0	<0.001	0.0 (0.0)
ANXIETY							
Any anxiety[5]	HADS (>7; 5) HADS (>8; 1)	6	645	49	27.0, 72.0	<0.001	97.1 (0.3)

N Number. CI Confidence Interval. I2 I-Squared Heterogeneity. [1]Mild depression categorised by combing "mild" thresholds on BDI (Beck Depression Inventory - 10-18) and MADRS (Montgomery-Asberg Depression Rating Scale - 7-19). [2]Moderate depression categorised by combing "moderate" thresholds on BDI (19-29) and MADRS (20-34). [3]Severe depression categorised by combing "moderate" thresholds on BDI (>29) and MADRS (>34).HADS-D Hospital Anxiety & Depression Scale - Depression. [4]Any depression categorised through participants scoring above the lowest reported threshold on any scale: BDI (>8); BDI (>9); HADS (>7); HADS (>8); Hamilton Depression Scale (HAMD, >13); Centre for Epidemiological Studies Depression scale (CESD, >10). DSM Diagnostic and Statistics Manual. MDD Major Depressive Disorder. AD Adjustment Disorder. [5]Any anxiety categorised through participants scoring above the lowest reported threshold on any scale: HADS (>7); HADS (>8).

Table 2. Mean scores of depressive and anxiety symptoms in early phase multiple sclerosis and clinically isolated syndrome.

Questionnaire	Pooled Mean (95% CI)	N studies	N participants	*p*-value	I^2 (Tau^2)	Interpretation
Depression						
BDI, 0–63 (MS)	7.32 (5.63 to 9.02)	12	530	< .0001	93.9 (7.0)	Minimal depressive symptoms (0 – 9)
BDI, 0–63 (CIS)	7.10 (5.55 to 8.65)	4	92	< .001	0.0 (0.0)	Minimal depressive symptoms (0 – 9)
HADS-D, 0–21(MS)	4.55 (3.41 to 5.69)	7	696	< .0001	93.2 (2.1)	Normal state (0 – 7)
HAM-D, 0–54 (MS)	12.65 (8.05 to 17.25)	2	75	< .0001	86.6 (9.6)	Moderate depressive symptoms (11 – 14)
CES-D (MS)	11.20 (9.90 to 14.50)	2	123	< .0001	77.0 (4.5)	No clinical significance (< 16)
SCL-90*, 0–5 (MS)	1.31 (-0.23 to 2.85)	2	67	.09	98.9 (1.2)	Minimal depressive symptoms
Anxiety						
BAI, 0–63 (MS)	11.38 (8.78 to 13.98)	2	47	< .0001	0.0 (0.0)	Mild anxiety symptoms (10 – 18)
STAI, 20–80 (MS)	42.59 (40.03 to 45.16)	3	354	< .0001	76.3 (3.9)	Mild anxiety symptoms
HADS-A, 0–21 (MS)	6.31 (5.79 to 6.83)	7	696	< .0001	61.2 (0.3)	Normal state (0 – 7)
SCL-90*, 0–5 (MS)	1.16 (-0.36 to 2.68)	2	67	.13	99.2 (1.2)	Minimal anxiety symptoms

N = number; 95% CI = 95% Confidence Interval; I^2 = I-Squared Heterogeneity; BDI = Beck Depression Inventory; HADS-D = Hospital Anxiety & Depression Scale – Depression; HAM-D = Hamilton Depression Scale; CES-D = The Center for Epidemiologic Studies Depression Scale; SCL-90 = Symptom Checklist - 90 item; STAI = State Trait Anxiety Inventory; HADS-A = Hospital Anxiety & Depression Scale – Anxiety; MS early phase multiple sclerosis; CIS = Clinically isolated syndrome.

* Included studies calculated SCL-90 scores by using a general severity index (GSI) from mean of 9 subscales (0–5).

Table 3. Univariate meta-regression analysis of covariates and pooled mean depressive and anxiety symptoms in early phase MS.

Depression	Pooled Mean (95% CI)	N studies	N sample	*p*-value	I^2 (%)
BDI, 0–63	7.32 (5.63 to 9.02)	12	530	< .0001*	93.9
Covariates	Beta (SE)	Lower CI	Upper CI	*p*-value	R-squared (%)
Age	-0.05 (0.10)	-0.27	0.17	.65	0
Percentage female gender	-0.02 (0.04)	-0.10	0.06	.61	0
Sample size	0.00 (0.00)	-0.01	0.01	.62	0
Disease duration	-0.05 (0.06)	-0.18	0.08	.44	0
EDSS	-1.21 (1.21)	-4.00	1.59	.65	100
Study Quality	0.02 (0.17)	-0.35	0.39	.93	.
Publication Year	0.07 (0.12)	-0.18	0.33	.53	.

Depression	Pooled Mean (95% CI)	N studies	N sample	*p*-value	I^2 (%)
HADS-D, 0–21	4.55 (3.41 to 5.69)	7	696	< .0001*	93.2
Covariates	Beta (SE)	Lower CI	Upper CI	*p*-value	R-squared (%)
Age	0.07 (0.21)	-0.42	0.55	.76	-67
Percentage female gender	-0.07 (0.10)	-0.30	0.17	.53	-81.44
Sample size	0.01 (0.00)	0.00	0.02	**.03**	100
Disease duration	-0.02 (0.04)	-0.14	0.09	.59	100
EDSS	-0.53 (1.52)	-5.40	4.32	.75	-112.76
Study Quality	0.38 (0.14)	0.05	0.71	**.03**	100
Publication Year	-0.05 (0.15)	-0.41	0.31	.75	-129.93

Anxiety	Pooled Mean (95% CI)	N studies	N sample	*p*-value	I^2 (%)
HADS-A, 0–21	6.31 (5.79 to 6.83)	7	696	< .0001*	61.2
Covariates	Beta (SE)	Lower CI	Upper CI	*p*-value	R-squared (%)
Age	0.34 (0.46)	-0.80	1.56	.44	-7.28
Percentage female gender	0.11 (0.17)	-0.33	0.55	.54	-11.44
Sample size	0.04 (0.01)	0.02	0.06	**.002**	92.1
Disease duration	0.04 (0.06)	-0.13	0.22	.53	-21.16
EDSS	-4.27 (5.33)	-27.24	18.67	.51	-11.57
Study Quality	0.60 (0.55)	-0.82	2.02	.32	3.91
Publication Year	0.20 (0.39)	-0.80	1.19	.63	-13.9

N = number; 95% CI = 95% Confidence Interval; I^2 = I-Squared Heterogeneity; * = P-value for the pooled mean scores of the depression or anxiety symptoms; BDI = Beck Depression Inventory; SE = Standard Error; CI = Confidence Interval; EDSS = The Expanded Disability Status Scale; HADS-D = Hospital Anxiety & Depression Scale – Depression; HAM-D = Hamilton Depression Scale; SCL-90 = Symptom Checklist - 90 item; STAI = State Trait Anxiety Inventory; HADS-A = Hospital Anxiety & Depression Scale – Anxiety.

All characteristics were treated as continuous variables and analysed as univariate meta-regression models.

Table 4. Methodological quality assessment of included studies on emotional outcomes in clinically isolated syndrome and early phase multiple sclerosis (N=51).

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Total	Quality*
Abdullah & Badr 2018	*Yes*	*No*	*Other*	*Other*	*No*	*No*	*No*	*No*	*Yes*	*No*	*No*	*No*	*Other*	*Yes*	3/14	**Poor**
Amato et al. 1995	*Yes*	*Yes*	*Other*	*Yes*	*No*	*Yes*	*Other*	*No*	*Yes*	*Yes*	*Yes*	*Other*	*Other*	*Yes*	7/14	**Fair**
Anhoque et al. 2011	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*Yes*	*Yes*	*No*	*Yes*	*No*	*Other*	*No*	6/14	**Fair**
Bonnett 2006	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Other*	*Other*	*Yes*	8/14	**Fair**
Brønnum-Hansen et al. 2005	*Yes*	*Yes*	*Other*	*Yes*	*No*	*Yes*	*Yes*	*Other*	*Other*	*Other*	*Yes*	*No*	*Other*	*Yes*	7/14	**Fair**
Calandri et al 2017	*No*	*No*	*No*	*Other*	*No*	*Other*	*No*	*No*	*No*	*No*	*No*	*Yes*	*Yes*	*No*	2/14	**Poor**
Cohen et al. 2017	*Yes*	*Yes*	*Other*	*Yes*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Other*	*No*	*No*	8/14	**Fair**
de Groot et al. 2008	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Other*	*Yes*	*Yes*	11/14	**Good**
de Lima et al. 2015	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	6/14	**Fair**
Deloire et al. 2006	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	7/14	**Fair**
Di Legge et al. 2003	*Yes*	*No*	*Other*	*Other*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Other*	*Yes*	*No*	7/14	**Fair**
Fazekas et al. 2013	*Yes*	*Yes*	*Other*	*Other*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	4/14	**Poor**
Fredrikson et al. 2003	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Other*	*Yes*	*Other*	*Yes*	*No*	*Other*	*No*	8/14	**Fair**
Giordano et al. 2011	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Other*	*Yes*	*Yes*	*Yes*	*Other*	*Yes*	*Yes*	11/14	**Good**
Hankomaki et al. 2014	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*No*	*No*	*Yes*	*Yes*	*Other*	*Yes*	*No*	6/14	**Fair**
Heiskanen et al. 2011	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*Yes*	7/14	**Fair**
Iaffaldano et al 2014	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	6/14	**Fair**
Janssens et al. 2006	*Yes*	*Yes*	*Yes*	*No*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Other*	*Yes*	*No*	9/14	**Fair**
Jonsson et al. 2006	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Other*	*No*	*Yes*	10/14	**Good**
Jun-O'Connell et al. 2017	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*Other*	*Yes*	*Other*	*Other*	*Yes*	6/14	**Fair**
Kern et al. 2014	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*Yes*	6/14	**Fair**
Kern et al. 2011	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*Other*	*Yes*	*Yes*	*Yes*	*Other*	*Other*	*No*	6/14	**Fair**
Kern et al. 2009	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	7/14	**Fair**
Kraemer et al. 2013	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*Other*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	5/14	**Poor**
Labiano-Fontcuberta et al. 2016	*Yes*	*Yes*	*Other*	*Other*	*No*	*No*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Other*	*Other*	*Yes*	6/14	**Fair**
Landro et al. 2004	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*Other*	*Yes*	*Other*	*Other*	*Yes*	7/14	**Fair**
Langdon et al. 2013	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	5/14	**Poor**

Liu et al. 2009	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*Other*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	6/14	**Fair**
Mattarozzi et al. 2012	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*Yes*	*Other*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	7/14	**Fair**
Millefiorini et al. 2002	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	6/14	**Fair**
Montanari et al. 2016	*Yes*	*Yes*	*Other*	*Yes*	*Yes*	*Other*	*Yes*	*Other*	*Yes*	*Other*	*Yes*	*Other*	*Yes*	*Yes*	9/14	**Fair**
Moreau et al. 2009	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Other*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Other*	*Yes*	*No*	10/14	**Good**
Planche et al. 2016	*Yes*	*Yes*	*Other*	*No*	*Yes*	*Other*	*No*	*Other*	*Yes*	*No*	*Yes*	*Yes*	*Other*	*Yes*	7/14	**Fair**
Possa et al. 2017	*Yes*	*No*	*No*	*Yes*	*No*	*No*	*No*	*No*	*No*	*No*	*No*	*No*	*Other*	*No*	2/14	**Poor**
Prokopova et al. 2017	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	5/14	**Poor**
Rojas et al. 2017	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*Other*	*Yes*	*No*	*Yes*	*Other*	*Other*	*Yes*	6/14	**Fair**
Ruet et al. 2013	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Other*	*No*	*Yes*	10/14	**Good**
Runia et al. 2015	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*Yes*	8/14	**Fair**
Shulz et al. 2006	*Yes*	*No*	*Other*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*Yes*	5/14	**Poor**
Siepman et al. 2008	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*Yes*	7/14	**Fair**
Simioni et al. 2008	*Yes*	*No*	*Other*	*Other*	*No*	*No*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Other*	*Other*	*No*	5/14	**Poor**
Steckova et al. 2014	*Yes*	*Yes*	*Other*	*Yes*	*No*	*No*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	6/14	**Fair**
Stenager et al. 1992	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*No*	*Yes*	*Other*	*Yes*	*No*	*Other*	*Yes*	9/14	**Good**
Suh et al. 2010	*Yes*	*Yes*	*Other*	*No*	*No*	*No*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Other*	*No*	3/14	**Poor**
Sullivan et al. 1997	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	6/14	**Fair**
Sullivan et al. 1995	*Yes*	*No*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*Other*	*Other*	*No*	5/14	**Poor**
Tan-Kristanto et al. 2015	*Yes*	*Yes*	*Other*	*No*	*Yes*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*No*	*Other*	*Yes*	6/14	**Fair**
Van der Hiele et al. 2014	*Yes*	*Yes*	*Other*	*Other*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*No*	*Other*	*Yes*	5/14	**Poor**
Vetrugno et al. 2007	*Yes*	*No*	*Other*	*No*	*No*	*No*	*No*	*No*	*Yes*	*Yes*	*Yes*	*No*	*Other*	*No*	4/14	**Poor**
Vitkova et al. 2014a	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*No*	*Other*	*Yes*	7/14	**Fair**
Vitkova et al. 2014b	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*	*Yes*	*No*	*Other*	*Yes*	7/14	**Fair**

Q1 = Research question clearly stated ; Q2 = Study population clearly defined; Q3 = Participation rate of eligible persons at least 50%; Q4 = Subjects selected or recruited from the same or similar population; Q5 = Sample size justification/statistical power of the study provided; Q6 = Exposure(s) of interest measured prior to the outcome(s) ; Q7 = Timeframe sufficient; Q8 = Different levels of the exposure analyzed; Q9 = Exposure measures defined in detail and reliable ; Q10 = Exposure(s) assessed more than once over time; Q11 = Outcome(s) measures defined in detail and reliable; Q12 = Outcome assessors blinded; Q13 = Loss to follow-up after baseline 20% or less; Q14 = Potential confounding variables measured and adjusted statistically; Yes = Yes (the item is fulfilled); No = No (the item is not fulfilled); Other = Other (cannot determine, not applicable, or not reported)

Appendix 1. Search strategy.

Embase Results (Apr 2017)

#60 #51 OR #52 OR #53 AND [article]/lim AND [english]/lim AND [adult]/lim AND [humans]/lim AND [medline]/lim NOT #59 681
#59 #51 OR #52 OR #53 AND [article]/lim AND [english]/lim AND [adult]/lim AND [humans]/lim AND [medline]/lim 723
#58 #56 OR #57 OR #58 3123746
#57 'letter' 1031084
#56 'case report' 2207819
#55 'case study' 100364
#54 #51 OR #52 OR #53 3464
#53 #27 AND #43 189
#52 #11 AND #27 AND #42 2439
#51 #49 AND #50 977
#50 #11 OR #43 192626
#49 #47 OR #48 201517
#48 'adjust':ab,ti 34581
#47 'adjustment':ab,ti 171012
#46 #27 AND #45 2527
#45 #43 OR
#44 28242 #44 #11 AND #42 27220
#43 'clinically isolated syndrome':ab,ti 2063
#42 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 2149788
#41 'newly diagnosed':ab,ti 61799
#40 'early episode':ab,ti 100
#39 'first stage':ab,ti 16216
#38 'first attack':ab,ti 1903

#37 'first phase':ab,ti 14165

#36 'first episode':ab,ti 16556

#35 'onset':ab,ti 547763

#34 'early period':ab,ti 7025

#33 'early phase':ab,ti 28665

#32 'early stage':ab,ti 96877

#31 'early':ab,ti 1622348

#30 'recently diagnosed':ab,ti 5065

#29 'after diagnosis':ab,ti 24685

#28 'early treatment':ab,ti 21726

#27 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 1733286

#26 'suicid*':ab,ti 78563

#25 'suicide':ab,ti 60503

#24 'mood':ab,ti 83311

#23 'satisfaction':ab,ti 134080

#22 'wellbeing':ab,ti 14426

#21 'quality of life':ab,ti 293141

#20 'depressive symptoms':ab,ti 44593

#19 'stress*':ab,ti 795239

#18 'stressor':ab,ti 13800

#17 'distress':ab,ti 118931

#16 'anxious':ab,ti 18624

#15 'mood disorder':ab,ti 6140

#14 'anxiety disorder':ab,ti 15765

#13 'anxiety':ab,ti 200576

#12 'depression':ab,ti 356568

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 192448

#10 'spinal cord syndrome'/exp 37

#9 'cerebellum syndrome'/exp 39

#8 'brainstem syndrome' 139

#7 'optic neuritis'/exp 7789

#6 'disseminated sclerosis'/exp 102745

#5 'myelitis'/exp 60478

#4 'demyelinating cns disease' 50

#3 'demyelinating autoimmune disease' 94

#2 'demyelinating disease'/exp 139863

#1 'multiple sclerosis'/exp 102232

Appendix 2. Observational studies on outcomes of depressive and anxiety symptoms in early phase multiple sclerosis.

Study	Follow-up, months	Total sample N (% women) at baseline	Time since diagnosis at baseline (months),	Depression			Anxiety		
				Outcome and cut-off points	Baseline	Follow-up	Outcome and cut-off points	Baseline	Follow-up
					Mean (SD) / Prevalence (N)	Mean (SD) / Prevalence (N)		Mean (SD) / Prevalence (N)	Mean (SD) / Prevalence (N)
Prospective cohort studies									
Amato et al. 1995, Italy	48	50 (64)	19 (-)	HAM-D (0–54)	14.9 (7.1)	12.9 (5.4)			
				Cut-off > 13	36% (N = 18)	Not rep.			
Deloire et al. 2006, France	Baseline	57 (75)	25 (26.9)	MADRS (0-60)	3.0 (0–21)*	Not rep.			
				Cut-off not rep.	Not rep.	Not rep.			
Giordano et al. 2011, Italy	6	120 (68)	7 (-)	HADS-D (0–21)	3.7 (3.3)	3.0 (IQR 1–5)*	HADS-A (0–21)	7.3 (4.1)	6.0 (IQR 4–9)*
				Cut-off > 7	11% (N = 13)	Not rep.	Cut-off > 7	43% (N = 52)	
Janssens et al. 2006, The Netherlands	24	101 (70)	8 (6.5)	HADS-D (0–21)	3.7 (3.2)	4.3 (3.6)	HADS-A (0–21)	6.5 (5.1)	6.2 (4.4)
				Cut-off > 7	Not rep.	Not rep.	Cut-off > 7	34% (N = 34)	30% (n=30)

Jonsson et al. 2006, Denmark	36	80 (76)	7 (range 1–7)	BDI (0–63)	Not rep.	Not rep.			
				Cut-off < 9	52% (N = 42)	Not rep.			
				Cut-off 10–15	30% (N = 24)	Not rep.			
				Cut-off 16–19	9% 19 (N = 7)	Not rep.			
				Cut-off 20–29	9% (N = 7)	Not rep.			
Mattarozzi et al. 2012, Italy	24	18 (-)	0 (-)	CMDI mood (0–70)	22.4 (5.2)	Not rep.	STAI (20–80)	41.1 (11.0)	Not rep.
				Cut-off not rep.	Not rep.	Not rep.	Cut-off not rep.		
Montanari et al. 2016, Italy	12	250 (74)	Range 12–24	HADS-D (0–21)	6.0 (2.7)	5.8 (2.7)	HADS-A (0–21)	5.6 (3.9)	5.2 (3.9)
				Cut-off > 7	23% (N = 46)	Not rep.	Cut-off > 7	27% (N = 54)	Not rep.
Moreau et al. 2009, France	3	255 (76)	5 (15.7)	BDI (0–63)	5.2 (5.2)	Not rep.	STAI (20–80)	42.3 (15.2)	Not rep.
				Cut-off > 15	6% (N = 16)	Not rep.	Cut-off > 37	51% (N = 129)	
				8–15	19% (N = 49)	Not rep.			
				4–7	20% (N = 52)	Not rep.			

				< 4	52% (N = 132)	Not rep.
Ruet et al. 2013, France	84	65 (69)	31 (38.2)	MADRS (0–60)	4 (range 0–28)*	Not rep.
				Cut-off not rep.	Not rep.	Not rep.

Cross-sectional studies

Study	Total sample N (% women) at baseline	Time since diagnosis at baseline (months), mean (SD)	Depression		Anxiety	
			Outcome and cut-off points	Mean (SD) / Prevalence (N)	Outcome and cut-off points	Mean (SD) / Prevalence (N)
Bonnet et al. 2006, France	43 (67)	24 (26.5)	MADRS (0–60)	6.3 (range 0–18)*		
	Low education group (n=19)		Cut off 7–19	37% (N = 7)		
			20–34	- (N = 0)		
			> 34	- (N = 0)		
	High education group (n=24)		MADRS (0–60)	4.3 (range 0–21)*		
			Cut off 7–19	22% (N = 5)		
			20–34	4% (N = 1)		
			> 34	- (N = 0)		
de Lima et al. 2015, Brazil	33 (100)	21 (12.4)	BDI (0–63)	9.1 (7.3)	BAI (0–63)	10.8 (10.6)
			Cut-off < 9	82% (N = 27)	Cut-off < 9	27% (N = 9)

			10–18	15% (N = 5)	10–18	64% (N = 21)
			19–29	0% (N = 1)	19–29	9% (N = 3)
			> 29	- (N = 0)	> 29	- (N = 0)
Hankomaki et al. 2014, Finland	36 (67)	2.5 (-)	BDI (0–63)	2.8 (3.5)		
			Cut-off not rep.	19% (N = 7)		
Heiskanen et al. 2011, Finland	81 (74)	~ 24 months	CES-D (0–60)	Not rep.		
Kern et al. 2014, Germany	26 (65)	16 (range 2 – 36)	BDI (0–63)	7.7 (5.9)		
			Cut-off not rep.	Not rep.		
Kern et al. 2011, Germany	32 (75)	14 (range 2 – 36)	BDI (0-–63)	8.1 (5.8)		
			Cut-off > 6	53% (N = 17)		
Kern et al. 2009, Germany	31 (81)	15 (10.8)	SCL–90	0.53 (0.52)		
			Cut-off not rep.	Not rep.		
Kraemer et al. 2013, Germany	25 (60)	15 (3.0)	BDI (0–63)	9.2 (1.1)		
			Cut-off > 17	- (N = 0)		
Landro et al. 2004, Norway	26 (73)	14 (15.1)	BDI (0–63)	10.1 (8.0)		
			Cut-off not rep.	Not rep.		
Liu et al. 2009, China	41 (63)	30 (-)	SCL–90	2.1 (0.8)	SCL–90	1.9 (0.7)
			Cut-off not rep.	Not rep.	Cut-off not rep.	
Millefiorini et al. 1992, Italy	18 (56)	~ 60 months	SCID	Not rep.		
			Any depression	72% (N = 13)		

		since diagnosis	Major depression	33% (N = 6)		
			Minor depression	39% (N = 7)		
Possa et al. 2017, Italy	38 (58)	4.7 (3.8)	MADRS (0–60)	7.9 (5.5)	STAI-Y1 (20–80) 'state'	36 (9.3)
			7–19	34% (N = 13)	Cut-off not rep.	
			20–34	5% (N = 2)		
			BDI-II (0–63)	7.4 (6.1)	STAI-Y2 (20–80) 'trait'	37.7 (9.2)
			85th – 90th	13% (N = 5)	Cut-off not rep.	
			91st – 95th	5% (N = 2)		
			> 95th	5% (N = 2)		
Prokopova et al. 2017, Slovakia	19 (53)	~ 2–3 months	BDI-SF (0–12)	Not rep.		
			Cut-off not rep.	Not rep.		
Rojas et al. 2017, Argentina	45 (73.3)	Not rep.	BDI-II (0–63)	Not rep.		
			Cut-off not rep.	Not rep.		
Schulz et al. 2006, Germany	21 (67)	15 (5.6)	CES-D (0–60)	13.2 (6.9)		
			Cut-off not rep.	Not rep.		
Siepman et al. 2008, The Netherlands	101 (70)	8 (6.5)	HADS-D (0–21)	3.7 (3.2)	HADS-A (0–21)	6.5 (4.1)
			Cut-off > 7	10% (N = 10)	Cut-off > 7	34% (N = 34)
Simioni et al. 2008,	109 (67)	34 (-)	HADS-D (0–21)	Not rep.	HADS-A (0–21)	Not rep.

Switzerland			Cut-off > 8	18% (N = 20)	Cut-off > 8	45% (N = 49)
Suh et al. 2010, The United States	96 (78)	36 (-)	HADS-D (0–21)	6.4 (4.7)	HADS-A (0–21)	6.5 (4.1)
			Cut-off not rep.	Not rep.	Cut-off not rep.	
Sullivan et al. 1997, Canada	50 (76)	~ 2 months	SCID	Not rep.		
			Cut-off not rep.	Not rep.		
			Major depressive disorder	39% (N = 18)		
			Adjustment disorder and depressed mood	22% (N = 11)		
Sullivan et al. 1995, Canada	45 (78)	~ 2 months since diagnosis	SCID	Not rep.		
			Cut-off not rep.			
			Major depressive disorder	39% (N = 18)		
			Adjustment disorder and depressed mood	22% (N = 10)		
Tan-Kristanto et al. 2015, Australia	129 (91)	25 (17.5)	DASS-D (0–42)	22.9 (9.1)	DASS-A (0–42)	22.5 (7.4)
			Cut-off 14–20	57% (N = 73)	Cut-off 10–14	8% (N = 10)
			21–27	16% (N = 21)	15–19	35% (N = 45)
			> 27	24% (N = 31)	> 19	54% (N = 70)
	44 (89)	~ 24 months	HADS-D (0–21)	4.5 (3.3)	HADS-A (0–21)	6.6 (3.5)

van der Hiele et al. 2014, The Netherlands	Paid employment (n=25)		Cut-off > 8	Not rep.	Cut-off > 8	Not rep.
	No paid employment (n=19)		HADS-D (0–21)	5.7 (4.7)		8.4 (3.0)
			Cut-off > 8	Not rep.	Cut-off > 8	Not rep.
Vetrugno et al. 2007, Italy	6 (33)	27 (15.7)	BDI (0–63)	5.7 (4.7)		
			Cut-off not rep.	Not rep.		
Vitkova et al. 2014a, Slovakia	124 (69)	~ 60 months since diagnosis	HADS-D (0–21)	4.8 (4.2)	HADS-A (0–21)	6.2 (4.3)
			Cut-off > 7	27% (N = 18)	Cut-off > 7 (N=26)	39% (N = 18)

N = study sample; SD = standard deviation; FU = Follow-up; HAMD = The Hamilton Depression Rating Scale; MADRS = the Montgomery-Asberg Depression Rating Scale; SF-36 = 36-Item Short Form Survey; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SEP-59 = the French version of the Multiple Sclerosis Quality of Life questionnaire; HADS-D = Depression items of Hospital Anxiety and Depression Scale; HADS-A = Anxiety items of Hospital Anxiety and Depression Scale; SCL-90 = the Hopkins Symptom Checklist subscales for depression; CMDI = the Chicago Multiscale Depression Inventory; MSQOL-54 = Multiple Sclerosis Quality of Life-54; SEIQoL-VAS = Schedule for the Evaluation of Individual Quality of Life - Visual Analogue Scale; SCID = Structured Clinical Interview for depression diagnostic criteria; ; CES-D = Center for Epidemiological Studies-Depression; BDI-SF = Beck Depression Inventory Short Form; STAI = The State-

Trait Anxiety Inventory; DASS-D = Depression items of Depression Anxiety Stress Scale; DASS-A = Anxiety items of Depression Anxiety Stress Scale

* values reported in median with range or interquartile range

Appendix 3. Observational studies on outcomes of depressive and anxiety symptoms in clinical isolated syndrome.

Study	Follow-up, months	Total sample N (% women) at baseline	Depression			Anxiety		
			Outcome and cut-off points	Baseline	Follow-up	Outcome and cut-off points	Baseline	Follow-up
				Mean (SD / Prevalence % (N)	Mean (SD / Prevalence % (N)		Mean (SD / Prevalence (N)	Mean (SD / Prevalence (N)
Prospective cohort studies								
Di Legge et al. 2003, Italy	33	37 (65)	BDI (0–63)	7.1 (4.8)	5.9 (6.6)	STAI-Y1 (20–80) 'state'	45.0 (6.4)	44.8 (4.9)
						Cut-off not rep.		
			Cut-off > 9	30% (N = 11)	22% (N = 3)	STAI-Y2 (20–80) 'trait'	46.6 (5.2)	45.2 (4.6)
						Cut-off not rep.		
Mattarozzi et al. 2012, Italy	24	62 (-)	CMDI mood (0–70)	21.3 (7.9)	Not rep.	STAI (20–80)	40.2 (10.5)	Not rep.
			Cut-off not rep.			Cut-off not rep.		
Runia et al. 2014, The Netherlands	35	127 (77)	HADS-D (0–21)	Not rep.	Not rep.	HADS-A (0–21)	Not rep.	Not rep.
			Cut-off not rep.	22% (N = 124)		Cut-off not rep.	36% (N = 124)	
Cross-sectional studies								
Study		T ot	Depression			Anxiety		

		Outcome and cut-off points	Mean (SD) / Prevalence (N)	Outcome and cut-off points	Mean (SD) / Prevalence (N)
Anhoque et al. 2011, Brazil	14 (71)	BDI (0–63)	6.0 (10.7)	BAI (0–63)	12 (7.1)
		Cut-off not rep.		Cut-off not rep.	
Fazekas et al. 2013, Austria	38 (63)	HADS-D (0–21)	2.0 (IQR 1–5)*	HADS–A (0–21)	5.5 (IQR 3–9)*
		Cut-off not rep.		Cut-off not rep.	
Iaffaldano et al. 2014, Italy	22 (73)	BDI (0–63)	7.3 (7.6)		
		Cut-off > 8	27% (N = 6)		
Labiano-Fontcuberta et al. 2016, Spain	25 (76)	HDRS (0–52)	10.2 (7.0)		
		Cut-off not rep.			
Langdon et al. 2013, Multicenter	130 (-)	CES-D (0–60)	Not rep.		
		Cut-off not rep.			
Planche et al. 2017, France	37 (78)	BDI (0–63)	Median (range) 9 (0–36)		
		Cut-off not rep.			
Simioni et al. 2008, Switzerland	56 (79)	HADS-D (0–21)	Not rep.	HADS–A (0-21)	Not rep.
		Cut-off > 8	27% (N = 15)	Cut-off > 8	100% (N = 56)
Štecková et al. 2014, Czech Republic	19 (63)	BDI (0–63)	9.8 (13.2)		
		Cut-off not rep.			

N = study sample; SD = standard deviation; FU = Follow-up; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; STAI = The State-Trait Anxiety Inventory; IQR = Interquartile range; HADS-D = Depression items of Hospital Anxiety and Depression Scale; HADS-A = Anxiety items of Hospital Anxiety and Depression Scale; HDRS = The Hamilton Depression Rating Scale; CES-D = Center for Epidemiological Studies-Depression; EQ-5D = EuroQol 5D questionnaire; FAMS = Functional Assessment of Multiple Sclerosis; CMDI = the Chicago Multiscale Depression Inventory; MSQOL-54 = Multiple Sclerosis Quality of Life-54; * values reported in median with range or interquartile range.

Appendix 4. Emotional outcomes of (health-related) quality of life and its associations to other emotional outcomes in early phase MS and in CIS.

Study	Follow-up	Total sample N (% women) at baseline	Time since diagnosis at baseline (months), mean (SD)	Outcome	Main emotional outcome findings
MS					
Abdullah & Badr 2018, Kuwait	No	80 (not rep.)	Not rep.	MSQOL-54	Mental health summary score, median (25^{th}/75^{th} percentiles) = 53.4 (34.7–71.4)
De Groot et al. 2008, the Netherlands	Yes			SF-36 (0–100)	
Disease started with relapse onset		128 (68)	2.12 (IQR 0.71–4.7)		Baseline / 36-months follow-up: Role emotional domain, mean (SD) = 74.1 (37.0) / 80.1 (35.0) Mental health domain, mean (SD) = 72.1 (17.5) / 72.6 (18.4)
Disease started with non-relapse onset		28 (50)	0.23 (IQR 0.14–0.33)*		Baseline / 36-months follow-up: Role emotional domain, median (IQR) = 100.0 (41.7–100)* / 100 (100–100)* Mental health domain = not rep. / not rep.
Calandri et al. 2017, Italy	No	102 (62)	19.2 (9.6)	SF-12	Mental health summary score (N=96), mean (SD, range) = 45.0 (11.5, 0–100)
Deloire et al. 2006, France	No	57 (75)	25.2 (26.9)	SEP-59	Investigated association between HRQOL and cognition. Self-perception of cognitive problems were strongly correlated with domains of role-emotional (r = 0.47; $p < .001$), emotional well-being (r = 0.37; $p < .01$,), and distress (r = 0.47; $p < .001$,).
Heiskanen et al. 2011, Finland	No	82 (74)	~ 24 months	MSQOL-54 (0–100)	Investigated factors related to HRQoL.

					Depression ($p < .0001$), feelings of burnout ($p < .0001$), and feelings of worthlessness ($p = .003$) were associated with declining in MSQOL-54 mental health summary scores. Perceptions of memory loss ($p < .0001$) and concentration difficulties ($p = .001$) were associated with lower MSQOL-54 mental health summary scores. Other emotion-related outcomes were also associated with MSQOL-54 mental health summary score, such as difficulties in maintaining social relationships ($p < .0001$), creating new ones ($p = .005$), changes in family relations ($p < .0001$), working life ($p < .0001$), and leisure activities ($p < .0001$).
Jun-O'Connell et al. 2017, the United States	No	142 (74)	12*	MSQOL-54 (0–100)	Total mental health summary score, median (IQR) = 66.3 (37.6) *Domains of MSQOL-54, N (%) =* Health distress = 8 (7) Overall quality of life = 11 (6) Emotional well-being = 20 (9) Emotional role limitations = 16 (16)
Kern et al. 2009, Germany	No	31 (81)	15.4 (10.8)	FAMS (0–176)	*Findings between FAMS and disability* = FAMS total score were negatively correlated with EDSS ($r = -0.58$, $p < .01$) and with an emotional well-being domain ($r = -0.45$, $p < .05$). Emotional well-being domain was higher in the low EDSS group (mean of 24.1; SD 3.2) than in the high EDSS group (mean of 19.1 (SD 5.4), $p = .004$. *Findings between FAMS and psychological distress questionnaire of SCL-90-R* = FAMS total score was correlated with depression in SCL-90 subscale ($r = 0.59$, $p < .01$) and emotional well-being domain was correlated with SCL-90 depression subscale ($r = -0.55$, $p < .01$).
Mattarozzi et al. 2012, Italy	Yes	18 (not rep.)	0	MSQOL-54 (0–100)	At baseline / 30-months follow-up: Total mental health summary score, mean (SD) = 56.9 (15.6) / 63.3 (14.9), NS
Montanari et al. 2016, Italy	Yes	250 (74)	Range from 12 to 24 months	SF-36 (0–100)	HRQoL was investigated as a predictor of emotional outcomes. At baseline, the SF-36 mental health ($p = 0.0061$) domain was an independent

					predictor of a HADS-D subscale score of ≥ 8. HADS-A subscale score of ≥ 8 was significantly associated with the SF-36 mental health (p <0.0001) domain. Follow-up ~ 12 months, no significant changes were seen over time for the SF-36 domain of role-emotional. Changes over time in the SF-36 mental health domain did not show statistical significance (p = 0.0682).
Possa et al. 2017, Italy	No	38 (58)	4.7 (3.8)	MSQOL-54 (0–100)	Total mental health summary score, mean (SD) = 69.57 (not rep.) *Domains of MSQOL-54, mean (SD) =* Health distress = 71.3 (19.1) Overall quality of life = 67.2 (15.7) Emotional well-being = 66.8 (15.2) Emotional role limitations = 68.5 (41.5) QoL reductions in self-perception and psychological wellbeing emerged, together with a peculiar perception of change in health that was not related to neurological disability.
Ruet et al. 2013, France	No	65 (69)	31.2 (38.2)	SF-36 (0–100)	Mental health composite score and subscales of role emotional and mental health at baseline were reduced in MS patients compared with healthy participants.
Simioni et al. 2008, Switzerland	No	109 (67)	33.6 (not rep.)	SEP-59	Total SEP-59 component score, mean (SD) = 46.4 (11.0)
Vitkova et al. 2014, Slovakia	No	66 (79)	34.8 (not rep.)	SF-36 (0–100)	Mental health composite score, mean (SD) = 56.8 (15.7)
CIS					
Cohen et al. 2017, France	Yes	35 (71.4)	0.87 (range 0–3)	SEP-59	SEP-59 mental health component score at baseline, mean (SD) = 67.2 (20.1) SEP-59 mental health component score at month 12 (N=28), mean = 71.3 SEP-59 mental health component score at month 24 (N=21), mean = 65.1 SEP-59 mental health component score at month 36 (N=15), mean = 71.0 No statistical significance were found during follow-ups.
Langdon et al. 2013, multicenter	No	130 (not rep.)	Not rep.	FAMS (0–176)/ EQ-5D	FAMS total score was negatively correlated with the MSNQ (r = –0.51, p = 0.01) EQ-5D = NS
Mattarozzi et al. 2012, Italy	Yes	62 (not rep.)	Not rep.	MSQOL-54 (0–100)	At baseline / 30-months follow-up: Total mental health composite score, mean (SD) = 52.7 (18.2) / 66.1 (17.4), NS
Simioni et al. 2008, Switzerland	No	56 (79)	16.8 (not rep.)	SEP-59	Total SEP-59 score, mean (SD) = 44.7 (9.7)

N = Study sample; SD = Standard deviation; HRQoL = Health-related quality of life; IQR = Interquartile range; SF-36 = 36-Item Short Form Survey; SEP-59 = The French version of the MSQOL-54 (SEP-59) questionnaire; r = correlation coefficient; MSQOL-54 = Multiple Sclerosis Quality of Life-54; FAMS = Functional Assessment of Multiple Sclerosis; EDSS = Expanded Disability Status Scale; SCL-90-R = Symptom Checklist-90-R; HADS-D = Depression subscale of Hospital Anxiety and Depression Scale; HADS-A = Anxiety subscale of Hospital Anxiety and Depression Scale; EQ-5D = EuroQol health-related questionnaire; MSNQ = the Multiple Sclerosis Neuropsychological Questionnaire; NS = not significant.

Supplementary file 1. Summary of engaging patient advisory board for the review process

To gather feedback from our Patient Advisory Board (PAB) on the topics of interest for this review, the following e-mail was sent to three people living with multiple sclerosis.

Dear [patient advisory board member],

I hope this e-mail finds you well and that the New Year has got off to a good start. I would like to take this opportunity to welcome you again to the RADAR-CNS patient advisory board as we embark on 2017.

To kick-start things, I have a couple of questions about a piece of research that we are planning to conduct as part of the RADAR-CNS project that I wondered if I could ask your advice about?

More specifically, we would like to perform a systematic review of previous research studies that have investigated mood-related difficulties sometimes experienced alongside symptoms of MS. Myself and a small team of clinicians/researchers (with a background in physiotherapy, neurology and clinical psychology) have been brainstorming ideas about a research question and have come up with a few ideas. The main ideas are to review previous research studies that have investigated the following:

1. The number of people who experience mood and anxiety difficulties (including symptoms of depression) in the early phases of MS either:
    a. After the first attack of symptoms but before a formal diagnosis of MS (sometimes referred to as 'Clinically Isolated Syndrome')
    b. In the months immediately following on from a formal diagnosis of MS
2. The experience of fluctuations in mood and anxiety difficulties (including symptoms of depression) across a period of time (for example, each day or week) in MS

From the perspective of someone living with MS, which would you consider the most interesting or informative topic to be out of these three ideas? Do you have any alternative suggestions about important topics within the area of mood and MS that you would like to see being explored?

We would really appreciate your help.

Best wishes,

Sara

Dr Sara Simblett

Research Associate RADAR-CNS

Response 1

PAB member 1 commented that "mood-related difficulties" is a broad spectrum of states. This member suggested being very specific about states we were most interested in or are deemed most relevant.

They spoke about how mood-related difficulties might have triggered a symptom of MS, might be a symptom or happen as a result of symptoms and diagnosis. They felt that the potential for stress/anxiety to trigger symptoms of MS was the most interesting area. They would like to know more about why people commonly believe that long periods of stress and anxiety might contribute to the incidence of MS symptoms. They encouraged the research team to speak to clinicians, particularly those who had developed theories on the role of stress in triggering symptoms of MS.

They felt that mood as a result of symptoms and diagnosis is less interesting as it seems commonly accepted that people suffer from depression often after many major illnesses and trauma. They questioned whether research in this area would help MS.

This member didn't feel that they could comment on experiences of mood difficulties in the early stages of MS as they did not experience any. However, they did say that they thought people suffer in this way after any type of diagnosis because of the uncertainty.

With regards to the potential choice of search terms, this person suggested that words such as stress and panic were included as well as anxiety to extract papers about mood-related difficulties. They did not think that post-traumatic stress disorder was an outcome of relevance.

Response 2

This member stated that they felt many people will go through several episodes of being symptomatic before they are diagnosed with MS. In terms of emotional impact, they felt that the stage before receiving a diagnosis, or when experiencing distressing symptoms (e.g. optic neuritis) for the first time, was the most stressful and not necessarily the period immediately after a diagnosis. This member suggested that 'health grief' may be common and an interesting outcome to explore.

This member said that the toughest time for them was when they first experienced disability. Loss of independence, feeling socially isolated and lacking "sense of purpose" in life were aspects that were particularly distressing and contributed to feeling depressed. Not knowing whether they would recover and changes to medication caused anxiety. Coming to terms with a permanent and progressive disability could trigger more emotional distress and leave people prone to depression. This member felt that emotional distress may have contributed to triggering symptoms of MS but as they have improved physically they are now feeling much less anxious and no longer feeling depressed.

To summarise, they said, question "1a" was not as significant for me. Both questions "1b" and "2" are important topics to raise awareness of and provide support.

Response 3

This member stated that it had been a long time since their diagnosis and felt unable to comment on question 1. In relation to question 2, they said that there are times when they get anxious and depressed about MS but that it is usually not severe. Anxiety, mood swings and depression are common and quite well documented among people with SPMS or who were diagnosed a few years ago but have not been prescribed a DMT to reduce the rate of progress.

They said that the period between initial suspicion and diagnosis and then immediately post diagnosis can be very emotional and difficult. They felt that this might be a difficult time for people to take part in research and that this might make it harder to conduct research in this area.

Summary of the responses

Our patient advisory board endorsed the focus on researching emotional outcomes in relation to MS. All said that as symptoms flare up or progressively become worse, this could put people at risk of developing additional problems with anxiety and depression. There were mixed or uncertain views about the emotional experiences associated with clinically isolated syndrome, mostly due to poor memory of this time. However, some indication that anxiety might be higher. It was decided that we would research emotional outcomes in relation to both stages.

The group raised interesting questions about the bi-directional relationship between emotional distress and the occurrence of symptoms. It was felt that research into this is too early to be able to conduct a meta-analysis. However, these ideas have been incorporated into other research ideas. As ‘stress’ was mentioned by several people, in addition to anxiety and depression, it was added as a search term in our systematic review of the literature.

Competing interest statement

The authors have no competing interests to report.

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