Depression in Multiple Sclerosis: A Meta-Analysis of Illness and Sociodemographic Correlates Based on the Diathesis-Stress Model.

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Tables and Figures

Abstract

Background: Multiple Sclerosis (MS) is a highly prevalent and chronic disease of the central nervous system. Among the wide-ranging effects are depression symptoms, which have a high co-occurrence with MS. To date, however, literature on the contribution of illness-related and sociodemographic factors to depression in this patient group is characterised by mixed findings. *Aim*: To consolidate available research examining the relationship between depressed mood and a variety of illness and sociodemographic risk factors utilising a well-known theoretical framework: the Diathesis-Stress Model of psychopathology. *Method*: Twenty independent studies, comprising a pooled sample of 22,880 adults with relapsing remitting or progressive forms of MS, were identified from the Embase, PsycINFO and PubMed databases. Pearson's *r* correlation coefficients with associated 95% confidence intervals and *p* values were calculated to determine the magnitude of the relationship between depression severity and seven risk factors: *MS severity, MS subtype, time since diagnosis, age, education level, relationship status* and *gender*. Fail-safe *N*s were also calculated to determine publication bias and heterogeneity examined using a random effects model. *Results*: Only female gender and older age correlated significantly with depression, although associated effects were small. These findings were also characterised by potential outlier effects. *Conclusions*: This review expands current knowledge of how depression interacts with illness-related and sociodemographic factors in adults with MS. Results endorse early screening of depression in females in addition to routine screening throughout the disease course. Large-scale, longitudinal studies are needed to confirm these findings and to explore patterns of depressive symptoms over time.

Declaration

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Chapter 1

Introduction

1.1 Multiple Sclerosis: Aetiology, Clinical Course and Epidemiology.

Multiple Sclerosis (MS) is a chronic and incurable disease that affects the central nervous system through demyelination (Zavoreo, Grzincic, Preksavec, Madzar, & Basic Kes, 2016). Demyelination involves inflammation, scarring and destruction of the fatty insulating myelin sheaths that protect the axons of neurons. When the myelin sheath is destroyed it severely impairs the ability of the nerves to conduct and transmit impulses between the brain and other parts of the body. The destruction of myelin sheaths in the brain forms lesions, or plaques, that permanently and negatively affect the functionality of the central nervous system (Ahmadi, Mobini, Kabiri, Bidaki, & Bozorg, 2018).

While the cause of MS is still not known, multiple hypotheses have been proposed. One such suggestion includes early exposure to the Epstein-Barr virus, a common herpes virus, during early childhood and adolescence (Howard, Trevick, & Younger, 2016). Lifestyle factors have also been implicated in the aetiology of MS, including vitamin D deficiency, oral contraceptive use and smoking (Orton et al. 2006; Wingerchuk, 2011). More recently, evidence to support a familial link and genetic mutations in MS development has been found, although this remains highly disputed (Howard, Trevick, & Younger, 2016).

Distinct clinical subtypes of MS, each associated with a different degree of recovery and/or relapse, have been defined by a consensus of MS specialists (Alhazzani et al., 2018; Lublin, & Reingold, 1996; Lublin et al., 2014). The most common form is Relapsing-Remitting MS (RRMS), which affects approximately 85% of persons with MS. RRMS is characterised by unpredictable intervals of ‘relapsing’ neurological symptoms followed by periods of disease

inactivity whereby the symptoms may completely remit (Gross & Lublin, 2017). Approximately 50% of patients with RRMS will go on to develop a progressive form of MS. This includes Secondary-Progressive MS (SPMS) which involves a gradual worsening of symptoms, with neurological disability between relapses. A smaller percentage (15% or less) will experience disease progression without any relapses. This is known as Primary-Progressive MS (PPMS).

Benign and malignant forms of MS have also been identified, although the use of such terms has been questioned. Exact definitions of benign MS vary, with prevalence estimates ranging from 6% to 64% (Sartori, Abdoli & Freeman, 2017). The most common definition involves little or no progression after the initial attack, resulting in stable disability after 20 years of diagnosis (Satori et al., 2017). Conversely, malignant MS is an aggressive and rare form of the disease. This subtype involves rapid progressions, resulting in death within a few years of diagnosis (Lublin et al., 2014).

Signs and symptoms of MS vary from individual to individual, depending on the disease course and degree of nerve damage. There are, however, common symptoms associated with disease onset. Typical symptoms include: motor coordination and balance problems; extreme fatigue; chronic neuropathic pain; incontinence; visual disturbances; cognitive changes - including problems with attention and concentration, verbal fluency, information processing and memory; and emotional problems, particularly depressed mood (Noseworthy, Lucchinetti, Rodriguez & Weinshenker, 2000).

MS is the most common chronic disease among adults. Worldwide, it is estimated that 23.4 out of every 100,000 people will develop MS (Al-Asmi et al., 2015). In Australia, new estimations suggest that 25,680 are now living with this disease (Ahmad et al., 2018). This represents an increase in the incidence of MS (from 21,200 or 95.2 per 100,000 persons in 2010;

Palmer, 2011). There are, however, discrepancies in incident rates across countries due to inconsistencies in measurement and epidemiological methods (Howard, Trevick & Younger, 2016). Increased survival rates of the disease also confound these data (Orton et al, 2006).

The predominance of MS in women, compared to men, is 2:1, although the course of the disease runs similarly regardless of gender (Noseworthy, Lucchinetti, Rodriguez & Weinshenker, 2000). There are also racial differences, with a higher frequency of MS among Caucasian people and a lower prevalence in those of African-America or Asian decent (Al-Asmi et al., 2015). The prevalence of MS also appears to increase with distance from the equator on both hemispheres, fuelling much research into a possible environmental cause (Dua et al., 2008).

1.2 Depression in MS

The personal and social impact of MS is compounded by a high prevalence of psychiatric comorbidity, particularly depression. This includes clinical depression, also referred to as Major Depressive Disorder (MDD; Haussleiter, Brüne, & Juckel, 2009). According to the current Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a diagnosis of MDD requires the presence of at least five symptoms over a 2-week period (American Psychiatric Association, 2013), two of which should include: (1) depressed mood and (2) loss of interest or pleasure in activities. Other key symptoms of MDD include: weight loss or weight gain, paired with an increase or decrease in appetite; insomnia (inability to sleep) or hypersomnia (sleeping a lot); psychomotor agitation (making quick and sometimes unnecessary movements, e.g. pacing, tapping fingers) or retardation (moving slowly with slow reaction times) and fatigue. Cognitive behavioural symptoms associated with MS include feelings of worthlessness; inability to concentrate or make decisions; and recurring thoughts of death or suicide ideation, suicide

attempts or formulating a plan to commit suicide (American Psychiatric Association, 2013). In combination, these symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning. While MDD can be diagnosed following one episode of a period more than 2 weeks, in most cases episodes of depression are recurrent (Otte et al., 2016).

Estimates of MDD range from 13-30% in those with MS, with a lifetime prevalence of around 50% reported (Alhazzani et al., 2018; Alsaadi et al., 2015). This is a stark contrast to the estimated MDD rate of 10-15% in the general population (American Psychiatric Association, 2013). This high prevalence, coupled with the fact that psychiatric comorbidity can exacerbate MS disability severity (Marrie et al., 2009), highlights the critical need for early prediction, diagnosis and effective treatment of depression in persons with MS (Azimian, Shahvarughi-Farahani, Rahgozar, Etemadifar, & Nasr, 2014).

There is also evidence that depression remains under-diagnosed in this group, with missed diagnosis noted in up to 30% of those who self-report symptoms (Skokoue, Soubasi and Gourzis, 2012). This is possibly due to denial of symptoms or false reporting – individuals with MS are less likely to self-report disabling depressive symptoms (Goldman Consensus Group, 2005; Skokoue et al., 2012). Correct diagnosis of MDD in MS is also challenging given the overlap between symptoms attributed to the demyelinating disease (e.g. tiredness or fatigue, sleep disturbances) and symptoms as a result of depressive disorder (Goldman Consensus Group 2005). Indeed, up to 70% of persons with MS have screened for probable depression based on the widely utilised Beck Depression Inventory (BDI) (Goldman Consensus Group, 2005). To lessen the probability of missed diagnosis, physicians have removed somatic items from the BDI that overlap with MS symptoms (Mohr et al., 1997). However, there is also evidence that the

removal of such items does not significantly change point prevalence estimates of depression in community samples with MS (Aikens, et al., 1999; Moran & Mohr, 2005). To reduce the possibility of missed diagnosis with self-reporting, there have recently been attempts to validate measures of depression commonly used in MS practice (Watson et al., 2014). The consensus is that there is no 'gold standard' for the assessment of depression in MS. Instead, a combination of self-report scales combined with clinical interview is necessary to improve the accuracy of screening (Goldman Consensus Group, 2005; Patten et al., 2015; Skokou et al., 2012).

1.3 Diathesis-Stress Model

A popular explanation for the high prevalence of depression in MS is the Diathesis-Stress Model (Gorforth, Pham & Carlson, 2011). Initially developed in the 1960s by psychologists Manfred Bleuler and David Rosenthal (1963) to explain the aetiology of schizophrenia, the model has been revised and applied to a wide range of mental health disorders, including depression (Monroe et al., 1991; Colodro-Conde et al., 2017). The model has also been applied to chronic illness groups (Babson, 2015).

According to this model, pre-existing factors within an individual may predispose or make them more vulnerable to develop depression. These vulnerabilities include biological and genetic factors that may affect the brains ability to cope with stress, or may impact on neurohormonal systems which, in turn, can have acute and chronic effects on our behaviour (Brown et al., 1989; Burke & Elliott, 1999). Banks and Kerns (1996) suggest that it is a balance of vulnerabilities and stressors that contribute to the onset of mental illness.

There is some evidence for a biological basis to depression in MS. Studies have identified a relationship between the disease's demyelination process and depression. The

suggestion is that inflammation in the hippocampus interferes with brain functionality and thereby contributes to regulation of normal mood states (Colasanti et al., 2015). Inflammatory lesions are low during the early stages of RRMS but persist in PPMS and gradually increase with disease duration and age (Fitzner & Simons, 2010). However, other studies have argued against this biological explanation, identifying no correlation between depressive severity and MS characteristics such as disease subtype, severity or time since diagnosis (Shnek et al., 1995).

Additional vulnerabilities that may contribute to depression in MS include psychological characteristics. This has been confirmed by meta-analytic data: a combination of cognitive and behavioural factors (e.g. coping strategies, attributional style) have been strongly and consistently linked to depressive symptomology (Dorstyn, Black, Mpofu & Kneebone, 2017). Less clear is the contribution of predisposing demographic factors to depression, such as age and gender, in addition to socio-contextual factors such as education level and relationship status. Despite a wealth of MS research examining the association between each of these factors with depression, reported correlations across studies have varied in both magnitude and significance (e.g. Buchanan et al., 2003; Maier et al., 2016; Mohammadi et al., 2015). By adhering to a diathesis-stress framework it may be possible to elucidate which of the abovementioned factors are significantly associated with depression in this patient group (see figure 1). Given the high prevalence of depression in persons with MS, knowledge of such factors will increase the chances of early identification of high-risk individuals and subsequent provision of adequate support and treatment.

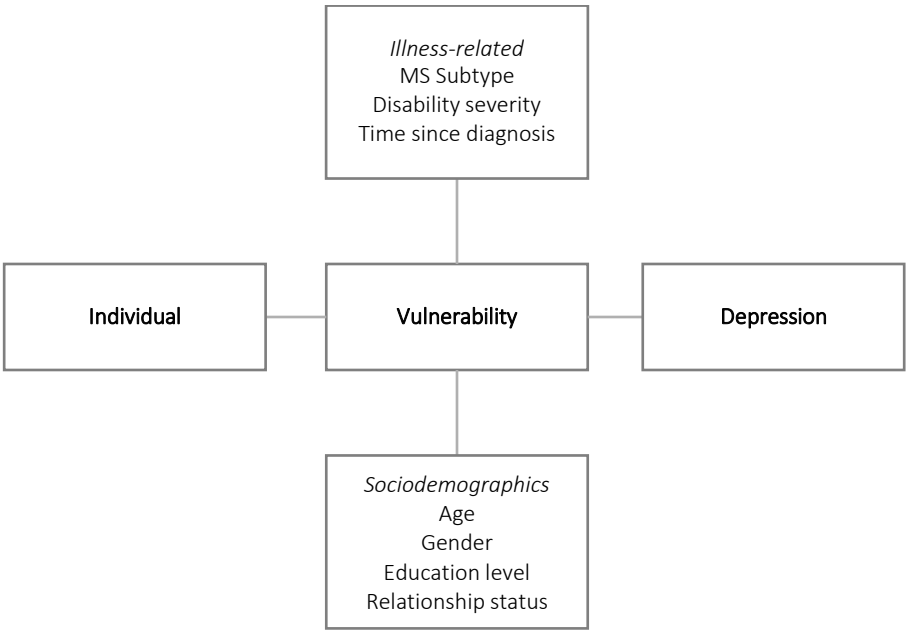


Figure 1. The Diathesis-Stress Model as applied to depression in MS

1.4 Illness-related Correlates

MS severity is a variable that has consistently demonstrated strong and positive correlations with depression severity. That is, individuals living with a higher degree of physical impairment are also more likely to report severe symptoms of depression (Azimian et al., 2014). This includes impairment due to MS-related fatigue, estimated to affect up to 90% of persons with MS (Bakshi et al., 2000; Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009). Fatigue caused by MS can be chronic and debilitating, interfering with day-to-day life and overall quality of life. However, given that symptoms of fatigue and depression also overlap it is difficult to determine how much of the fatigue is caused by the MS or how much is caused by the depression itself (Bakshi et al., 2000). Moreover, some studies have identified no significant relationships between MS symptom severity and depression (Alsaadi et al., 2015; Koch et al., 2009). Notably, studies have varied in how they have operationalised and measured MS severity. This includes the use of symptom specific measures (e.g. Fatigue Impact Scale) in addition to the assessment

of neurological impairment more broadly, based on the widely used Kurtzke Expanded Disability Status Scale (EDSS). The EDSS, which is usually administered by a neurologist, is considered to be the standard measure of neurological impairment in MS research. The EDSS quantifies impairment on a scale from 0 (normal neurological examination) to 10 (death due to MS; Kurtzke, 1983). More recently, a self-report version of the EDSS – the Patient Determined Disease Steps (PDDS) has been developed (Hohol et al., 1995). While the PDDS provides a simple, practical tool to follow MS disease progression in patients over time, it is highly recommended that the EDSS be used in therapeutic decision making (Koch et al., 2009).

Few studies have examined the contribution of *MS subtype* to the development of depression. The limited available data suggest that there is a correlation: those with progressive forms of the disease (e.g. SPMS, PPMS) have reported higher levels of depression than peers with relapsing MS (Maier et al. 2015). However, there is also suggestion that those with PPMS have a low risk of lifetime depressive disorder (Zabad et al., 2005). The reasons for this are unclear, although it may be due to the late-onset of PPMS, which typically occurs at a time when people have established social 'buffering' supports (Zabad et al., 2005).

A similar argument has been made for *time since diagnosis*. There is suggestion that depression is heightened in the first year after diagnosis, after which time depressive symptoms become stable (Chwastiak et al., 2002; Mohammadi et al., 2015). In saying this, longer time since diagnosis has also been shown to be predictive of greater depression severity (Sabanagic-Hajric et al., 2016). The small sample sizes of some of these studies does, however, limit the generalisability of these findings.

1.5 Sociodemographic Correlates

Evidence for the role of demographic factors underpinning depression in MS has yielded conflicting results. This includes *age* as a potential risk factor. Specifically, younger adults with MS (i.e. those under 35) have identified more severe symptoms of depression in comparison to older peers (Alajbegovic et al., 2011; Johansson et al., 2016). One explanation is that the younger cohort often includes individuals who are newly diagnosed with MS and, as such, have had less time to become accustomed to the symptoms and stress of living with their illness (Chwastiak et al., 2002). However, several population-based studies have found no association between age and depression or, conversely, an age-related increase in the prevalence of depression among persons with MS (Buchanan et al., 2003; Luppa et al., 2012; Maier et al., 2016; Mohammadi et al., 2015).

The association between *gender* and depression in MS is also unclear. Some studies have demonstrated a difference in depression prevalence between genders, with females experiencing more severe depression than males (Ahmadi et al., 2018; Buchanan et al., 2003; Luppa et al., 2012). This is consistent with studies conducted in the general population, with higher rates of depression identified among females (Albert, 2015). This gender disparity has been attributed to a combination of individual and neurological factors (e.g. female gender roles, hormone sensitivity; Maciejewski et al., 2001). However, there is also evidence that women with MS do not experience higher rates of depression and, in addition, that female gender is not a significant predictor of changes in depressive symptoms over time (Bael et al., 2007). One explanation for the mixed results may be the use of different screening instruments for depression. In particular, persons with MS may not recognise the symptoms of depression themselves – particularly if they are experiencing symptoms such as anger or irritation rather than low mood.

Other studies propose the contribution of social, contextual factors such as *educational level* in the development of depression following MS. An association between lower educational attainment (i.e. primary or secondary education) and an increased of risk for depression has been established (Al-Asmi et al., 2015; Maier et al., 2016; Mohammadi et al., 2015). The suggestion is that higher education leads to more fulfilling careers and higher wages which, in turn, can reduce financial stress; an issue which is often linked to health problems such as depression. Meta-analytical data confirms the association between stable paid employment and lowered depression in MS (Dorstyn et al., 2019). The protective effect of higher (tertiary) education does, however, vary across MS subgroups - including younger age and female gender (Gerhard et al., 2018). In addition, the aforementioned studies have not routinely controlled for disability severity, which has been strongly linked to depressive symtpoms in MS (Azimian et al., 2014).

Interpersonal relationships have also been identified as having a protective effect on depression in adults with MS. Most studies have identified a higher level of depression in single or divorced persons due to the stresses of living with the disease without support (Al Asmi et al., 2015), although this association has not always been demonstrated (Alsaadi et al., 2015). The assumption is that a relationship can bolster mental health. However, relationships characterised by strong marital discord can also heighten stress and depression, as demonstrated in the general population (Bulloch et al., 2009). Clarification of this complex relationship can be achieved through closer examination and synthesis of the broarder MS literature on depression and relationship support.

1.6 The Present Study

In summary, a combination of illness-related and sociodemographic and variables have been implicated in the development of depression among adults with MS. These findings are, however, inconsistent across studies. A meta-analytic review would help to consolidate this literature and provide a clear overview of conflicting findings (Borenstein, Higgins, Hedges, & Rothstein, 2017). Although previous meta-analyses have examined psychological correlates of depression in MS (Dorstyn et al., 2017, 2019), the contribution of illness-related and socio-contextual variables, both potential contributors to psychopathology in MS according to the diathesis-stress model, remains unclear. By adhering to a diathesis-stress framework in may be possible to elucidate which of the abovementioned factors are significantly associated with depression in MS. Given the high prevalence of depression in this patient group, in comparison to the general population (American Psychiatric Association, 2013), knowledge of such factors with increase the chances of early identification of high-risk individuals and subsequent provision of adequate support and treatment.

The current review will address this research gap and use meta-analytic techniques to investigate the prominent illness (e.g. MS subtype and severity) and sociodemographic (e.g. age, gender) variables that may differentiate persons with MS who are depressed from peers who are not. The findings will be examined in relation to the different depression measures that characterise this research. The aims are to: 1). Identify the strength of the relationships between depression and the aforementioned correlates, in the context of study heterogeneity, and 2). Identify areas warranting further research.

Chapter 2

Method

2.1 Literature Search

Studies examining correlates of depression in persons with MS were identified through a search of the Embase, PsycINFO and PubMed databases. Each database was searched from inception until October 2018. The search terms included a broad list of keywords and phrases related to *MS* (e.g. disseminating sclerosis) and *depression* (e.g. depressive disorder) in order to capture all relevant articles. Search terms were tailored to the Emtree (Embase), Thesaurus (PsycINFO), and MeSH (PubMed) vocabulary with input from a senior research librarian (See Appendix A for complete logic grid). References lists from relevant systematic reviews (Dorstyn, Black, Mpofu, & Kneebone, 2017; Boeschoten, et al., 2017) and identified studies were additionally searched to ensure no eligible studies were missed. No additional studies were identified through this process.

2.2 Eligibility Criteria

Eligible studies had to recruit an adult sample (aged 18 years or older) diagnosed or reported having been diagnosed, with MS. Studies also had to include an assessment of depression or depressed mood, using a validated multi-item self-report or clinician-based instrument (see Appendix B). In addition, studies had to report a bi-variate correlation, or association, between depression and MS severity (i.e. degree of neurological disability) or sample sociodemographics (e.g. age, gender). Only quantitative studies which included data to enable the calculation of effect-size *r* were eligible. Studies reporting statistical procedures involving multiple independent variable (e.g. regression R^2 and β coefficients), were not included

to ensure measures of effect size exclusively examined the relationship between depression and a given illness or sociodemographic characteristic and, therefore were approximately equivalent (Lipsey & Wilson, 2001, pp. 67). Finally, studies that had not been published in journals in English, or with English translation, were excluded to ensure methodological rigour (Jini, Holenstein, Sterne, Bartlett & Egger 2002).

Of 11,708 studies initially identified, 8529 non-duplicate articles were screened. The titles and abstracts of each article was reviewed against the eligibility criteria which further narrowed the field of included articles to 215. The full-text articles of each study were retrieved and screened against the eligibility criteria narrowing down the final group of studies to 21. Two studies had the possibility of overlapping samples (Jones, 2012; Jones, 2014), this was confirmed following contact with the lead author. Both studies were subsequently combined and treated as one independent study, by using data from the publication with the largest sample size (Jones, 2012). This resulted in a final sample size of 20 independent studies (see figure 2). Inter-rater agreement was quantified by allocating a random subset of 50 potentially eligible studies to a second-rater (an undergraduate psychology study, E.P). Overall there was an excellent agreement rate of 93% (Kappa = 89%).

2.3 Data Extraction and Organisation

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, a data extraction spreadsheet was formulated to collate the necessary data from each study (Moher et al., 2009).

Data obtained from each study included:

a) Study characteristics, such as sample size, country and depression measure used.

b) Illness-specific information, including MS subtype, years since disease diagnosis, and level of disability (operationalised as scores on the Expanded Disability Status Scale [EDSS; Kurtzke, 1983] or the Multiple Sclerosis Impact Scale [MSIS-29; Hobart et al., 2001])

c) Sociodemographic information, namely age, gender, relationship status (Married/In a Relationship vs. Single/Divorced/Widowed/Separated), and education level (Primary/Secondary vs. Tertiary).

d) Correlational data that could be converted to *r*, namely, independent samples *t*-tests and chi-squared values involving continuous variables (e.g. age) that were dichotomized (e.g. ≤35, 36-50 and ≥50; Alajbegovic et al., 2011). Lead authors of four papers were contacted for additional data. One author replied (Zavoreo, 2016) and supplied exact *p*-values that were converted to *r* using an online effect size calculator (Wilson, n.d.).

2.4 Risk of Bias Assessment

Studies were assessed for potential sources of methodological bias using the QualSyst tool: a scoring system developed for the quality assessment of quantitative studies in systematic reviews (Kmet, Lee & Cook, 2004). This approach involves rating each individual study against 11 specified criteria. More specifically, included studies were assigned a score of '*2'* (met), '*1*' (partially met) or '*0'* (unclear or not met) for each item. The overall proportion of studies that met each criterion was then calculated.

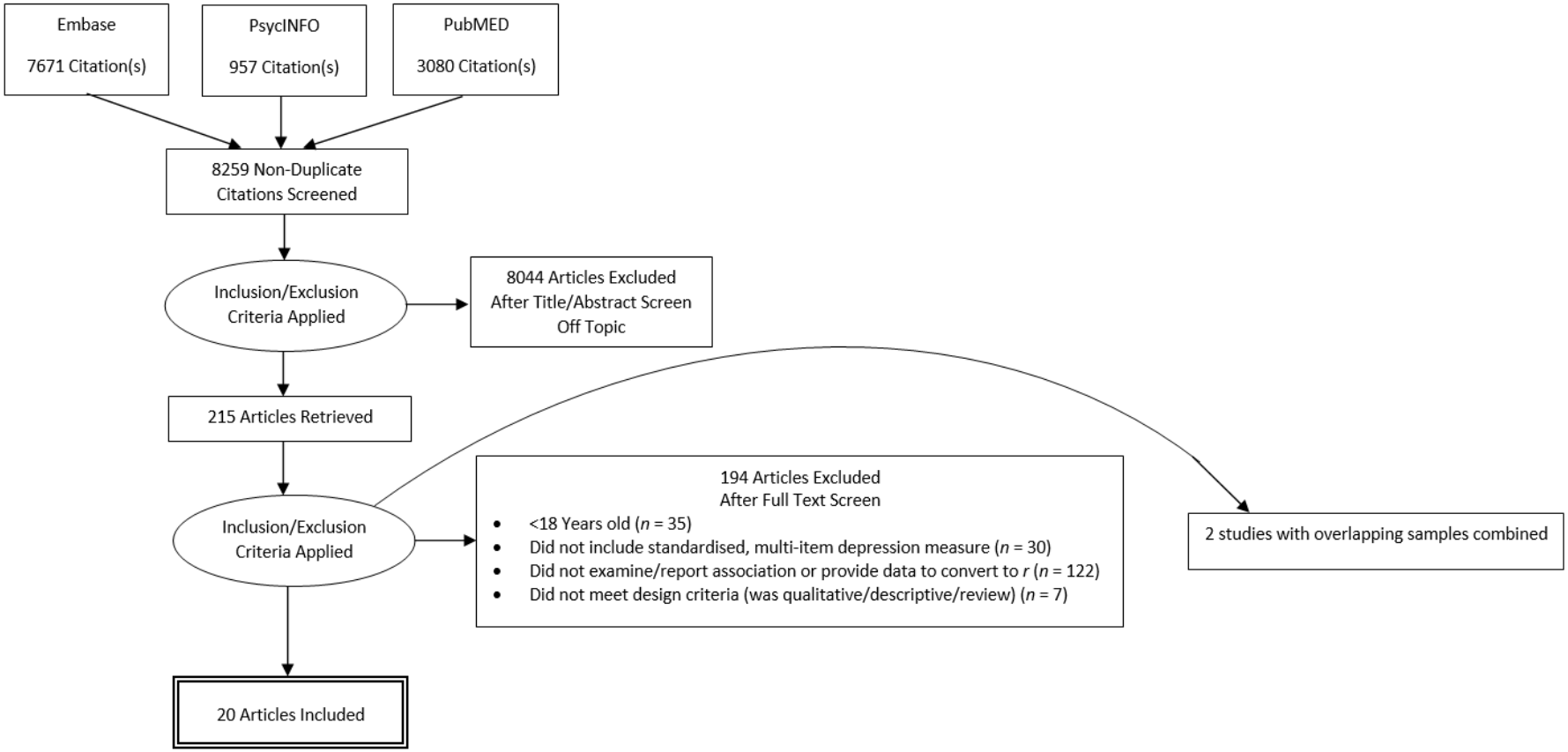


Figure 2. PRISMA Flow Chart of Study Selection (Moher et al., 2009).

2.5 Effect Size Calculations

Effect size *r* was the primary estimate used in this meta-analysis, with *r* values of .10, .30 and .50 representing small, medium and large associations respectively (Cohen, 1992). Data for each depression correlate, in each study, were collected and entered into Meta-Essentials software (Suurmond, van Rhee & Hak, 2017). A random effects model was used to estimate the population effect (Field & Gillett, 2010). This model is recommended as a default by Cumming (2012) as it accounts for both within and between-study heterogeneity. This includes heterogeneity that is typical of a clinical population such as MS (i.e. highly variable clinical course and symptom manifestation; Disanto et al., 2011) in addition to the methodological variation that characterised studies in this review (e.g. use of various depression measurements). Individual correlations were converted to Fisher's *Z*, to normalize the distribution of *r*. Fisher's *Z* values were then back-transformed to *r* for subsequent interpretation. Several papers (Al-Asmi et al., 2015; Buchanan et al., 2003; Chwastiak et al., 2002; Johansson et al., 2016 & Maier et al., 2015) included more than one correlate for age (i.e. different age categories); these were averaged to ensure data independence. Similarly, for the longitudinal studies included (Berzins et al., 2017; Brown et al., 2009; Edwards et al., 2016 & Johansson et al., 2016) only baseline data were used. Effect sizes from different studies based on the same combination of depression measures were then pooled. A total *r* for each illness and sociodemographic category was also obtained. Pooled estimates were weighted based on each study's inverse variance (r_w), accommodating for higher variability in smaller sample sizes (Chueng & Vijayakumar, 2016).

Exact *p*-values and 95% confidence intervals (CIs) were calculated to assess the statistical significance and accuracy of each effect size, respectively. An effect size was considered statistically significant if the associated *p*-value was <0.05. CIs represent the range of

values in which the true effect estimate lies; narrower CI's represent higher precision. In a 95% CI there is only a 5% chance that the true value is not represented within the range of CIs (Cumming, 2012).

Fail-safe Ns (N_{fs}) were calculated for both individual and pooled *r*s to negate the potential for publication bias in this meta-analysis. Publication bias occurs when the results of included studies are different to unpublished studies (Zakzanis, 2001). N_{fs} represents the number of hypothetical publications that would be required to render and individual *r* or pooled r_w to a small statistically unimportant effect size (i.e. $r = \pm .1$; Orwin, 1983). For the purpose of this meta-analysis, an N_{fs} was considered adequate if it exceeded the number of studies contributing to a given analysis (i.e. $N_{fs} > N_{studies}$).

Three statistics were used to measure between-study heterogeneity. *T* represents the standard deviation of the observed effect. Cochran's chi-squared test *(Q)* analyses the ratio of observed variation to within-study error; a significant (i.e. $p<.05$) result suggests the presence of true heterogeneity (Berman & Parker, 2002). Finally, I^2 represents the proportion of variation across studies due to clinical or methodological heterogeneity rather than sampling error alone (Higgins & Thompson, 2002). I^2 is expressed as a percentage, with larger values suggest greater inconsistency (or heterogeneity) of effect estimates across studies (Borenstein, Higgins, Hedges, & Rothstein, 2017).

2.6 Sensitivity Analyses

Sensitivity analyses were conducted for each illness and sociodemographic category to determine the robustness of the observed findings. This involved repeating each meta-analysis by iteratively removing one study at a time. If removal of an individual study resulted in a

change to the magnitude, or the statistical significance, of a pooled effect size then the findings were considered meaningful (Borenstein et al., 2009; Cohen, 1998).

Chapter 3

Results

3.1 Study Characteristics

Twenty independent studies, comprising a total sample size of 22,880 participants with relapsing or progressive forms of MS, provided data for this review (Appendix C). Sample sizes varied from smaller community cohorts to large samples derived from national datasets such as the MS Register based in the United Kingdom. The majority of studies (80%) were cross-sectional in design. Most studies relied on self-report data to measure depression symptom severity. This commonly included the Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Center for Epidemiologic Studies Depression Scale (CES-D) and Patient Health Questionnaire 9 (PHQ-9), each utilised by at least three studies. Two studies relied on objective (clinician-based) measures. Kaplan et al. (2009) utilised MDD criteria outlined by the Diagnostic and Statistical Manual (DSM-IV). Similarly, Buchanan et al. (2003) relied on numerical coding, from The International Classification of Diseases (9th revision) Clinical Modification (ICD-9-CM), a diagnostic system developed by the World Health Organisation.

3.2 Sample Characteristics

As seen in Table 1, the majority of participants were female (71%) living with chronic RRMS, typical of the MS profile (Noseworthy, Lucchinetti, Rodriguez & Weinshenker, 2000). Both young and older adults were represented (age range 18-82). Nineteen studies measured disability severity using the Expanded Disability Status Scale (EDSS), with the majority of participants able to walk independently without an aid. A single study (Jones, 2014) used the

Multiple Sclerosis Impact Scale (MSIS-29), reporting a moderate level of disability among their community sample. Additional demographic details, such as relationship status and education level were not routinely reported ($N_{studies}$ = 6). Where these data were available the majority of participants were married or in a committed relationship and had tertiary education or a high school diploma.

Table 1

Participant Characteristics across Included Studies

	$N_{studies}$	Participants		*M*	*SD*
		n	*%*		
Total sample	20	22,880	100	-	-
Sociodemographics					
Age (Years)	15	8243	100	43.66	6.7
Gender					
Male	17	3752	29	-	-
Female	17	9181	71	-	-
Educational achievement					
≤ High school	7	779	47	-	-
> High school	7	868	53	-	-
Relationship status					
Married/committed relationship	7	1263	64	-	-
Not partnered/single	7	714	35	-	-
Illness Factors					
Time since diagnosis (years)	10	4418	100	9.62	5.56
EDSS score	9	7259	100	3.86	1.28
MS subtype					
Unknown	15	1362	10.6	-	-
Progressive					
Primary progressive	15	1766	13.8	-	-
Secondary progressive	15	1773	13.9	-	-
Progressive relapsing	15	42	0.3	-	-
Relapsing-remitting	15	7848	61.4	-	-

$N_{studies}$ = Number of studies; *n* = Number of participants; *M* = Mean; *SD* = Standard Deviation; EDSS = Expanded Disability Status Scale; (-) = data not provided or not applicable

3.3 Risk of Bias Assessment

As seen in Figure 3, below, most studies reported their objectives, study design and recruitment procedures sufficiently (Criterion 1-3: 95%-100% met). Key sample parameters, such as age, gender and MS subtype, were also fully or at least partially described (Criterion 4: 90% met). Depression, as a primary or secondary outcome, was clearly defined (Criterion 5: 100% met) and the majority of studies were sufficiently powered to detect a significant relationship between depression scores and sample MS or sociodemographic characteristics (Criterion 6: 76% met). Statistical analyses were usually pre-specified in the Methods section of each study (Criterion 7: 95% met), while estimates of variance (e.g. SDs, ranges) were routinely reported (Criterion 8: 80% met). Aside from the paper by Zavoreo et al. (2016), studies included statistical (sensitivity) analyses to control for potential sample confounds (Criterion 9). Both significant and non-significant results were explained (Criterion 10: 95% met). Finally, conclusions were supported by the presented data (Criterion 11: 100%).

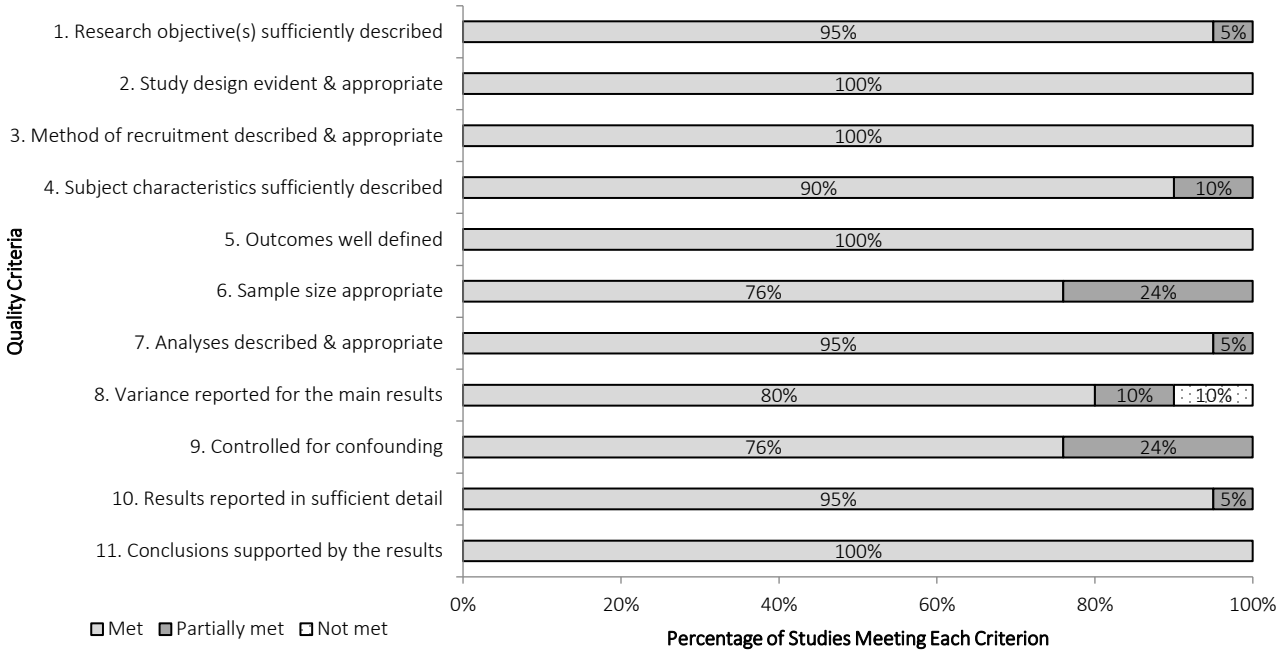


Figure 3. Risk of Bias Assessment (based on QualSyst tool; Kmet et al., 2004)

3.4 Effect Size Estimates

Seven risk factors for probable depression in persons with MS were identified by the 20 included studies. This included three illness-related factors: *years since diagnosis, MS subtype* and *MS severity* and four sociodemographic factors: *gender, age, education* and *relationship status*. Pooled effect size estimates for each factor are listed in Table 2. Table 3 then lists the effects reported by individual studies, grouped by measure. These results are discussed in detail below.

3.5 Illness-related Factors

3.5.1 MS severity. Ten studies examined the relationship between MS severity and depression. The pooled r_w was small to moderate and non-significant; those with a greater level of functional disability were not necessarily more likely to report depressive symptoms than those with lower levels of functional disability. The low N_{fs} value associated with this finding, however, suggests that more research is needed to confirm this result. Estimates provided by individual studies varied substantially (Table 3). Specifically, the BDI and DSM-IV criteria produced a medium effect, effects associated with the CES-D and PHQ-9 were small while the HADS demonstrated a strong positive correlation.

3.5.2 MS subtype. Seven studies examined the relationship between MS subtype and depression (Table 2). Individual estimates for each depression measure, in addition to the overall pooled effect size, were weak and non-significant: individuals with a relapsing form of MS were not necessarily more likely to report depressive symptoms than peers with a progressive MS. The three studies that utilised the BDI, in particular, reported mixed findings. Johannson et al. (2016) and Mohammadi et al. (2015) both reported small effect sizes, although in different

directions (i.e. both positive and negative values). In comparison, Maier et al. (2016) reported a moderate and positive correlation. The N_{fs} values for these findings were, however, not adequate ($N_{fs} < N_{studies}$).

3.5.3 Time since diagnosis. Ten studies examined the association between time since diagnosis (specified in years) and depression (Table 2). Between studies heterogeneity was noted (Table 3). This was largely due to the four studies that utilised the BDI: Maier et al. (2016), Sabanagic-Hajric et al. (2016) and Zavoreo et al. (2016) all reported small positive correlations while Mohammadi et al. (2015) appeared to be an outlier with a small negative correlation and a CI that did not overlap with the other studies. Again, however, the Nfs was not high enough to be considered adequate ($N_{fs} < N_{studies}$).

3.6 Sociodemographic Factors

Of the four factors that were examined in this category, only two were identified as significant and positive correlations of depressed mood: older age and female gender (Table 2).

3.6.1 Age. Twelve studies examined the relationship between age and depression. The overall effect size was small but significant ($p = .04$). This finding was, however, characterized by substantial between-study heterogeneity and potential publication bias ($N_{fs} < N$). As shown in Table 3, five different measures for depression were used across the 12 studies: three self-reports and two clinician ratings. Of these, only the BDI and ICD-9-CM identified significant associations, albeit in different directions. According to the BDI, participants who were older reported more severe depression symptoms. This finding was robust ($N_{fs} > N_{studies}$). However, with the ICD-9-CM younger participants reported greater depression symptoms.

3.6.2 Education. Six studies examined the relationship between education and depression (Table 2). The resulting weighted *r* was weak and non-significant: depression severity did not differ according to education level. Again, there was high heterogeneity; the Hospital Anxiety and Depression Scales (HADS) produced a medium effect, however the BDI and Patient Health Questionnaire (PHQ-9) were associated with small and even negligible effects (Table 3). The N_{fs} was not high enough to be considered adequate.

3.6.3 Relationship status. Six studies examined the association between relationship status and depression (Table 2). The pooled effect size was weak (r <.10) and not significant. When considering individual measures only one of the four measures utilised, the BDI, produced a significant result (Table 3), a finding that was relatively consistent across the two studies that used this measure. However, given that the overall N_{fs} was low, relative to the number of studies that examined this variable, these results should be interpreted with caution.

3.6.4 Gender. Fifteen studies examined the relationship between gender and depression (Table 2). The overall effect was significant, albeit small. There was little to no difference in the effect size regardless of the depression measure used (I^2 < 8%; Table 3). These findings were, however, susceptible to potential publication bias ($N_{fs} < N_{studies}$).

Table 2

Data on Depression Correlates ($N_{studies}$=20)

Variable	$N_{studies}$	$N_{participants}$	r_w	95% CI		*p*	N_{fs}	Heterogeneity			
				Lower	Upper			Q	*p*	I^2	*T*
Illness-related											
MS severity	10	6096	0.19	-0.07	0.43	.15	9	456.56	<.01	98.03	0.41
MS subtype	7	6514	0.07	-0.03	0.14	.06	0	26.73	<.01	77.55	0.08
Time since diagnosis	10	4418	0.03	-0.04	0.10	.44	7	32.65	<.01	72.44	0.09
Sociodemographic											
Age*	12	15857	0.11	0.01	0.22	.04	1	103.11	0.00	89.33	0.16
Education	6	994	0.10	-0.03	0.22	.13	0	17.33	<.01	71.15	0.13
Relationship status	6	14777	0.09	0.00	0.18	.05	1	15.54	0.01	67.83	0.09
Gender*	15	20929	0.03	0.02	0.05	<.01	11	15.08	0.37	7.19	0.01

Abbreviations: $N_{studies}$ = number of studies providing data for this variable; $N_{participants}$ = number of participants from studies providing data for this variable; r_w = weighted mean correlation, CI = 95% confidence interval for r_w; N_{fs} =fail safe *N* statistic.

* indicates statistically significant *r: p < .05*

Table 3

Depression Correlates Grouped by Measure ($N_{studies}$=20)

Variable	Measure	$N_{studies}$	$N_{participants}$	r_w	95% CI		p	N_{fs}	Heterogeneity			
					Lower	Upper			Q	p	I^2	T
Illness-related												
MS severity	BDI	5	994	0.17	-0.15	0.46	.29	4	97.86	0.00	95.91	0.36
	CES-D	1	412	0.02	-0.07	0.12	.63	0				
	DSM-IV	1	37	0.23	-0.10	0.53	.17	1				
	HADS	2	4573	0.42	-0.06	0.74	.08	6	13.99	0.00	92.85	0.35
	PHQ-9	1	80	-0.08	-0.29	0.15	.51	0				
Total		10	6096	0.19	-0.07	0.43	.15	9	456.56	0.00	98.03	0.41
MS subtype	BDI	3	766	0.11	-0.11	0.32	.34	0	18.50	0.00	89.19	0.18
	CES-D	2	1151	0.03	-0.03	0.09	.27	1	0.11	0.74	0.00	0.00
	HADS	2	4597	0.03	0.00	0.06	.03	1	0.79	0.37	0.00	0.00
Total		7	6514	0.07	-0.03	0.14	.06	0	26.73	0.00	77.55	0.08
Time since diagnosis												
	BDI	4	795	0.08	-0.08	0.24	.32	1	14.75	0.00	79.66%	0.15
	CES-D	3	1241	0.04	-0.02	0.10	.16	2	0.66	0.72	0.00%	0.00
	DSM-IV	1	37	0.09	-0.24	0.40	.61	0				
	HADS	1	2265	-0.06	-0.10	-0.02	<.01	0				
	PHQ-9	1	80	-0.13	-0.34	0.10	.27	0				
Total		10	4418	0.03	-0.04	0.10	.44	7	32.65	0.00	72.44%	0.09
Sociodemographic												
Age	BDI	6	1047	0.21	0.05	0.36	.01	7	30.55	0.00	83.63	0.18
	CES-D	2	502	0.08	-0.04	0.19	.17	0	1.32	0.25	24.36	0.05
	DSM-IV	1	37	0.06	-0.27	0.38	.72	0				
	ICD-9-CM	1	14009	-0.09	-0.10	-0.07	<.01	0				
	PHQ-9	2	262	-0.01	-0.14	0.11	.84	2	0.33	0.57	0.00	0.00
Total		12	15857	0.11	0.01	0.22	.04	1	103.11	0.00	89.33	0.16
Education	BDI	3	675	0.05	-0.18	0.27	.66	2	15.98	0.00	87.48	0.19
	HADS	1	57	0.21	-0.06	0.45	.12	1				
	PHQ-9	2	262	0.13	0.01	0.25	.04	1	0.01	0.91	0.00	0.00
Total		6	994	0.10	-0.03	0.22	.13	0	17.33	0.00	71.15	0.13

Table 3 Cont.

Variable	Measure	$N_{studies}$	$N_{participants}$	r_w	95% CI		*p*	N_{fs}	Heterogeneity			
					Lower	Upper			*Q*	*p*	I^2	*T*
Relationship status	BDI	2	449	0.15	0.04	0.26	.01	1	1.27	0.26	21.30	0.04
	HADS	1	57	0.23	-0.03	0.47	.08	1				
	ICD-9-CM	1	14009	0.01	0.00	0.03	.16	1				
	PHQ-9	2	262	0.07	-0.08	0.22	.36	1	1.43	0.23	30.08	0.06
Total		6	14777	0.09	0.00	0.18	.05	1	15.54	0.01	67.83	0.09
Gender	BDI	4	749	0.05	-0.09	0.18	.49	2	5.15	0.08	61.13	0.09
	CES-D	2	502	0.10	-0.05	0.24	.20	0	1.91	0.17	47.52	0.08
	DSM-IV	1	37	0.17	-0.16	0.47	.31	1				
	HADS	4	5230	0.04	0.01	0.07	.01	2	1.36	0.71	0.00	0.00
	HSCL-25	1	140	-0.05	-0.21	0.12	.58	1				
	ICD-9-CM	1	14009	0.03	0.01	0.04	<.01	1				
	PHQ-9	2	262	0.05	-0.07	0.17	.43	1	0.14	0.71	0.00	0.00
Total		15	20929	0.03	0.02	0.05	<.01	11	15.08	0.37	7.19	0.01

Abbreviations: $N_{studies}$ = number of studies providing data; $N_{participants}$ = number of participants providing this data; r_w = weighted mean correlation, CI = 95% confidence interval for r_w; N_{fs} =fail safe *N* statistic.; BDI = Beck Depression Inventory; HADS = Hospital Anxiety and Depression Scale; PHQ-9 = Patient Health Questionnaire 9; HSCL-25 = Hopkins Symptom Checklist-25; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; CES-D = Centre for Epidemiologic Studies Depression Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th Edition.

3.7 Sensitivity Analysis

Data extraction identified several potential 'outlier' effects which may have influenced the results. A one-study removed sensitivity analyses was conducted to examine the individual contribution of each study to the six risk factors associated with significant heterogeneity (Table 4). Although the degree of association did not significantly change across the performed sensitivity analyses, significance levels did. For *MS severity*, the combined effect became significant after removing Mohammadi et al.'s (2015) study. The pooled effect size for *MS subtype* also became significant when removing Mohammadi et al.'s (2015) study in addition to the study by Maier et al. (2016). Finally, the removal of three studies by Jones et al. (2012), Maier et al. (2016) and Sabanagic-Hajiric et al. (2016), resulted in a significant effect for *time since diagnosis*. For *age* the overall effect became non-significant when four studies were removed: those by Alajbegovic et al. (2011), Calandri et al. (2016), Maier et al. (2016) and Sabanagic-Hajiric et al. (2016). The pooled effect for *education* became significant when Mohammadi et al.'s (2015) study of 226 Iranian women was removed. When removing Buchanan et al's (2003) study, the pooled effect for *relationship status* became significant.

Table 4

Changed results from sensitivity analyses

Variable	Removed Study	$N_{studies}$	$N_{participants}$	r_w	95% CI		*p*	Area of Change
					Lower	Upper		
Illness-related								
MS severity	Mohammadi (2015)	9	5870	0.25	0.01	0.45	.04	Significance
MS subtype	Maier (2016)	7	6173	0.03	0.01	0.06	.02	Significance
	Mohammadi (2015)	7	6288	0.09	0.01	0.17	.03	Significance
Time since diagnosis	Jones (2012)	9	2153	-0.06	-0.10	-0.02	<.01	Significance
	Maier (2016)	9	4067	0.18	0.08	0.28	<.01	Significance
	Sabanagic-Hajiric (2016)	9	4298	0.20	0.02	0.36	.03	Significance
Sociodemographic								
Age	Alajbegovic (2011)	11	15807	0.08	-0.02	0.18	.11	Significance
	Calandri (2016)	11	15767	0.11	-0.00	0.22	.06	Significance
	Maier (2016)	11	15506	0.10	-0.01	0.21	.06	Significance
	Sabanagic-Hajiric (2016)	11	15737	0.08	-0.02	0.17	.11	Significance
Education	Mohammadi (2015)	5	768	0.17	0.09	0.23	<.01	Significance
Relationship status	Buchanan (2003)	5	768	0.13	0.05	0.21	<.01	Significance

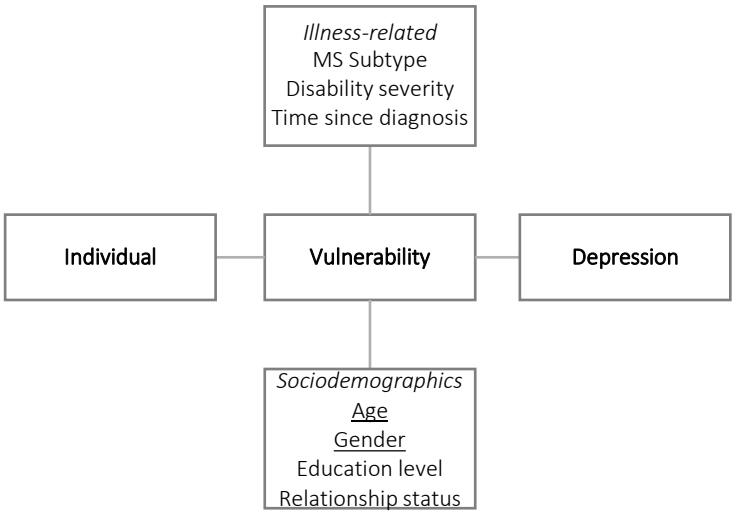
Abbreviations: $N_{studies}$ = number of studies providing data for this variable; $N_{participants}$ = number of participants from studies providing data for this variable; r_w = weighted mean correlation, CI = 95% confidence interval for r_w

Chapter 4

Discussion

4.1 Key Findings

This meta-analysis examined potential risk factors associated with depression in persons with MS. Seven risk factors for probable depression were examined, based on the results from 20 independent studies, comprised of 22, 880 persons with relapsing or progressive forms of the disease. The results revealed only two potentially important risk factors for depression in this group: female gender and older age. Conversely, no significant relationship between depression and *MS severity*, *MS subtype*, *time since diagnosis, education level* or *relationship status* appeared. In combination, these findings suggest that depression following MS is not significantly associated with illness factors, including degree of disability impairment. Rather, a combination of pre-existing vulnerability factors interact with personal factors that occur during and after diagnosis to determine depression severity (see figure 4). These findings are evaluated, in consideration of clinical and research implications and methodological limitations below.



Key: Underlined text: Factors found to be statistically significant in this study. Normal text: Factors identified but not found to be statistically significant in this study.

Figure 4. Results of Current Meta-analysis According to the Diathesis-stress Model

4.1.1 Illness-related factors. The pooled effect size estimates for all illness-related factors examined were non-significant. At face value this could mean that neither MS severity, subtype or time since diagnosis have a signficant impact on the development of depression in this patient group. However, previous research has shown that comorbidity with chronic illness has a substantial effect on depression (Read et al., 2017; Walsh, 2009). What is known is that prevalence estimates of depression in MS are signficantly higher than the general population (American Psychiatric Association, 2013; Boeschoten et al., 2017; Schubert & Foliart, 1993). Studies have also identified relationships between brain lesion location and severity with depressive symptoms in MS (Bakshi et al., 2000; Colasanti et al., 2015). Considering this evidence, in addition to the results of the current meta-analysis, it may be that depression is related to MS only as far as changes in brain matter and function occur. Future research might consider measuring disability impairment with objective measures of brain function, such as MRI imaging. It is also important to note that heterogeneity was high among the studies that examined *MS subtype* and *MS severity* in particular which, added to the low N_{fs} statistic for each factor and the possible outliers identified via sensitivity analysis, suggests that more research into the association between MS severity/subtype and depression is needed before any concrete conclusions can be drawn.

4.1.2 Sociodemographic factors. The impact of female gender as a risk factor for depression in MS is consistent with meta-analyses involving the general population (Salk et al., 2017). A previous meta-analysis by Luppa et al. (2012) on depression in late-onset MS revealed a similar finding, with females being more likely than males to report depressive symptoms. It is suggested that environmental effects, in particular the perceived quality of social support and use of proactive coping styles might explain this gender difference (Luppa et al., 2012).

Alternatively, it may be that gender differences in help-seeking behaviours may explain this correlation (McCabe et al., 2004). The low between-study heterogeneity noted for gender also suggests that the reported effect estiates were relatively consistent across different depression measures. However, the low N_{fs} statistic raises the possibility of publication bias, hence it is important to consider these results with caution.

The finding that greater depressive symptoms were associated with older age contrasts with previous studies conducted in the general population. This includes a study by Fiske et al. (2009) who found younger persons were more inclined to have severe depressive symptoms. Fiske et al. (2009) suggests that late onset depression is characterised by a diathesis-stress perspective, whereby risk and protective factors become more or less prominent, and thus, change in importance as age progresses. Our results do, however, support previous meta-analysis by Luppa et al. (2012) whereby older persons with MS identified worsening depressive symptoms. Notably, this meta-analysis focused on late-onset of MS, hence there was no data for younger participants (<70 years of age). It may be that depressive symptoms vary qualitatively with age. In fact according to meta-analytic data, older adults are less likely to endorse affective symptoms (e.g. distress) and far more likely to describe somatic symptoms (eg. disrupted sleep) than their younger peers (Fiske et al., 2009). However, the findings of our study may also reflect variation related to the individual measures used for depression, rather than a distinct effect of age itself. In fact between-study heterogeneity identified some imprecision in our results relating to age, with the single study that utilised the diagnostic, clinician-based measure (ICD-9-CM) reporting a result in the opposite direction, that is, younger adults were more depressed (Buchanan et al., 2003).

The pooled effect size estimate for *relationship status* was non-significant. A recent meta-analysis has, however, identified the importance of supportive relationships for maintaining psychological health following a diagnosis of MS (Dorstyn et al., 2017). This may be partly due to how relationship status was operationalised in this review. Rather than examine perceived quality of supports, categorial data (i.e. relationship status) was examined. This narrow definition, paired with the relatively small amount of studies that tested this variable, may help to explain the non-significant result for relationship status in the present review.

Likewise, *education level* was not a signifciant factor in the current review. Meta-analytic data suggests that stable paid employment is strongly related to lowered depression rates post-MS (Dorstyn et al., 2017), highlighting the possible protective factor of higher (tertiary) education which, in turn, can lead to successful employment and better paid jobs. Again, however, the high heterogeneity and a small number of included studies that examined this factor may have influenced the results.

4.2 Clinical Implications and Future Research

Results from this meta-analysis demonstrate that the aetiology of depression in MS is complex and cannot simply be explained in the form of a diathesis-stress model. Given that only two biological factors were found to have associations with depression has some important implications. Indeed, there is opportunity for targeted screening and intervention to improve well-being of persons with MS. This should include early screening of depression among females as well as routine screening for both genders as their disease progresses. As older age has been shown to be correlated with depression levels, it is important to focus on correct diagnosis of depression in older persons with MS (Luppa et al., 2012). With previous studies

showing the difference in depressive symptoms throughout the aging process (Fiske at al., 2009), further research could be used to determine which depression measures have higher reliability and validity in the older cohort versus their younger peers.

4.3 Methodological Limitations

The results of this meta-analysis should be considered in the context of several limitations that were encountered during study screening and data extraction. First, the search criteria may have failed to include all possible relevant studies. To minimize this limitation, multiple search strategies were used, including electronic database searches and manual search of reference lists from identified studies and previous MS reviews. Additionally, N_{fs} statistics were calculated to address the problem of publication bias. It is, however, acknowledged that this statistic does not completely alleviate the possibility of publication bias (Orwin, 1983).

Second, many of the vulnerability and risk factors for depression, such as education level and relationship status, were examined by few studies. This limits the generalisability of the conclusions that can be drawn from the data. More large-scale research into these areas is needed before firm conclusions can be drawn in relation to the association between sociodemographic factors and depression.

Third, the data was largely reliant on self-report, with two single studies (Buchanan et al., 2003; Kaplan et al., 2009) incorporating clinician-administered measures. The limited data prevented any subgroup analyses from being undertaken to determine whether there may have been significant different in effect estimates, depending on whether depression symptoms were self-reported of not. Meta-analytic data with the general population suggests that both types of measures are adequate at diagnosing depression, although clinician-based measures have

superior reliability (Cuijpers et al., 2010).

Despite the lack of evidence for associations between several of the examined factors in this study with depression in MS further study is needed - particularly given the high levels of heteroengeneity and publication bias shown through the results of this meta-analysis. It would benefit the area of study to look further into these factors in relation to depression. For example, the possibility for education level to be a protective factor for depression, in relation to employment status and its correlation with depression as shown in previous studies (Dorstyn et al., 2017). As well as the possible correlation between relationship status and depression, whilst accounting for supportive relationships versus non-supportive.

4.4 Conclusion

The findings of the present review highlight the key role of two risk factors in the experience of depression in persons with MS: female gender and older age. Both sociodemographic characteristics can be used to help identify those subgroups with MS who are at risk of developing depression following diagnosis. With early and accurate assessment comes targeted intervention which can help to promote general emotional well-being. Further large-scale and longitudinal research is needed to clarify the significant associations identified in this review, but also to track the trajectory of depression symptoms for these high-risk subgroups over time. Further research is also needed to confirm whether the non-significant associations identified are not simply the result of publication bias, as shown through the results of this meta-analysis.

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Appendices

Appendix A

Search Strategies by Database

Embase

Depression		Multiple Sclerosis
Depression:de OR Depression/exp OR Depression:ti,ab OR Depressed:ti,ab OR Depressive:ti,ab OR Melancholia*:ti,ab OR 'Mood Disorder*':ti,ab OR 'Affective Disorder*':ti,ab	AND	'Multiple Sclerosis' OR 'Multiple Sclerosis' OR 'Disseminated Sclerosis'

PsycINFO

Depression		Multiple Sclerosis
Major Depression.sh OR "Depression (Emotion)".sh OR Depression.ti,ab OR Depressed.ti,ab OR Depressive.ti,ab OR Melancholia*.ti,ab OR Mood Disorder*.ti,ab OR Affective Disorder*.ti,ab	AND	Multiple Sclerosis.sh OR Multiple Sclerosis.ti,ab OR Disseminated Sclerosis.ti,ab

PubMed

Depression		Multiple Sclerosis
Depression[mh] OR Depressive Disorder[mh] OR Depression[tiab] OR Depressed[tiab] OR Depressive[tiab] OR Melancholia*[tiab] OR Mood Disorders[mh:noexp] OR Mood Disorder*[tiab] OR Affective Disorder*[tiab]	AND	Multiple Sclerosis[mh] OR Multiple Sclerosis[tiab] OR Disseminated Sclerosis[tiab]

Appendix B

Eligible Depression Measures

- Beck Depression Inventory (BDI)
- Beck Depression Inventory-II (BDI-II)
- Beck Depression Inventory-Short Form (BDI-SF)
- Hospital Anxiety and Depression Scale (HADS)
- Centre for Epidemiologic Studies Depression Scale (CES-D)
- Centre for Epidemiologic Studies Depression Scale-10 (CES-D-10)
- Chicago Multiscale Depression Inventory (CMDI)
- Hamilton Depression Rating Scale (HRSD)
- Echelle d' Humeur D´epressive (Depressive Mood Scale; EHD)
- Zung Self-Rating Depression Scale (ZSRS)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Patient Reported Outcome Measurement Information System Depression Short-Form (PROMIS-D-8)
- Patient Health Questionnaire-9 (PHQ-9)
- Structured Clinical Interview for DSM Disorders (SCID)

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Appendix C

Descriptive Characteristics of Included Studies (N=20 studies)

Lead Author (date)	Total *N*	Gender (*N*)		Age M(SD) or Range	Time since diagnosis (yrs) M (SD)	MS type (*N*)					EDSS	Measure	Study design
		M	F			RRMS	SPMS	PPMS	PRMS	Unknown			
Alajbegovic (2011)	50	17	33	21-60	-	-	-	-	-	-	-	BDI	CS
Al-Asmi (2015)	57	16	41	≤40 - >40	-	54	1	2	-	-	-	HADS	CS
Alsaadi (2015)	80	28	52	18-65	7.8 (±4.6)	-	-	-	-	-	1.7	PHQ-9	CS
Beiske (2008)	140	46	94	>18	18.8 (±1.0)	103	-	37	-	-	4.1	HSCL-25	CS
Berzins (2017)	182	46	136	<35->65	-	-	-	-	-	-	-	PHQ-9	Longitudinal
Brown (2009)	101	20	81	42.6 (±10.7)	8.3 (±7.2)	70	31	-	-	-	3.6	BDI	Longitudinal
Buchanan (2003)	14009	-	-	≤30->81	-	-	-	-	-	-	-	ICD-9-CM	CS
Calandri (2016)	90	35	55	20-65	1.59 (±0.76)	85	4	1	-	-	-	CES-D	CS
Chwastiak (2002)	739	208	575	21-83	12.5 (±9.5)	382	222	135	-	-	5.5	CES-D	CS
Dahl (2009)	172	61	111	23-82	-	-	-	-	-	-	3.8	HADS	CS
Edwards (2016)	489	-	-	54.27 (±10.43)	17.85 (±9.62)	259	109	79	42	-	-	PHQ-9	Longitudinal
Johansson (2016)	199	64	135	<47-≥47	-	122	77		-	-	-	BDI	Longitudinal
Jones (2012)*	4617	1355	3253	50.9 (±11.5)	12.2 (±9.4)	2849	434	665	-	669	-	HADS	CS
Jones (2014)*	4516	1305	3211	50.7 (±11.2)	10.9 (±8.9)	2804	366	668	-	674	-	HADS	CS
Kaplan (2009)	37	12	25	20-55	12.6 (±8.08)	37	-	-	-	-	3.3	DSM-IV	CS
Koch (2009)	412	125	287	49 (39-57) ^	-	152	138	122	-	-	6.0	CES-D	CS
Maier (2016)	351	112	239	42.9 (±9.6)	-	247	94	-	-	-	2.96	BDI	CS
Mohammadi (2015)	226	-	226	35.7 (±8.07)	1.84 (±0.79)	169	53	4	-	-	-	BDI	CS
Sabanagic-Hajric (2016)	120	38	82	20-60	6 (4-11) ^	120	-	-	-	-	-	BDI	CS
Theaudin (2016)	711	222	489	44.8 (±10.3)	-	395	244	53	-	19	3.8	HADS	CS
Zavoreo (2016)	98	42	56	23-47	5 (±1.5)	-	-	-	-	-	-	BDI	CS

Abbreviations: *N* = total sample size; M = mean; SD = standard deviation; yrs = years; RRMS = Relapsing-Remitting Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis; PPMS = Primary-Progressive Multiple Sclerosis; EDSS = Expanded Disability Status Scale; BDI = Beck Depression Inventory; HADS = Hospital Anxiety and Depression Scale; PHQ-9 = Patient Health Questionnaire 9; HSCL-25 = Hopkins Symptom Checklist-25; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; CES-D = Centre for Epidemiologic Studies Depression Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th Edition; (-) = data not provided.^ median and inter-quartile range; *studies with overlapping samples combined and treated as one independent study. CS = Cross-sectional