Employment and Multiple Sclerosis: A Meta-analysis of Clinical and Demographic Correlates

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ABSTRACT

Background: Individuals with neurodegenerative multiple sclerosis (MS) experience some of the highest rates of unemployment in early adulthood. Although psychological characteristics associated with successful return-to-work have been meta-analysed, the impact of illness and demographic variables remains unclear. *Objective:* To compare clinical and demographic characteristics of employed persons with MS with peers who are not in the workforce, and to map these differences against the International Classification of Functioning, Disability and Health (ICF). *Methods:* Twenty-five independent studies (7053 employed, 11043 not employed) were identified from a search of the Embase, PsycINFO and PubMed databases. Standardised mean differences (Hedge's *g*) with 95% confidence intervals and *p* values, fail-safe *N*s and heterogeneity statistics were calculated. Effect sizes were categorised according to ICF domains: 'body functions and structures', 'activities and participation' and 'personal factors'. *Results:* Body functions and structures were routinely assessed, with significant medium to large effect sizes observed for MS subtype (g_w= 0.80) and fatigue symptoms (g_w= -0.51): those employed commonly had a non-progressive illness subtype and were less affected by fatigue. The employed group also reported significantly greater activity and participation levels (i.e. lowered disability g_w= -1.16, mobility g_w= -2.43), were younger (g_w= -0.62) and had a shorter disease duration (g_w= -0.63). Gender and pain were not significant factors. *Conclusions:* Vocational interventions for persons with MS require multidisciplinary input, aimed to improve impairment and disability of those who experience a relapse. Longitudinal data is needed to determine whether clinical and demographic variables remain a barrier to employment over time.

DECLARATION

This thesis contains no material which has been accepted for the award for any other degree or diploma in any University, and, to the best of my knowledge, contains no materials previously published except where due reference is made.

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CHAPTER 1

Introduction

Multiple Sclerosis

Definition and aetiology. Multiple Sclerosis (MS) is a progressive inflammatory disease affecting the central nervous system (CNS) (Sweetland et al., 2012). It is also one of the most common causes of neurological disability in young adults and adults, worldwide (Moore et al., 2013; Sweetland et al., 2012). Characterised by recurrent episodes of inflammation, the complete aetiology and underlying mechanisms of MS are still not fully understood. However, it has been suggested that the pathogenesis of MS is autoimmune in nature, a process whereby the immune system turns on itself, attacking the myelin sheath which coats, insulates and protects nerves of the brain and spinal cord (Bishop and Rumrill, 2015; Roessler et al. 2001). Damage to any part of the myelin sheath disrupts nerve impulses traveling to and from the brain and spinal cord, leading to disruptive effects on virtually every physical, sensory, mental and emotional activity of an individual (Li et al., 2015). The damaged myelin forms scar tissue (*sclerosis*), giving the disease its name (Li et al., 2015).

Genetic and environmental factors have also been implicated in MS (Bishop and Rumrill, 2015). The risk of developing MS is increased to 40-fold if a sibling has the disease (Love, 2006). Virological studies suggest that infectious agents, namely Epstein–Barr virus and human herpes virus, may even play a role (Love, 2006). Similarly, lower levels of ultraviolet light exposure, vitamin D deficiencies and cigarette smoking strongly affect disease susceptibility (Milo and Miller, 2014). Further evidence for the involvement of environmental factors comes from epidemiological studies, with high geographical locations (i.e. northern USA, Europe,

south eastern Australia) identified as high prevalence areas (Milo and Miller, 2014). Migration from a high- to a lower-prevalence area, before the age of 15, may even reduce the future likelihood of developing MS (Bishop and Rumrill, 2015; Love, 2006).

Prevalence and incidence. Approximately 2.5 million people around the world have MS (Milo and Miller, 2014). In Australia alone, approximately 23,700 are diagnosed with this disease (Australian Bureau of Statistics, 2009). Notably, this figure has increased globally over the last 10 years, from 30 to 33 per 100,000 people (Browne et al., 2014; WHO, 2008). Improved diagnostic methods and treatments, socioeconomic development, changes in lifestyle, and the establishment of national registers may, in part, explain the increase in prevalence (Browne et al., 2014).

MS occurs in most ethnic groups but is most common amongst Caucasians, particularly in western countries (i.e. North America or Western Europe), where prevalence rates fluctuate between 50 to 150 per 100,000, compared to low risk countries (i.e. Eastern Asia) where rates can be as low as 5 per 100,000 (Lau et al., 2016; Milo and Miller, 2014). Females account for the majority of cases (typically a 2-3:1 female to male ratio) (Amatya et al., 2017; Browne et al., 2014). While MS can occur at any age, symptom-onset typically occurs during early adulthood (i.e. between the ages of 20 and 50) (Milo and Miller, 2014; Schapiro 2003).

Courses of MS. The progression of MS typically follows one of four courses: *relapsing-remitting, secondary progressive, primary progressive* and *progressive relapsing*. Approximately 85% of people begin their MS journey with a diagnosis of *relapsing-remitting* MS (Mäurer and Rieckmann, 2000; Milo and Miller, 2014). This involves acute episodes, also referred to as relapses, exacerbations or flare-ups, that typically occur every one to two years and may last for days, weeks or even months

before either partially or completely resolving (i.e. remissions) (Glanz et al., 2012; Mäurer and Rieckmann, 2000). A *secondary relapsing-remitting disease* course occurs in at least 50% of those that are initially diagnosed with relapsing-remitting MS and involves a steady progression towards disability, with or without the presence of remissions (Koch et al., 2010). Approximately 10% of the MS population have a *primary progressive* course, which is characterised by gradual accrual of disability (Glanz et al., 2012; Miller and Leary, 2007). These patients experience no distinct relapses, with rare occasions of stability, facing only temporary improvements in their condition (Koch et al., 2010; Miller and Leary, 2007). *Progressive relapsing* MS, described in earlier disease course definitions, develops in approximately 5% of people and is characterised by worsening neurological function and, ultimately death (Lublin et al., 2014). People previously diagnosed as progressive relapsing would now be considered primary progressive: *active* (at the time of relapses) or *not active* (Lublin et al., 2014). In addition to these subtypes, the terms *clinically isolated syndrome*, which may or may not develop into MS, and *malignant* MS, which quickly leads to significant disability and death (Milo and Miller, 2014), are routinely used in the MS literature. Patients with the more common relapsing remitting or progressive MS subtypes could be considered to have malignant MS (Bishop and Rumrill, 2015).

Physical symptoms. Presentations of MS are reflected by symptoms that reflect CNS involvement. The type and severity of symptoms experienced depend on both the size and location of the CNS lesions (Boe Lunde et al., 2014). As an example, plaques in the frontal or parietal lobes in the brain are often associated with cognitive and emotional impairments, whereas those found in the cerebellum, spinal cord and brain stem typically cause deficits of physical function (Bishop and Rumrill, 2015).

Whilst the presentation of MS symptoms varies from individual to individual,

common symptom patterns are experienced (Bishop and Rumrill, 2015). The most commonly reported symptom is fatigue, estimated to affect as many as 92% of this population (Multiple Sclerosis Coalition, 2014; Shiavolin et al., 2013). Fatigue can be defined as perceived lack of physical and/or mental energy, which significantly interferes with usual and desired activities (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). It can be broadly divided into primary (i.e. MS-specific fatigue appearing without a cause) or secondary fatigue (i.e. as a result of another condition) (Tur, 2016). While the pathogenesis of fatigue remains uncertain, it has been suggested that brain regions may play a role – namely the brain stem, premotor and limbic areas (Krupp, 2003; Tur, 2016). Fatigue can contribute to reduced roles and responsibilities within the home, work and social environments, by decreasing cognitive function (e.g. attention, concentration) and/or impeding physical activity, resulting in an inability to complete one's work (including housework) (MacAllister and Krupp, 2005). Physical factors (i.e. heat intolerance, infections, decreased mobility) and psychological distress can also exacerbate the clinical picture of fatigue in MS (O'Connor et al., 2005; Tellez et al. 2006). Unsurprisingly, then, fatigue has a substantial impact on quality of life for this cohort (Hadjimichael et al., 2008; Tur, 2016).

Another classic symptom associated with MS is pain, typically defined as an unpleasant sensory experience characterised by potential or actual damage (Solaro et al., 2012). The reporting rates of pain typically vary widely, from 28% to as high as 90% (Clifford and Trotter, 1984; Ehde et al., 2006; Heckman-Stone and Stone, 2001). MS-related pain can be musculoskeletal (i.e. leg spasms, back pain) or neuropathic (i.e. constant, burning or tingling primarily in the lower limbs) in origin, in addition to taking an acute or chronic course (Solaro et al., 2012). The scope and nature of MS-

related pain is still poorly understood (Ehde et al., 2005). However, those who present with pain are more likely to report reduced overall physical functioning, poorer mental health and quality of life than peers who report being pain-free (Shahrbanian et al., 2013).

Persons with MS may also present with spinal cord symptoms, including decreased motor control, impaired muscle strength, spasticity and impaired balance (Salter et al., 2010), experienced by up to 50% of those diagnosed (Pike et al., 2010; Van Asch, 2011). Motor impairments can significantly restrict an individual's ability to participate in vocational, family, social and recreational activities due to travelling and access difficulties (Johnson et al., 2009; Salter et al., 2010). Similarly, poor hand function due to reduced dexterity can lead to difficulties with handwriting or other manual tasks (O'Connor et al., 2005). The Extended Disability Status Scale (EDSS), a highly valued measurement tool, is typically used to quantify and monitor level of MS-related impairment across four functional systems: pyramidal (i.e. weakness or difficulty in moving limbs e.g. walking), cerebellar (i.e. loss of bodily movements, coordination or tremor), sensory (i.e. numbness or loss of sensations), and visual functions (i.e. optic neuritis or blurred/grey vision) (Kurtzke, 1983). The EDSS is internationally accepted, recommended as a key endpoint in clinical trials, and often used to determine when an individual should leave work (Cadden and Arnett, 2015; Meyer-Moock et al., 2014).

The aforementioned physical symptoms are rarely life-threatening yet progressively worsen over time. MS is therefore considered to be a chronic disease associated with long-term implications (Roessler and Rumrill, 2003). Indeed, people with MS are expected to live 90% of their lifespan. For example, someone diagnosed at age 50, would be expected to live for at least 20 more years (Khan and Pallant,

2007). With no current cure, successful management of this disease centres on drug treatments, also known as disease-modifying therapies, to improve clinical recovery from relapses and to reduce the risk of further relapse. Combined with physical and psychological therapies, medications such as Interferon beta can help to alleviate and improve symptom patterns (i.e. by reducing frequency of relapses and slowing disease progression) (Bermel et al., 2013; Glanz et al., 2012).

MS and Employment

The onset of MS typically occurs during one's peak years of normal productivity and employment, seriously disrupting career pathways (Moore et al., 2013; Shahrbanian et al., 2013). Employment goes beyond simply providing people with their incomes (Bishop and Rumrill, 2015). It provides opportunities for social interactions and security, in addition to giving people a sense of purpose and identity, by promoting and maintaining self-esteem (Moore et al., 2013). By being employed, individuals are able to focus on their work activities, rather than the symptoms and disability associated with their MS. In this respect, work provides a purposeful distraction (Shahrbanian et al., 2013). In comparison, losing the ability to work has been associated with lowered quality of life, due to fears of reduced income as well as an increase in emotional distress (Shahrbanian et al., 2013). These findings are consistent with those of the wider population: employment significantly contributes to both physical and psychological wellbeing (Linn et al., 1985; McKee-Ryan et al., 2005).

Point estimates of unemployment vary from 22% to 80% across MS studies, (Salter et al., 2017; Shahrbanian et al., 2013). Furthermore, although two thirds of this cohort are employed at the time of their diagnosis (Rumrill et al., 2008), this

figure decreases markedly within 5 years post diagnosis with up to 80% of persons with MS becoming unemployed (Shahrbanian et al., 2013; Sweetland et al., 2012). This is a concerning statistic, particularly when compared to the employment rates for other severe and chronic disabilities (e.g. up to 65% of adults with a traumatic spinal cord injury are employed up to 20 years post-injury) (Ma et al., 2014). Unsurprisingly, then, job retention and rehabilitation is a primary concern after a diagnosis of MS and the identification of constructs contributing to their employment is required (Cadden and Arnett, 2015).

Typical employment patterns see people move from high-demand jobs to lesser demanding jobs before they retire (Sweetland et al., 2012). Of concern is that many people stop working even before the onset of significant physical disability (Strober and Arnett, 2016; Rumrill et al., 2007). Commonly cited reasons include concerns regarding future impairment (e.g. fear of incontinence associated with bladder and bowel problems), negative opinions and lack of support from work colleagues and employers, fears of disability discrimination and a general lack of information about employees' legal work entitlements (Johnson et al., 2004).

In sum, current research supports the benefits of employment for those with MS. It is therefore necessary that further research prioritises the understanding of both facilitators and barriers to work participation in order to ensure that vocational interventions are targeted and relevant (Roessler and Rumrill, 2003; Shahrbanian et al., 2013). This is particularly important as many people with MS still have the capacity, and would like to return to work (Sweetland et al., 2012). Ideally, vocational rehabilitation programs should be introduced soon after diagnosis and involve multi-professional, evidence-based approaches to address disease-related impairments, limitations, or restrictions (Escorpizo et al., 2011). Despite the need for

such programs, particularly for those developing disability within the work force and needing direction regarding the sustainment of their employment, vocational intervention studies remain limited in quantity and quality (Patti et al., 2007). This is, in part, due to a multitude of factors and attributes being identified as moderators of the post-MS employment process, making it difficult to identify specific rehabilitation targets.

International Classification of Functioning, Disability and Health (ICF) and MS

The concept of employment and vocational rehabilitation for people with MS is best understood from a biopsychosocial framework. One such framework is the International Classification of Functioning, Disability and Health (ICF), developed by the World Health Organisation (WHO) in 2001. The ICF views work participation as a dynamic construct involving three domains or components: *Body functions and structures*, *Activities and Participation* as well as contextual *environmental* and *personal* factors (Conrad et al., 2014; Khan et al., 2013; Martins, 2015) (see Figure 1). In relation to MS, individuals experience a variety of impairments (e.g. fatigue, pain), alongside activity limitations (e.g. self-care), which, ultimately, impact on their social participation (i.e. ability to work). These factors may be exacerbated by environmental barriers (e.g. difficulty accessing work) in addition to personal factors, such as their ability to cope with work-place demands in the face of their illness and educational level, both considered to be protective factors against unemployment (Roessler et al., 2004; Sweetland et al., 2012). To ensure the best quality vocational rehabilitation service for individuals with MS, then, it is important that all these domains are considered (Conrad et al., 2014).

A major advantage of the ICF is its ability to describe a person's health

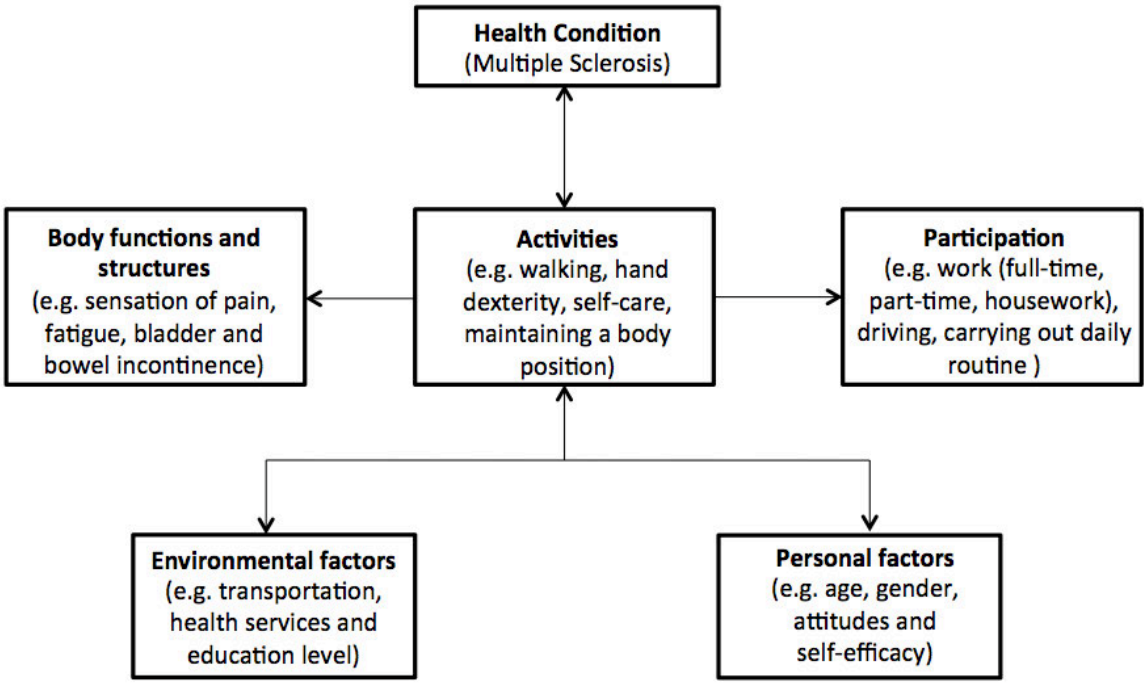


Figure 1. *The ICF's biopsychosocial model of functioning, disability and health as it relates to Multiple Sclerosis* (adapted from Khan et al., 2013).

experience holistically, allowing comparisons between patients in different environments and settings (Khan and Pallant, 2007). This framework also acknowledges that people have a unique array of strengths and vulnerabilities with the onset of an illness and associated disability, such as MS (Khan and Pallant, 2007). In relation to employment for this cohort, the ICF can be used to map the key factors associated with ability to work, whether they are as a result of the disease itself (i.e. physical symptoms and impacts), the working environment (both physical and social), or even the demands of the job (i.e. multi-tasking or full-time work with long hours) (Sweetland et al., 2012). Each ICF component is explored in more detail, below.

Body functions and structures. This component includes the functioning (i.e. at the level of the body) and impairments that individuals with MS face in their day to

day lives (Conrad et al., 2014). Psychological variables and cognitive impairments are categorised under this domain. Previous meta-analytic data confirms the strong relationship between depressed mood and anxiety and continued employment following a diagnosis of MS (Dorstyn et al., 2017). There is also a growing recognition concerning the impact of cognitive issues (i.e. deficits in memory and concentration and executive functioning), particularly in the context of employment (Rosti-Otajärvi and Hämäläinen, 2014).

Physical symptoms typically experienced by persons with MS are also categorised as problems in body functions and structure. For those with MS, this includes worsening MS symptoms, namely fatigue and pain, and a progressive disease course, both identified as risk factors for future employment loss, although the strength of these relationships has been debated (Julian et al., 2008; Simmons et al., 2010; Shahrbanian et al., 2013; Sweetland et al., 2012).

Fatigue. As previously mentioned, fatigue reduces the capability of people with MS to complete their work and as a result, people are more likely to be employed or reduce their work hours (Krupp, 2003; Shiavolin et al., 2013). However, fatigue is a subjective experience that can be difficult to measure and, within the workplace itself, it can even be misinterpreted as laziness (Shiavolin et al., 2013). To date, there are no anatomical or biological markers for fatigue. As such, MS studies have relied on self-reported data for its measurement, such as the Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS), whereas other studies have examined the effects of fatigue on general functioning (i.e. attention or concentration) (Krupp, 2003). Given its high prevalence within the MS cohort, assessing fatigue is essential, particularly considering the evidence highlighting the efficacy of evidence-based fatigue-targeted interventions (e.g. physical activity, cognitive behavioural therapy) (Krupp et al.,

2010). However, MS studies that have examined differences in fatigue levels by employment status have produced mixed results: some have identified significantly lower fatigue levels among employed peers (Cadden and Arnett, 2015; Krause et al., 2013), whilst others have not (Smith and Arnett, 2005; Van der Hiele et al. 2015). Just how substantial the effect of fatigue is for those in and out of the work force is, therefore, not fully understood (Sweetland et al., 2012).

Pain. Primarily measured by self-report, MS-related pain is a complex personal experience (Shahrbanian et al., 2013). This may partly explain why findings on the relationship between pain and employment status following a diagnosis of MS are conflicting. For example, Piwko et al. (2007) and Ehde et al. (2003) reported that pain did not significantly impact on employment rates in their community samples, estimated to be 23% and 34% respectively. However, Ehde et al. (2006) found that people with MS who described pain were typically less employed. These findings may also reflect the use of small convenience samples, potentially leading to the experience of pain being underestimated (Shahrbanian et al., 2013). In addition, MS studies have utilised varying definitions and measurements of pain: some have focussed exclusively on pain duration, severity and/or location, whilst others have adopted non-standardised pain measures which can lead to spurious results (Ehde et al., 2006; Svendsen et al., 2003). Furthermore, the few studies that have examined the extent to which community functioning is affected by pain, have demonstrated pain frequency and severity as either significantly impacting on ability to work (Moore et al., 2013), or having small and non-significant effects (Boe Lunde et al., 2014). These mixed findings warrant further investigation on the pain experiences of employed and unemployed persons with MS.

Activity limitations and participation. These two components of the ICF are

concerned with physical disability and impairment. While activity limitations generally consider the abilities of individuals with MS to perform daily tasks, or lack thereof, participation refers to the life issues that an individual may face (Conrad et al., 2014). For someone with MS, capacity to perform work tasks may be affected which, ultimately, can impact on employment (Khan et al., 2013). Indeed, reduced functioning (e.g. impaired mobility and/or hand dexterity) remains a primary reason for leaving the workforce (Shahrbanian et al., 2013; Shiavolin et al., 2013; Johnson et al., 2009). A decline in functional mobility can also contribute to loss of social connections as well as an inability to perform or participate in self-care and independent living (Paltama et al., 2007). Even for those who experience mild mobility loss in the early stages of MS, activity and participation levels may be significantly affected (Goldman et al., 2008; Paltama et al., 2007). However, the degree to which mobility is related to employment, over and beyond other physical MS-related symptoms, is yet to be examined (Salter et al., 2010). In addition, there is evidence to suggest that remaining at work with MS can be deleterious to one's social health, particularly if one is unable to participate in work social activities and/or becomes isolated from work peer groups as a result of difficulties performing tasks (Sweetland et al., 2012).

Environmental factors. Environmental factors encompass the issues that can arise from the work place, whilst also taking into account the social impacts (Johnson et al., 2004). There is evidence to suggest that people with MS withdraw from the workforce as a result of insufficient information regarding their legal rights within a work setting (Macdonald-Wilson et al., 2003; O'Connor et al., 2005). Dissatisfaction with the provision of work-place accommodations and an overall lack of support from work peers have also been identified as contributing to early retirement for those with

MS (Johnson et al., 2004; Sweetland et al., 2012). The impact of the aforementioned environmental variables on employment status was recently confirmed in a meta-analytic review of 33 studies involving 22,864 participants with relapsing or progressive MS (Dorstyn et al., 2017). It was found that environmental variables, namely ability to cope with stress, played a role in the relationship between MS and employment, warranting a targeted focus in rehabilitation settings (Dorstyn et al., 2017).

Personal Factors. Although personal factors (e.g. age, gender) have yet to be classified by the ICF for MS, due to the large societal and cultural variance, they are still present within the framework. It is important that studies continue to collect data fitting into this domain as a way of adding to its development (WHO, 2013). For individuals with MS, age has been implicated as an important predictor of employment: older age being positively correlated with higher rates of unemployment (Bishop and Rumrill, 2009; Edgley et al., 1991). However, older age generally also means that individuals have lived with their MS for a longer period of time (Julian et al., 2008). Indeed, those with longer disease durations (i.e. time since diagnosis) are more likely to have increased levels of disability and thereby, are also more likely to be unemployed (Sweetland et al., 2012; Julian et al., 2008).

MS studies have also identified gender as a key variable: women with MS are less likely to be employed than men and more likely to leave the workforce due to associated responsibilities at home (i.e. additional "home maker" tasks) (Larocca et al., 1985; Roessler et al., 2001; Roessler et al., 2005). However, this data is not consistent. For example, Simmons et al. (2010) reported lower rates of unemployment among men with MS. Other studies have found no relationship between gender and employment status in this group (Bishop and Rumrill, 2009; Roessler et al., 2001). It

follows that further quantitative review of this research is needed to help clarify the relationship between personal attributes and employment status post-diagnosis.

Current Study

There is a rising interest in the concept of employment for people with MS. However, the reasons for unemployment are not routinely detailed in studies. Consequently, it is not easy to determine what exactly causes people with MS to leave the workforce (Shahrbanian et al., 2013). Furthermore, whilst previous narrative and meta-analytic reviews have focused on psychosocial correlates of employment (Dorstyn et al, 2017) and the rising recognition of cognitive impairments (Rosti-Otajärvi and Hämäläinen, 2014), the contribution of illness (e.g. MS subtype, fatigue, pain) and demographic factors (e.g. age, gender) in the employment process remains unclear. This additional information can help to inform effective, targeted vocational rehabilitation and management for job-seekers with MS (Shahrbanian et al., 2013).

This research gap will be addressed in the current study by utilising a universal, well-established framework, the ICF, to investigate the inter-relationship between prominent clinical and demographic factors that differentiate employment status for those with MS (Shahrbanian et al., 2013). The presentation of these attributes and symptoms will be compared between two groups of adults with MS: those who are employed and those who are not employed. A secondary aim will be to identify which ICF domain(s) have the strongest association with employment and to examine the findings in relation to the individual measures and sample sizes utilised across studies.

To address these aims, a quantitative meta-analysis will be undertaken. This methodology involves the integration of results from numerous independent studies in order to determine the mean and variance of underlying effects within populations. In

this instance, a meta-analytic review will provide a more precise and powerful estimate of the effects of the risk factors for unemployment following MS than would otherwise be provided by an individual study (Field and Gillet, 2010; Haidich, 2010).

CHAPTER 2

Method

Literature Search Procedure

A comprehensive search of the Embase, PsycINFO and PubMed databases was conducted in order to source eligible articles that reported clinical and demographic variables by employment status for adults with MS. The search strategy dated from database inception (Embase, 1947, PsychINFO, 1967 and PubMed, 1996) to June 2017. Search terms were developed in consultation with a research librarian to ensure accuracy, and included a broad range of key words, combining 'multiple sclerosis' with employment synonyms such as 'job', 'work' or 'occupation' (see Appendix A for complete logic grids). Email alerts were set up for each database to identify any new results that matched the search criteria. In addition, the corresponding authors of ten articles were contacted in order to seek additional data information regarding their study eligibility, with six responding (Bøe Lunde et al. 2014; Glad et al., 2010; Grytten et al., 2016; Finlayson et al., 2012; Julian et al., 2008; Li et al., 2015; Mifune et al., 2014; Pearson et al., 2016; Ruet et al., 2013; Tauhid et al., 2014). Finally, a manual search of the reference lists of eligible articles was conducted and one additional article identified (Piwko et al., 2007).

Eligibility Criteria for Studies

In order to be included in this meta-analysis, eligible studies needed to: (a) involve an adult sample (i.e. 18 years or older) that were diagnosed, or had reported being diagnosed, with MS; (b) assess MS-related factors including disability severity, disease duration and physical symptoms (e.g. fatigue, pain), via a standardised self-report questionnaire or clinician-based rating scale, and/or report sample

demographics (e.g. age, gender) (Milo and Miller, 2014). To ensure generalisability of the reported findings, a study had to include MS-related or demographic variables that had been investigated by three or more studies included this review (Valentine, Pigott, Rothstein, 2010). Studies also had to (c) examine the association between these aforementioned variables and employment, as a primary or secondary outcome. Employment was operationalised as 'paid employment'; classified as full-, part-time or casual work consistent with the International Labour Organization (1982). There were, however, inconsistencies across studies in the definition of 'unemployment'. To retain conceptual similarity between studies, various subgroups were combined into a 'non-employed' comparison group. This included those not in the workforce (i.e. homemakers, students, volunteers), retirees or disabled individuals, as well as unemployed persons who may, or may not, be seeking work. Studies had to (d) report parametric data differentiated by employment status (employed vs 'not employed') in order to calculate Hedges' *g* effect sizes (i.e. means, standard deviations, *t*-tests, *F*-statistics, odds ratios and point-biserial correlation coefficients), thereby only considering univariate data (Field and Gillet, 2010; Jackson et al., 2011; Lipsey and Wilson, 2001). Furthermore, studies were required to be published in the English language, which are considered to represent better overall methodological quality (Jüni et al., 2002).

Studies were excluded if they (a) included participants with clinically isolated syndrome (i.e. benign MS) or clinically probable MS, either of which may not develop into MS (McDonald et al., 2001; Polman et al., 2005; Polman et al., 2011), or (b) only had psychological (i.e. affective, emotional), or socio-environmental (e.g. social support) outcome variables, which have been examined in previous review papers (Dorstyn et al., 2017; Rosti-Otajärvi and Hämäläinen, 2014). Similarly, studies

which (c) exclusively focused on MS-related cognitive impairment (e.g. reductions in speed and efficiency in information processing, deficits in episodic and long-term memory etc.) were excluded, given the high prevalence (up to 70%) of cognitive impairment in MS in addition to the high volume of research in this area, warranting a more detailed solo focus (Bishop and Rumrill, 2015). Finally, (d) studies were excluded if they were not published in a journal, therefore excluding any grey literature (e.g. dissertations).

The initial database search identified 3,723 articles, following the removal of duplicates (Figure 2). The application of the eligibility criteria to the titles and abstracts of the articles yielded 319 studies. The full text versions of these articles were then retrieved and the criteria were re-applied to them. A subset of 28 articles were checked by a second researcher (DD) and 90% agreement was achieved ($k = 1.2$, $p > 0.05$). Independence of data was checked, with three studies having potential sample overlap due to their use of the North American Research Committee on Multiple Sclerosis registry (NARCOMS) (Salter et al. 2017; Salter et al., 2010; Julian et al., 2008), of which two had similar time frames for recruitment (Salter et al., 2010; Julian et al., 2008). Two additional studies by Van der Hiele et al. (2014, 2015) were also combined into one study. In both cases, the data from the most recent publication were utilised. This process resulted in 25 studies providing usable, independent data (Figure 2).

Data Collection and Preparation

Consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; Moher et al., 2009), a data extraction sheet was developed to summarise key information from each study (see Appendix B). This

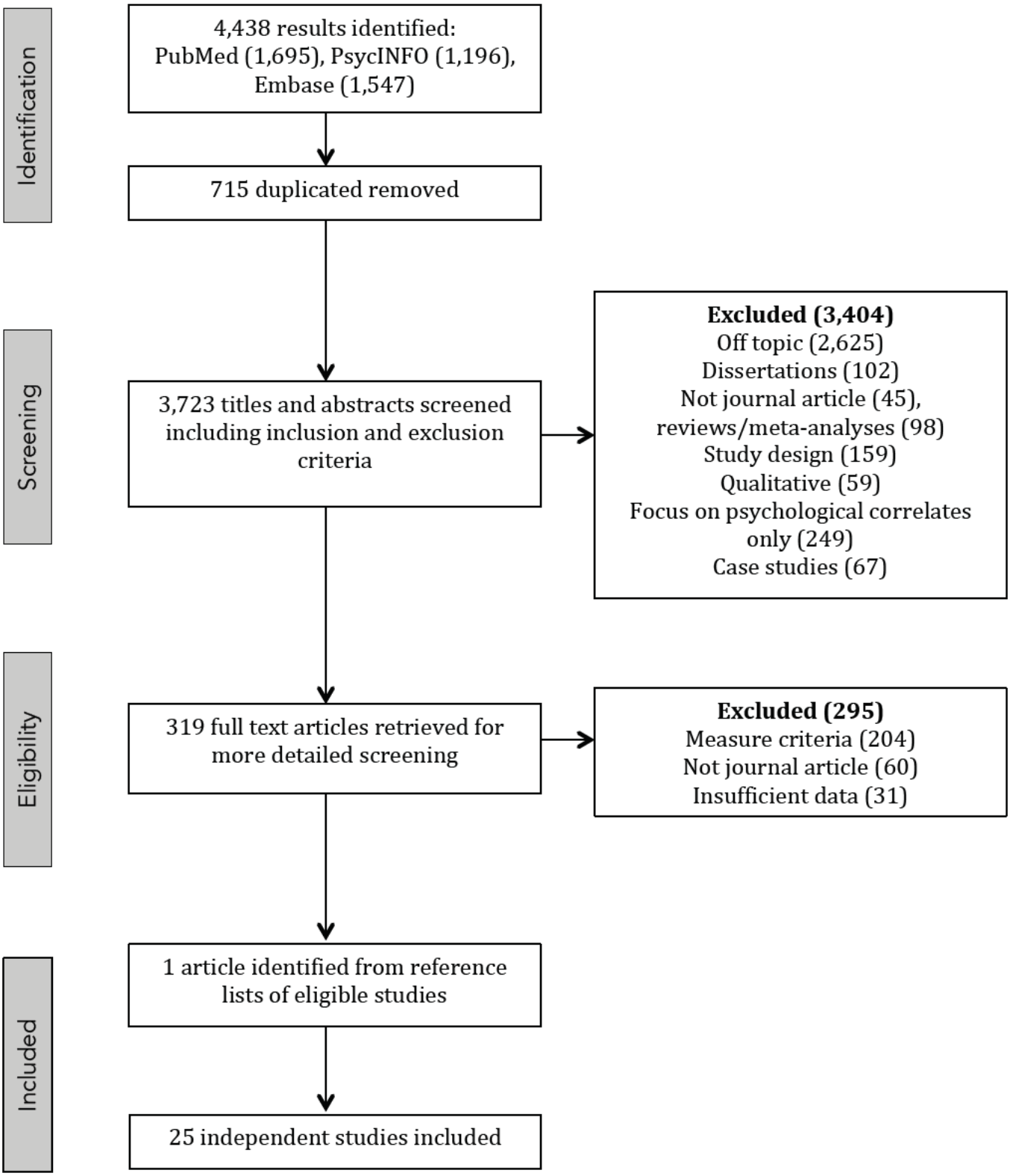


Figure 2. *PRISMA flowchart of the study selection process (Moher et al., 2009).*

included: (1) total sample size and demographics (i.e. age, gender and education), (3) MS subtype and duration, (3) definition of employment, (4) outcome measurement and (5) statistics necessary for calculating Hedges' *g* effect size (e.g. means, standard deviations, Pearson's *r* correlations).

Prior to data analysis, the data for eight studies, which provided *p* values for chi-square, Fischer Exact tests or independent *t*-tests, or reported Pearson's *r*, were converted to Hedges' *g* (Boe Lunde et al., 2014; Ehde et al., 2006; Johansson et al., 2008; Krokavcova et al., 2012; Lau et al., 2016; Piwko et al., 2007; Salter et al., 2010 and 2017). In addition, Strober et al. (2014) reported means and standard deviations for two trials administered as part of the Nine-Hole Peg Test (NHPT) (i.e. dominant hand tested first, followed by the non-dominant hand): these scores were pooled to produce a composite score, consistent with the data reported by a second study which also utilised this measure (Krause et al., 2013). In addition, four independent studies reported statistical data across different employment groups (e.g. 'employment unaffected' vs 'employment changes'; 'full-time' vs 'part-time'; 'working' vs 'hours cut back') (Chiu et al., 2015; Johansson et al., 2008; Moore et al., 2013; Smith and Arnett, 2005). The data for each study was collated into one category: paid employment (consistent with the definition of employment by the International Labor Organization, 1982). Finally, individual data for progressive MS disease subtypes (i.e. primary-progressive, secondary-progressive, progressive-relapsing), which accounted for 12.14% of the total sample, were pooled and compared against the prominent relapsing-remitting subgroup, which accounted for 87.86% of the sample.

To ease data intepretation, individual measures and demographic characteristics were grouped according to the ICF domains and subdomains that they represented: 1) *body functions*, describing the physical symptoms or impairments an indiviudal with

MS may experience (i.e. clinical subtype, fatigue, pain); 2) *activities and participation*, focusing on the impact MS has one's ability to perform tasks (i.e. disability level, mobility); and 3) *personal* factors which include a broad range of categories yet to be classified by the ICF (Kahn et al., 2013). In this review, three personal subdomains were identified: age, gender and disease duration (defined as time since diagnosis).

Statistical analysis and Interpretation

Hedge's *g* (Borenstein et al. 2009), which represents a standardised mean difference between two groups (i.e. employed and non-employed adults with MS), was the principal effect size utilised in this meta-analysis. Hedge's *g* effect sizes are particularly helpful as they are considered to be unbiased estimates and work particularly well for small sample sizes (Borenstein et al. 2009). Effect sizes represented small (0.2), medium (0.5) or large (0.8) group differences, as proposed by Cohen (1988). Data were entered into the Comprehensive Meta-analysis Software (CMA, Version 3.0).

Effect sizes were calculated in a series of stages. First, standardised mean differences (*g*) were calculated for each demographic variable and physical measure reported by a study. Second, to ensure consistent interpretation of effect sizes across multiple measures, *g* values were standardised for each subdomain: a negative *g* indicated that those with MS who were not employed reported greater disability/ symptomatology/lower functioning in comparison to employed peers. The direction of some measures (e.g. NARCOMS Performance Scales, whereby higher scores indicate more impairment), were rescaled to conform to this effect size rule. In relation to gender and disease course, positive scores indicated a larger proportion of

women and individuals with progressive MS among the non-employed cohort. Third, effect sizes from different studies that used the same measure were pooled and averaged. Fourth, *g* values were categorised according to ICF domain and subdomain (Kahn et al., 2013). Fifth, effect sizes within each ICF subdomain were pooled. If a study provided multiple subscale scores for a subdomain (i.e. the Multiple Sclerosis Functional Composite), a mean effect estimate for that study was initially calculated. This helped to ensure data independence (Lipsey & Wilson, 2001). When pooling studies for each ICF subdomain, effect sizes were weighted by the respective study's inverse variance, to compensate for the fact that smaller sample sizes are often associated with increased variablity (Borenstein et al., 2009). Given the high levels of clinical heterogeneity present within the MS research, particularly for progressive MS (Bomprezzi et al., 2003; Disanto et al., 2011; Wingerchuk and Carter, 2014), in addition to the heterogeneity of some of the constructs examined (e.g. pain) it was deemed inappropriate to combine the pooled *g*'s across ICF sub-domains (Lipsey and Wilson, 2001).

In order to determine the precision of both individual and pooled effect size estimate, 95% confidence intervals (CIs) - which highlight the range of plausible values for a calculated population mean, were calculated (Cummin and Finch, 2005). CIs are considered to be statistically significant when their range does not include the value of zero (Thompson, 2007). *P* values were additionally calcuated for all effect estimates in order to determine whether any differences discovered between employed and non-employed groups were statistically significant (Cohen, 1988). Forest plots were generated to graphically illustrate the individual and pooled effect estimates within each ICF subdomain (Sedgwick, 2015).

In order to address an inherent problem with meta-analysis, the issue of

publication bias (Lipsey & Wilson, 2001), fail-safe *N* statistics (*Nfs*) were calculated using the formula by Orwin (1993). *Nfs* represents the hypothetical number of studies required in order for a *g* value to be rendered meaningless (i.e. a small effect or $g < 0.20$). For the purpose of this particular study, a *Nfs* value was considered appropriate if its value was greater than the amount of studies that contributed to a given analysis (i.e. $Nfs > N_{studies}$).

Given that effect estimates were calculated from a range of different statistics provided by individual studies, the quality of each individual *g* was rated using a Likert scale recommended by Lipsey & Wilson (2001). Ratings ranged from 1 (indicative of a highly estimated effect size – e.g. calculated from a *p*-value or *N*) to 5 (indicating no estimation, i.e. descriptive data, such as means and standard deviations). Two reviewers were involved in the rating process (a1647568 and DD), independently evaluating each study, after which consensus ratings were determined. There was high inter-rater (88%) agreement.

Finally, heterogeneity was calculated for all pooled effect estimates in order to assess inconsistency in *g* values across studies, due to sample and/or methodological characteristics (e.g. sample size, outcome measurement; Higgins et al., 2003). This included the I^2 statistic, which is expressed as a percentage (Higgins et al., 2003): values below 40% are considered to be non-significant (thereby suggesting the presence of true heterogeneity); values higher than 50% indicating substantial to considerable heterogeneity (Higgins and Green, 2011). A negative I^2 value is denoted as 0. A second heterogeneity index, Cochran's chi-squared statistic (denoted by *Q*), was also calculated. A non-significant *Q* suggests the presence of true heterogeneity (Higgins et al., 2003).

The random-effects model was applied for these statistical analyses. This

model assumes that identified effects from individual studies represent a random sample from a distribution of true treatment effects, most commonly a normal distribution (Borenstein et al., 2010). This model, which accounts for both within-study and between-study variation, aims to estimate the mean of a distribution of effects, rather than one true effect (Borenstein et al., 2010; Cumming, 2012, Cumming and Finch, 2005). Given the heterogeneity present within MS research, both clinically (i.e. highly variable clinical courses and symptom manifestation) and methodologically (e.g. the use of multiple outcome measurements and scales; Disanto et al., 2011), the random-effects model's was deemed appropriate for this meta-analysis.

The conclusions drawn from this meta-analysis are based on a combination of the aforementioned statistics. Specifically, an ICF subdomain was considered clinically and statistically important if the weighted effect size (g_w): (a) presented a medium to large mean group difference ($g \geq 0.50$) between employed and non-employed persons with MS; (b) was statistically significant (e.g. CIs did not include zero, $p< 0.05$); and (c) the *Nfs* was sufficiently large to suggest that the findings were unlikely to be compromised by publication bias (i.e. $Nfs > N_{studies}$). The interpretation of effect sizes was considered in the context of study heterogeneity.

CHAPTER 3

Results

Study Characteristics

Twenty-five independent studies were included in this meta-analysis, providing data for a pooled sample of 18,096 adults with MS (7,053 employed, 11,043 not employed). Publication dates ranged from 1989 to 2017, with articles published in 20 different journals. This included several publications from *Multiple Sclerosis (*$N_{studies}$ =6) and *PloS ONE,* a multi-disciplinary open access journal ($N_{studies}$ =2). There were also single publications from rehabilitation science (e.g. *Disability and Rehabilitation*, *International Journal of Rehabilitation Research*) and discipline-specific journals (e.g. *Journal of Nursing Studies, Journal of Neurology, Neurosurgery and Psychiatry*; *Journal of the International Neuropsychological Society*) (See Appendix C for full list).

The data for this meta-analysis originated from 14 countries, primarily the United States of America ($N_{studies}$ =9), Canada ($N_{studies}$ =3) and Australia ($N_{studies}$ =2) (see Appendix C and D). Single studies from Asia (Japan, Hong Kong), Europe (Germany, Italy, Netherlands, Norway, Sweden, Slovakia), New Zealand, Turkey and the United Kingdom also featured. The mean sample size was 724 (median = 120), ranging from small convenience samples (e.g. N = 50; Smith and Arnett, 2005) to registry data (N = 8180; Salter et al., 2010) Three studies contributed to 83% of the overall sample size: Pearson et al. (2016) collected data from the New Zealand National Prevalence study, conducted on the census date in 2006, and Salter et al. (2010, 2017) retrieved their data from a global MS registry, the North American Research Committee on Multiple Sclerosis (NARCOMS). Despite their over-representation in the pooled sample size, Salter et al. (2010), only contributed a

single-effect estimate and Salter et al. (2017), two effect estimates to this meta-analysis. In addition to established databases or registries ($N_{studies}$ =3), participants were recruited through MS centres or societies ($N_{studies}$ =18); hospitals or medical centres ($N_{studies}$ =5) and university clinics ($N_{studies}$ =2). All included studies adopted a cross-sectional design ($N_{studies}$ =25).

A total of 15 standardised measures and 9 subscales were utilised across the 25 studies. While measures for fatigue and pain were primarily based on self-report (e.g. Brief Pain Inventory) (Moore et al., 2013), disability level and mobility function involved clinician-based assessments (e.g. Multiple Sclerosis Functional Composite, MSFC or the EDSS) (Gulick et al., 1989; Honarmand et al., 2011; Krause et al., 2013, Strober et al., 2014). The most commonly utilised measure was the Extended Disability Status Scale (EDSS) ($N_{studies}$ =13), followed by the 9-item Fatigue Severity Scale ($N_{studies}$ =4), the uni-dimensional Fatigue Impact Scale ($N_{studies}$ =3) and the MSFC, which measures leg function/ ambulation, arm/hand function and cognitive function ($N_{studies}$ =3). Importantly, these measures are all validated, reliable and have had increasing use in MS clinical trials and studies (Fischer et al., 1999; Fisk, 1994; Krupp et al., 1989; Kurtze, 1983; Ritvo et al., 1997). The remaining measures were primarily used by single studies.

Participant Characteristics

Demographic and MS details for participants are displayed in Table 1. For studies that reported gender by employment status, the majority of participants were female (72%). This is consistent with the usual 3:1 female-male ratio witnessed within the literature (Amatya et al., 2017). Additional demographic or MS variables by employment group were, however, not routinely reported. Where this data was

available, it appears that adults who were not employed were most likely to have a progressive disease course. Both employment groups (employed vs. not employed) had a similar proportion of males and females and were comparable in sample size, age, disease duration (i.e. time since diagnosis) and education.

Body Function and Structure Factors Associated with MS and Employment. This ICF domain was commonly examined, with 17 individual studies examining the association between MS subtype, physical symptoms and employment. Table 2 lists the effect estimates, rank ordered from highest to lowest, for each subdomain.

MS subtype. Based on a pooled effect from 12 studies, a large group difference was noted (g_w= 0.80, p<0.001): those employed were more likely to have a relapsing-remitting (RRMS) rather than progressive (primary progressive, secondary progressive, relapsing-progressive) form of MS. Although this finding is consistent with previous literature, this sample was characterised by a larger proportion of individuals with RRMS (Boe Lunde et al. 2014; Julian et al., 2008). Importantly, the very large *Nfs* suggests that a substantial number of unpublished studies with non-significant findings would be needed to overturn this result.

Fatigue. Nine independent studies contributed to the examination of fatigue utilising five standardised measures. This included a composite score, based on the FIS and FSS, utilised by Cadden and Arnett (2015). Overall, employed persons with MS experienced less fatigue in comparison to non-employed peers. This finding was not affected by publication bias (i.e. *Nf*s > $N_{studies}$). There were, however, mixed results. Three measures (Modified Fatigue Impact Scale (MFIS), composite FIS/FSS, visual analogue scale for fatigue VAS-F) were associated with significant and medium to large group differences (g_w=-0.6 to g_w=-1.01). However, Smith and Arnett (2005) and Van der Hiele et al. (2015)

Table 1.

Sample Demographic and MS Characteristics (N= 18,096 participants).

Variable	Employed			Not employed			Total		
	$N_{studies}$	$N_{participants}$	*M* (SD)	$N_{studies}$	$N_{participants}$	*M* (SD)	$N_{studies}$	$N_{participants}$	*M* (SD)
Sample size	25	7,053	282 (675.5)	25	11,043	442 (1191.3)	25	18,096	380 (1024.7)
Age (years)	15	1,553	42.9 (8.3)	15	1,826	47.8 (8.5)	15	3,379	45.5 (8.8)
Disease duration (years)	13	1,619	9.1 (6.8)	13	1,953	13.5 (8.2)	13	3,572	11.5 (7.9)
Gender									
Male (%)	14	233 (12.6)		14	282 (15.3)		14	515 (27.9)	
Female (%)	14	586 (31.8)		14	741 (40.2)		14	1,327 (72.0)	
Education (years)	7	346	14.7 (2.3)	7	316	14.0 (2.1)	7	662	14.4 (2.2)
MS subtype									
Relapsing-remitting	13	2,551		13	2,913		13	5,464	
Progressive (SPMS, PPMS, PRSM)	13	186		13	569		13	755	

$N_{studies}$: number of studies providing data; $N_{participants}$: number of participants providing this data; M: Mean; SD: standard deviation; MS: multiple sclerosis.

did not identify a significant group effect with the FIS. Notably, these authors reported greater variability among their employed and non-employed participants, which may account for their non-significant finding. The FSS and Fatigue Questionnaire (i.e. FQ, assesses physical and mental symptoms of fatigue) (Chalder et al., 1993) provided small significant effect sizes but were associated with low fail-safe *N* statistics (i.e. *Nf*s > $N_{studies}$), indicating the presence of publication bias.

Pain. Four independent studies contributed to this subdomain. Only two measures, the Short Form Health Survey Bodily Pain subscale, which evaluates the frequency and interference of pain on ability to work (Ware and Sherbourne, 1992), and Brief Pain Inventory (BPI), which assesses the location, frequency and severity of pain (Cleeland, 1989), produced significant and medium effects. Those who were employed reported less sensory intensity of pain and pain impairment across different life areas. These findings were, however, based on single studies so need to be interpreted cautiously.

Activity and Participation Factors Associated with MS and Employment Status

Sixteen independent studies investigated the role of activity and participation limitations on employment among adults with MS (Table 3). These studies focused on the impact of disability severity and mobility impairment specifically.

Disability level. Of the thirteen studies that examined this construct, 12 utilised the EDSS ($N_{studies}$=12). This particular measure was associated with a large and clinically significant effect estimate: those who were employed reported less neurological impairment (defined as weakness or difficulty in moving limbs, loss of bodily movements, loss of sensations or numbness, and loss of visual functions) (Kurtzke, 1983). However, the pooled effect for this subdomain was small and did not

meet the criteria set for significance in this review (i.e. $d \geq 0.50$; 95% CIs did not span zero; $Nfs > N_{studies}$). This finding was primarily due to the small effect size associated with Salter et al's (2017) national study, which utilised the PDSS. This finding is consistent with validation studies, which report a more conservative estimate of disability status with the PDDS given its primary focus on motor and ambulatory dysfunction (Learmonth et al. 2013). The low *Nfs* value associated with this domain does, however, suggest that this finding may be spurious.

Mobility. Six studies examined the association between mobility and employment in adults with MS. Three individual performance measures were utilised. Namely, the NARCOMS Performance Scales (mobility subscale), Activities of Daily Living Self-care Multiple Sclerosis Scale (ADL SFMSS, walking subscale), Multiple Sclerosis Functional Composite (MSFC), and a composite score involving five subscales (Groove Peg-Board (GPB), Finger Tapping Test (FTT), Nine Hole-Peg Test (NHPT), Timed 25-foot Walk Test (T25W), Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRRSMC) (Cadden & Arnett, 2015). All measures were associated with very large and significant group differences. That is, functional performance, defined as ambulation (i.e. ability to walk) and dexterity (i.e. arm/hand function) and subsequent impact on ability to self-care and contribute to work roles, were less significant issues for those who were employed. Notably, the *Nfs* for this domain was substantial, which gives us more confidence about the robustness of this finding.

Personal Factors Associated with MS and Employment Status

Nineteen independent studies investigated the role of individual, personal factors on employment activity following a diagnosis of MS (Table 4). This included

demographic (i.e. age, gender) and MS-specific (i.e. disease duration) variables.

Age. Fifteen studies examined the association between age and employment status in an adult community sample with MS. A moderate and negative effect size was found: those who were employed were generally younger. This finding was statistically and clinically significant (e. $d \geq 0.50$; 95% CIs $\neq 0$, $p < 0.05$) and robust (*Nf*s = 32). However, individual effect sizes varied from very large (g= -2.5, Smith and Arnett, 2005) to small (g=-0.17, Lau et al., 2016). The largest effect estimates, which were based on two small N studies ($N < 55$) (Button et al., 2013; Cadden & Arnett (2015); Smith & Arnett (2005), may also overestimate the true effect size.

Disease duration. Fifteen studies examined the relationship between time since MS diagnosis and employment status. The overall medium and significant group difference suggests that those employed typically had lived with their MS for a shorter period of time. The majority of studies reported moderate to large effect sizes (g *r*ange = 0.3 to 0.8), with two studies reporting very large values (-1.25 and -2.34 respectively; Krokavcova et al., (2012); Smith & Arnett (2005)).

Gender. This subdomain, examined by 14 studies, was associated with a small and non-significant effect estimate. In contrast to previous literature, then, females with MS in this pooled sample were not at greater risk of work loss (Roessler et al., 2005). The findings may, however, also reflect the gender profile of studies that contributed this data, which primarily comprised of females (72%).

Quality of Effect Size Computations

Most studies ($N_{studies}$ = 17) did not require data conversion, providing means and standard deviations, which could directly be converted to g. This indicates a relatively high consistency and quality in regards to the calculation of effect sizes in this meta-

analysis (Lipsey and Wilson, 2001). Three studies (Krokavcova et al., 2012; Salter et al., 2010, Salter et al., 2017) required some estimation (i.e. providing Pearson correlations and chi-square analyses), and were therefore associated with a slightly lower confidence rating of '3'. A further five studies (Boe Lunde et al., 2014; Ehde et al., 2006; Johansson et al., 2008; Lau et al., 2016; Piwko et al., 2007) required significant estimation (i.e. provided exact *p*-values), and were thus assigned a confidence rating of '1'.

Heterogeneity Statistics

Measures of heterogeneity, for each ICF component and subdomain, are listed in Table 5. Significant and considerable or substantial (I^2= > 50%) variation in effect estimates were noted across the pooled studies, indicating the presence of clinical and/or methodological variation (Higgins and Green, 2011). The subdomain associated with the highest heterogeneity, mobility (I^2= 98.49%), included Salter et al.'s (2010) large-scale study which was based on national registry data. Removing this study from the analysis reduced the associated variability for this subdomain by 26% (Q (4) =14.63, p=0.006, I^2= 72.65%). The multiple outcome measures adopted by individual studies in this meta-analysis, in addition to the complex and multi-faceted nature of ICF subdomains, would also lead to differences in observed effects (Haidich, 2010).

Table 2.

Standardised mean differences (Hedges' g) in body function between employed and not employed groups.

	Measure	Subscale	$N_{studies}$	$N_{participants}$	Hedge's g	Mean g_w	95% CI		p	N_{fs}	Forest Plot of Effect Sizes
							Lower	Upper			
MS Subtype			12	2,705		0.80*	0.60	1.01	<0.001	36	
		Total	**12**	**2,705**		**0.80***	**0.60**	**1.01**	**<0.001**	**36**	
Fatigue	FIS^		2	105		-2.03	-5.05	0.98	0.19	18	
	MSQLI	MFIS	1	87	-1.01*		-1.55	-0.65	<0.001	4	
	FIS, FSS		1	52	-0.73*		-1.30	-0.16	0.01	3	
	VAS-F		1	120	-0.60*		-0.97	-0.23	0.001	2	
	FSS		3	476		-0.42	-0.64	-0.21	<0.001	3	
	FQ		1	184	-0.29		-0.58	0.00	0.05	0	
		Total	**9**	**1,024**		**-0.51***	**-0.65**	**-0.37**	**<0.001**	**14**	
Pain	SF-36	Bodily Pain	1	180	-0.59*		-0.90	-0.28	<0.001	2	
	BPI		1	370	-0.54*		-0.86	-0.22	0.001	2	
	BS-11, HUI-3		1	477	-0.19		-0.46	0.08	0.17	0	
	SRP		1	510	-0.11		-0.38	0.16	0.42	0	
		Total	**4**	**1537**		**-0.35**	**-0.58**	**-0.11**	**0.004**	**3**	

Abbreviations: $N_{studies}$: number of studies providing data; $N_{participants}$: number of participants providing data; g: Hedge's g; $g_{w:}$ weighted mean effect size (note: weighting only applied to effect sizes pooling two or more studies); 95% CI: lower and upper limit of 95% confidence interval; *p:* probability-value (significance); *Nfs*: approximate fail-safe *N*.

Measure Abbreviations: BPI (Brief Pain Inventory); BS-11 (Box-Score 11); FIS (Fatigue Impact Scale); FQ (Fatigue Questionnaire); FSS (Fatigue Severity Scale); HUI-3 (Health Utilities Index Mark 3); MFIS (Modified Fatigue Impact Scale); MSQLI (Multiple Sclerosis Quality of Life Inventory (MSQLI); SR (Self-Report Pain); SF-36 (36-Item Short Form Survey); VAS-F (Visual Analogue Scale for Fatigue).

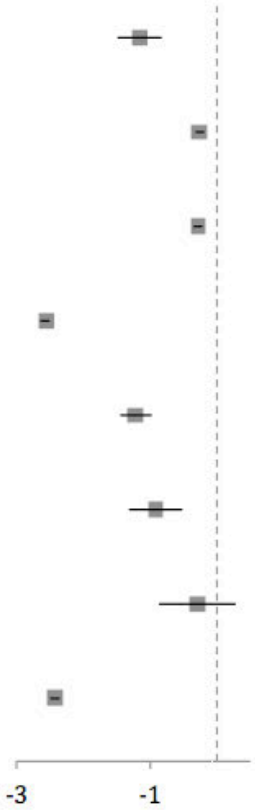
***** Effect size met the criteria for significance in this review: i.e. $d \geq 0.50$; 95% CIs $\neq 0$; *Nf*s > $N_{studies}$.

^ Involved the combined studies: Van der Hiele et al. (2014 & 2015); and Strober et al. (2010) with Julian et al. (2008).

Table 3.

Standardised mean differences (Hedges' g) in activities between employed and not employed groups.

	Measure	Subscale	$N_{studies}$	$N_{participants}$	Hedge's g	Mean g_w	95% CI Lower	95% CI Upper	p	N_{fs}	Forest Plot of Effect Sizes
Disability Level	EDSS^		12	2,995		-1.16*	-1.48	-0.84	<0.001	58	
	PDDS		1	5,062	-0.26		-0.31	-0.20	<0.001	0	
		Total	**13**	**8,057**		**-0.28**	**-0.34**	**-0.23**	<0.001	**5**	
Mobility^	NARCOMS PS	Mobility	1	8180	-2.56*		-2.64	-2.52	<0.001	12	
	ADL SFMSS	WADL	1	508	-1.22*		-1.44	-0.99	<0.001	5	
	MSFC	T25W, NHPT, PASAT	3	270		-0.92*	-1.31	-0.53	<0.001	11	
	-	GPB, FTT, NHPT, T25W, MRRSMC	1	51	-0.29		-0.86	0.27	0.31	0	
		Total	**6**	**9,009**		**-2.43***	**-2.49**	**-2.37**	**<0.001**	**67**	



Abbreviations: $N_{studies}$: number of studies providing data; $N_{participants}$: number of participants providing data; g: Hedge's g; g_w: weighted mean effect size (note: weighting only applied to effect sizes pooling two or more studies); 95% CI: lower and upper limit of 95% confidence interval; *p:* probability-value (significance); *Nfs*: approximate fail-safe *N*.
Measure Abbreviations: ADL SFMSS (Activities of Daily Living Self-care Multiple Sclerosis Scale); EDSS (Extended Disability Status Scale); FTT (Finger

Tapping Test); GPB (Grooved Pegboard Test); MFIS (Modified Fatigue Impact Scale); MRRSMC (Maximum Repetition Rate of Syllables and Multisyllabic Combinations); MSFC (Multiple Sclerosis Functional Composite); NARCOMS PS (North American Research Committee on Multiple Sclerosis Registry Performance Scales); NHPT (Nine-Hole Peg Test); PASAT (Paced Auditory Serial Addition Test); PDDS (Patient Determined Disease Steps); T25W (Timed 25-Foot Walk Test); WADL (Walking ADL (Activities of Daily Living) Subscale).

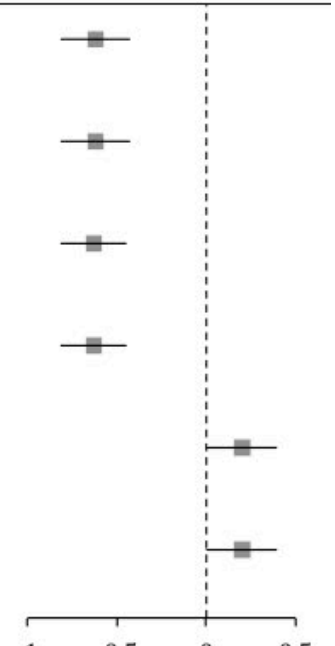
***** Effect size met the criteria for significance in this review: i.e. $d \geq 0.50$; 95% CIs $\neq 0$; *Nf*s > $N_{studies}$.

^ Involved the combined studies: Van der Hiele et al. (2014 & 2015); and Strober et al. (2010) with Julian et al. (2008).

Table 4.

Standardised mean differences (Hedges' g) in personal factors between employed and not employed groups.

Measure		$N_{studies}$	$N_{participants}$	Mean g_w	95% CI Lower	95% CI Upper	p	N_{fs}	Forest Plot of Effect Sizes
		15	3,379	-0.62*	-0.81	-0.43	<0.001	32	
***Age*^**									
	Total	**15**	**3,379**	**-0.62***	**-0.81**	**-0.43**	**<0.001**	**32**	
		15	3,629	-0.63*	-0.81	-0.45	<0.001	32	
***Disease Duration*^**									
	Total	**15**	**3,629**	**-0.63***	**-0.81**	**-0.45**	**<0.001**	**32**	
		14	1,851	0.20	0.003	0.39	0.05	0	
Gender									
	Total	**14**	**1,851**	**0.20**	**0.003**	**0.39**	**0.05**	**0**	



Abbreviations: $N_{studies}$: number of studies providing data; $N_{participants}$: number of participants providing data; *g*: Hedge's *g*; g_w: weighted mean effect size (note: weighting only applied to effect sizes pooling two or more studies); 95% CI: lower and upper limit of 95% confidence interval; *p:* p-value (significance); *Nfs*: approximate fail-safe *N*.

*Effect size met the criteria for significance in this review: i.e. $d \geq 0.50$; 95% CIs $\neq 0$; *Nfs* > $N_{studies}$.

^ Involved the combined studies: Van der Hiele et al. (2014 & 2015); and Strober et al. (2010) with Julian et al. (2008).

Table 5.

Heterogeneity Statistics by ICF Component.

ICF domain/subdomain	$N_{studies}$	$N_{participants}$	Heterogeneity tests			
			Q	df	*p*	I^2 (%)
Body Functions and Structures						
MS Subtype	12	2,705	47.67	11	0.00	76.92
Fatigue	9	1,024	58.41	8	0.00	86.31
Pain	4	1,537	7.93	3	0.05	62.17
Activities and Participation						
Disability level	14	8,057	382.37	13	0.00	96.6
Mobility	6	9,009	348.33	5	0.00	98.57
Personal Factors						
Age	15	3,379	62.36	14	0.00	77.55
Gender	14	1,851	47.24	13	0.00	72.48
Disease Duration	15	3,629	67.57	14	0.00	79.28

$N_{studies}$ = number of studies providing data; $N_{participants}$ = number of participants providing data; Q = chi square statistic (heterogeneity), df = degrees of freedom; p=p-value (significance); I^2 = measure of study inconsistency.

CHAPTER 4

Discussion

Key Findings

The data from 25 independent studies, involving 18,096 adults with relapsing-remitting or progressive forms of MS, was analysed in order to examine MS-specific and demographic factors that may contribute to employment outcomes for this group. Overall, the results indicate that employed individuals experience greater physical functioning and less severe MS symptoms than their non-employed counterparts. Age and disease duration were also important correlates, although gender was not. The findings, their implications and future research directions will subsequently be discussed in this chapter.

MS subtype was identified as the subdomain within *body structures and functions* with the largest relationship with employment: those employed were more likely to experience a relapsing-remitting disease course (Salter et al. 2017; Strober et al., 2012). It has been suggested that progressive MS may impede employment success due to the more severe nature of these disease courses (i.e. worsening function with little respite), making it even more difficult for both the employee and employers to organise appropriate accommodations within the workplace (Busche et al., 2003). Future research should investigate the difference between MS subtypes more closely, identifying job retention factors that differentiate these (Salter et al., 2017). Fatigue was also found to be significantly lower in employed individuals with MS compared to those non-employed (Shiavolin et al., 2013). This is in line with previous literature that reports fatigue as a primary cause for individuals leaving their work or indeed, reducing their working hours (Simmons et al., 2010; Smith and Arnett, 2005). Given its disabling nature in its own right, combined with its tendency

to exacerbate other symptoms (i.e. pain, loss of mobility), these results underscore the importance of making fatigue a key target in vocational rehabilitation for those with MS (Van der Hiele et al., 2015). Notably, pain did not appear to differentiate employed and non-employed persons, as least for the sample of participants studied in this meta-analysis. This is despite the presence of small to moderate effect sizes for this ICF subdomain. This may, in part, be due to problems with the operationalisation and measurement of pain. Indeed, the statistics calculated from all four studies that measured this construct varied in their self-reported aspects of pain, including the frequency and presence of pain but also its interference in one's ability to work (Ehde et al., 2006; Moore et al., 2013). Given that up to 90% of persons with MS report problems with chronic pain, it may also be that pain in these sample studies were under-reported (Piwko et al., 2007). More studies utilising larger sample sizes are required to confirm the true impact that MS-related pain has on functioning, including employment (Shahrbanian et al., 2013). Future studies should also differentiate acute from chronic pain in addition to focusing on different pain locations (e.g. leg pain or headaches) that MS individuals commonly will present with, to ensure a more comprehensive understanding of the pain experience (Ehde et al., 2006; Solaro et al., 2012).

In relation to *activity limitations and participation*, mobility had the strongest relationship with employment. This is in line with previous literature reporting reduced mobility and hand function as key predictors in employment status changes (i.e. transitions in and out of the work force) (Julian et al., 2008, Salter et al., 2010). Considering that the effect of reduced mobility is most apparent in the early stages of disability in people with MS, studies focusing on disability progression over an extended period of time may be able to shed more light on whether the relationship

between mobility and employment status is causal (Salter et al., 2010). Disability level was also a clinically significant factor differentiating people with MS by employment status (Cadden and Arnett, 2015; Honarmand et al., 2011; Salter et al., 2017). With physical disability remaining a top reason for leaving the work force, the importance of targeting this through vocational rehabilitation programs cannot be ignored (Shahrbanian et al., 2013).

The current meta-analysis also identified two significant *personal factors*: age and MS duration. Older people with MS are more likely to be unemployed (Krause et al., 2013; Lau et al., 2016). This is largely due to the fact that age impacts both the severity and prognosis of MS, with older age typically presenting with a more rapid decline in disability (Greer and McCombe, 2011). Considering that MS is characterised by a disease course that worsens with time, this is perhaps the primary reason why age has been so consistently reported as an influential factor within the literature (Julian et al., 2008). Notably, age at MS onset was not routinely described among the studies in this review. It is important that future studies report both year and symptoms of onset. This is primarily because the onset and progression of disability and worsening of symptoms in older people is considered to be more rapid and indeed, older patients are more likely to have progressive disease courses (Polliack et al., 2001). There is, however, also evidence to suggest that current age, moreso than age of MS onset, is more influential in the progression of clinical disability (Ligouri et al., 2000).

Similarly, disease duration (i.e. time since diagnosis) was a significant factor in employment: individuals with MS who were working typically presented with shorter disease durations (Strober et al., 2012). As with age, longer disease durations are characterised by higher accounts of disability and worsening of symptoms (Sweetland

et al., 2012). Interestingly, gender, was not a significant factor for this sample (Roessler et al., 2005). This is in contrast to previous literature, which has found females as a risk factor for predicting unemployment, with up to 60% of females reported leaving their jobs due to perceived difficulties in managing both their work and home demands (McFadden et al., 2012). In saying this, there is also evidence to suggest that males are more likely to have a later age onset then females as well as a more progressive disease course (Greer and McCombe, 2011; Koch et al., 2010). In any case, future research should devote attention to the impact of gender in the context of employment status, in order to better ascertain where the risk truly lies as well as the differences in clinical expression and responses to treatment between sexes to ensure the right targets are addressed in a rehabilitation context (Harbo et al., 2013; Greer and McCombe, 2011).

Clinical Implications

Effective management of MS involves a consideration of its extensive variability (i.e. subtype, severity of physical symptoms, level of disability) and impact on an individual's daily routine. The ICF is a framework that can guide clinical care, by considering MS in the context of body functions and structures, activity limitations, participation, environmental and personal factors (Kahn et al., 2013). To some extent the current meta-analysis provides empirical support for the continued use of the ICF in MS research, helping to provide a structure to a complex construct such as employment.

The findings of this review suggest that clinical and demographic characteristics are significantly associated with employment status and, as such, are key targets for vocational rehabilitation interventions. This should include multidisciplinary

interventions that aim to: (a) reduce fatigue, (b) enhance mobility function and (c) regulate, improve and manage disability level. These interventions also need to be targeted to MS subtype, disease duration and age (Rumrill et al., 2015). Despite the lack of significant results in this meta-analysis, attention should still be devoted to the further investigation of pain and gender within the MS cohort, given their prevalence and conflicting results, respectively (Greer and McCombe, 2011; Shiavolin et al., 2013).

Unfortunately, the identification of factors contributing to successful employment outcomes for persons with MS, alongside the implementation of targeted vocational interventions, has received less research funding and attention than they warrant (Kahn and Amatya, 2016; Rumrill et al., 2015). The provision of MS-specific vocational rehabilitation services is also limited by resource issues (Rumrill et al., 2015). Despite there being employment-focused projects, the available efficacy research is largely characterised by descriptive research designs, qualitative data and relatively small sample sizes (Julian et al., 2008). It is therefore vital that large-scale effectiveness studies be undertaken to ensure that vocational programs are both evidence-based and effective in the services they provide for people with MS (Kahn and Amatya, 2016).

Nonetheless, the available vocational research has typically involved interventions with a counselling or guidance focus, in addition to on-the-job support, assistive technology services and job placement (Chiu et al., 2015). All of these therapy components are considered critical to positive employment outcomes (Chiu et al., 2015; Chiu et al., 2013). The type of vocational services that people with a disability, in general, receive also vary between those that are currently employed but seeking alternative work (i.e. assistive technology, counselling, cognitive re-training

etc.) versus those that are not currently in the workforce (i.e. job readiness, seeking and placement) (Tansey et al., 2015). Individual studies have attempted to bridge this gap by asking participants, themselves, what they seek and/or require in a vocational program. Results indicate a preference for a focus on the performance of activities (e.g. improved mobility), rather than a reduction in impairment (e.g. pain), as this would in turn help alleviate their symptoms anyway (e.g. cognitive difficulties) (Yorkston et al. 2003). The findings of the current review certainly suggest that mobility function, alongside fatigue management, is a key factor in the design of any vocational program targeted to those with MS. Furthermore, by combining these findings alongside significant, contributing psychological and environmental factors, as highlighted by Dorstyn et al. (2017), a holistic and biopsychosocial focus that is consistent with the ICF is necessary to ensure effective vocational rehabilitation.

Limitations

A number of methodological limitations need to be considered when interpreting the results from this meta-analysis. Restricting the electronic database searching to journal articles gives rise to the problem of publication bias. In order to minimise this bias, the search criteria used for each database were kept relatively broad (i.e. not specifying clinical or demographic variables), in addition to the reference lists of included studies and available reviews being checked. Fail-safe *N*'s were also calculated, although their presence does not completely resolve publication bias (Orwin, 1983).

Although the strict inclusion and exclusion criteria ensured a group of relatively homogenous studies, not all reported key details examined in this review, such as MS subtype. Where studies provided this data, many often assessed employment as a

secondary demographic variable, comparing physical symptoms against healthy controls or between different MS subtypes, rather than by employment status (Shahrbanian et al., 2013).

A related limitation is the operational definition of employment adopted by this review. Studies typically reported this as a dichotomous variable; hence it was not possible to investigate how different facets of employment (i.e. full-time, part-time etc.) may be affected by MS symptoms (Cadden and Arnett, 2015; Julian et al., 2008; Salter et al., 2017). Similarly, the 'not employed' MS group in this meta-analysis incorporated a broad group of students, volunteers, people with disabilities and retirees, all of which may well have very different experiences of MS and its symptoms (Li et al., 2015; Mollaoglu et al., 2009). This may have skewed the results, by overestimating or even underestimating reported group differences. Future research should explore the different types of employment status in more depth. This would simultaneously allow for better tailoring of vocational programs. For example, Smith and Arnett (2005) discovered that for those that cut back on their hours at work attributed it primarily to fatigue and would benefit from interventions targeting this, while those that left employed work credited it predominantly to physical and neurological symptoms.

A final limitation concerns the reliance on cross-sectional data in this meta-analysis. While significant relationships were noted, these relationships do not necessarily imply causation. For example, while it is understood that activity limitations (i.e. inability to walk or move effectively around particular work settings, such as building construction sites) may lead to unemployment; it has also been found that consequences of unemployment, primarily stress, can exacerbate these activity limitations (Mohr et al., 2004; Strober and Arnett, 2016). Longitudinal studies are

essential in order to clarify whether the factors examined in this review have a causal relationship with employment status for people with MS, to better target vocational programs for this cohort (Ehde et al., 2006; Salter et al., 2010; Shahrbanian et al., 2013).

Conclusions

Underpinned by the biopsychosocial framework of the ICF, this meta-analysis confirms the important contribution of MS and demographic characteristics in the employment process. The findings confirm that employed persons report better physical functioning in addition to improved activity and participation levels. Individual, personal factors of younger age and shorter disease duration also appear to be important. Knowing that physical symptoms and impairments are primary reasons for individuals with MS leaving the work force, it is essential that vocational rehabilitation programs be targeted to those with the greatest need, that is, older adults with the most significant disabilities. The value of addressing vocational issues at an early stage after a diagnosis of MS as well as in the longer-term is also critical. Continued research into the factors within ICF domains will hopefully improve the bleak unemployment rates confronting people with MS.

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Appendices

Appendix A

Logic grids for each electronic database

Pubmed (English Limit Activated)

Employment/Unemployment AND →	Multiple Sclerosis
"Employment"[mh] OR employ*[tw] OR unemploy*[tw] OR "unemployment"[mh] OR "occupations"[mh] OR occupation*[tw] OR "work"[mh] OR vocation*[tw] OR work resumption[tw] OR workplace*[tw] OR Work place*[tw] OR return to work[tw] OR work force[tw] OR workforce[tw] OR labour force[tw] OR labor force[tw] OR Career*[tw] OR Job*[tw]	"Multiple sclerosis"[mh] OR Multiple Sclerosis[tw] OR Disseminated Sclerosis[tw]

PsycINFO (English Limit Activated)

Employment/Unemployment AND →	Multiple Sclerosis
exp employment OR employ*.mp. OR unemploy*.mp. OR reemployment*.mp. OR occupation*.mp. OR work.mp. OR vocation*.mp. OR work resumption.mp. OR workplace*.mp. OR work place*.mp. OR return to work.mp. OR work force.mp. OR workforce.mp. OR lab?r force.mp.	Multiple sclerosis.mp OR Disseminated Sclerosis.tw OR Multiple Sclerosis.sh

OR career*.mp. OR job*.mp.	

Embase (With "NOT [medline/lim)" set)

Employment/Unemployment AND →	Multiple Sclerosis
Employment:de OR Employment/exp OR employ* OR Unemployment:de OR Work:de OR Occupation:de OR occupation*:de OR vocation*:de OR "vocational rehabilitation":de OR "vocational education":de OR "work resumption":de OR workplace:de OR "work place*" OR "return to work":de OR "return to work" OR "work force" OR workforce OR "lab*r force" OR career* OR Job*	"Multiple Sclerosis":de OR "Multiple Sclerosis" OR "Disseminated Sclerosis"

Appendix B

Data Extraction Sheet – Study ID no.1

Reference: Boe Lunde, H. M. B., Telstad, W., Grytten, N., Kyte, L., Aarseth, J., Myhr, K. M., & Bø, L. (2014). Employment among patients with multiple sclerosis-a population study. *PloS one*, *9*(7), e103317. DOI: 10.1371/journal.pone.0103317.

Definition of Employment

Employed (full-time or part-time) vs. Not Employed (sick leave, unemployment, disability pension, retirement, pension etc.).

Diagnosis of MS

All participants diagnosed and registered by Department of Neurology at the hospital, meeting McDonald Diagnostic criteria.

Further Study Characteristics

Country: Norway
Recruitment: Central Hospital of Sogn & Fjordance County
Study Design: Cross-sectional
Authors contacted for information about their data & responded

Study reference: Boe Lunde et al.							
***N* (Total Sample=213)**		**Age**		**Gender**		**Disability Level (EDSS score)**	
Employed	*Not employed*	*Employed M (SD)*	*Not employed M (SD)*	*Employed*	*Not employed*	*Employed M (SD) (N =89)*	*Not employed M (SD) (N=107)*
96	117	N/A	N/A	M: 27, F: 69	M: 39, F: 78	3.09 (1.44)	5.15 (2.11)
MS Subtype (*N*)		**Disease Duration (Years)**		**Education (Years)**		**Fatigue**	
Relapsing-Remitting	*Progressive*	*Employed M (SD)*	*Not employed M (SD)*	*Employed*	*Not employed*	*Employed M (SD) (N=83)*	*Not employed M (SD) (N= 91)*
5,464	755	15.1 (10.0)	22.1 (11.8)	N/A	N/A	4.49 (1.55)	5.42 (1.47)
Chronic Pain							
Not employed	*Employed*						
p-value of 0.42 from chi-square analysis (Fisher's Exact test).							

NOTE: N/A not available or not reported

Appendix C

Study Characteristics

Studies	Sample Size (*N*)	Country	Journal	Study Design	Recruitment of Participants
Boe Lunde et al. 2014	213	Norway	PloS ONE	Cross-Sectional	Central Hospital
Busche et al. 2006	96	Canada	The Canadian Journal of Neurological Sciences	Cross-Sectional	MS Clinics
Cadden & Arnett 2015	53	Unites States of America	International Journal of MS Care	Cross-Sectional	Neurology Practice and MS Society
Chiu et al 2015	157	Unites States of America	Work	Cross-Sectional	National MS Society and University Teaching Hospital
Dorstyn et al. 2017	95	Australia	Disability and Rehabilitation	Cross-Sectional	Social net-working sites of community MS agencies
Ehde et al. 2006	180	Unites States of America	Multiple Sclerosis	Cross-Sectional	MS Association
Gulick et al. 1989	508	United States of America	International Journal of Nursing Studies	Cross-Sectional	MS Society
Honan et al. 2015	111	Australia	Journal of the International Neuropsychological Society	Cross-Sectional	MS Society
Honarmand et al. 2011	106	Canada	Journal of Neurology	Cross-Sectional	MS Clinics
Incerti et al. 2017	60	Italy	Neurological Sciences	Cross-Sectional	MS Centre
Johansson et al. 2008	201	Sweden	Journal of Neurology, Neurosurgery and Psychiatry	Cross-Sectional	MS Centre, University

Krause et al. 2013	87	Germany	Multiple Sclerosis	Cross-Sectional	MS Centre
Krokavcova et al. 2012	184	Slovakia	International Journal of Rehabilitation Research	Cross-Sectional	Neurology departments and MS societies
Lau et al. 2016	59	Hong Kong	Neurology Asia	Cross-Sectional	Hospitals
Mollaoglu et al. 2009	120	Turkey	Journal of Clinical Nursing	Cross-Sectional	MS Society
Moore et al. 2013	157	United Kingdom	Multiple Sclerosis	Cross-Sectional	MS Database
Niino et al. 2014	184	Japan	Clinical and Experimental Neuroimmunology	Cross-Sectional	Medical Centres, University & Medical Schools
Pearson et al. 2016	1703	New Zealand	Acta Neurologica Scandinavia	Cross-Sectional	National Study
Piwko et al. 2007	297	Canada	Pain Research and Management	Cross-Sectional	MS Clinics and Society
Salter et al. 2010, Julian et al. 2008*	8180	North America	Current Medical Research and Opinion	Cross-Sectional	NARCOMS registry
Salter et al. 2017	5062	North America	Journal of Medical Economics	Cross-Sectional	NARCOMS registry
Smith & Arnett 2005	50	United States of America	Multiple Sclerosis	Cross-Sectional	Local MS support groups and Neurologist practice
Strober et al. 2012	101	United States of America	Multiple Sclerosis	Cross-Sectional	MS Clinics
Strober et al. 2014	77	United States of America	Multiple Sclerosis	Cross-Sectional	MS Centre and Medical School
Van der Hiele et al. 2014 & 2015*	55	Netherlands	PloS ONE	Cross-Sectional	Hospital

* Studies with overlapping samples are combined and treated as one independent study.

Appendix D

Study Characteristics for the Full Sample Size

Studies	N_{Total}	*N* *Employed*	*N* *Unemployed*	Age M (SD)	Disease Duration M (SD)	MS Subtype R (*N*)	MS Subtype P (*N*)	Outcome Measures
Boe Lunde et al. 2014	96	50	46	32.7 (9.9)	18.9 (11.5)	112	101	EDSS, FSS, SRP
Busche et al. 2006	213	96	117	47.2 (9.0)	-	43	53	-
Cadden & Arnett 2015	53	33	20	51.7 (9.4)	15.0 (8.5)	30	23	EDSS, Composite Mobility Score (GPB, FTT NHPT, T25W, MRRSMC)
Chiu et al 2015	157	82	75	-	-	-	-	-
Dorstyn et al. 2017	95	73	22	44.4 (9.2)	8.5 (7.7)	25	4	-
Ehde et al. 2006	180	61	119	-	-	101	79	SF-36 (Bodily Pain Subscale)
Gulick et al. 1989	508	110	398	48.8 (8.8)	13.6 (8.2)	-	-	ADL SFMSS (WADL Subscale)
Honan et al. 2015	111	62	49	47.3 (10.9)	10.3 (7.6)	74	37	-
Honarmand et al. 2011	106	41	65	44.7 (8.3)	9.8 (7.9)	66	40	EDSS, MSFC
Incerti et al. 2017	60	31	29	44.7 (10.2)	-	55	15	EDSS

Johansson et al. 2008	201	117	84	-	-	127	92	FSS
Krause et al. 2013	87	48	39	38.2 (11.8)	8.4 (7.0)	57	30	EDSS, MSQLI (MFIS), MSFC
Krokavcova et al. 2012	184	80	104	40.5 (6.2)	6.4 (5.2)	-	-	EDSS
Lau et al. 2016	59	33	26	36.9 (9.2)	-	54	5	EDSS
Mollaoglu et al. 2009	120	48	72	-	-	-	-	VAS-F
Moore et al. 2013	157	89	68	44.0 (9.2)	11.3 (8.7)	97	60	BPI, EDSS
Niino et al. 2014	184	91	93	39.2 (11.0)	5.0 (2.0)	167	17	EDSS, FQ
Pearson et al. 2016	1703	808	895	38.8 (9.6)	10.3 (8.3)	921	770	EDSS
Piwko et al. 2007	297	68	229	49 (11)	-	149	148	BS-11, HUI-3
Salter et al. 2010, Julian et al. 2008*	8180	2789	5391	53.8 (10.4)	15.5 (9.3)	-	-	NARCOMS PS
Salter et al. 2017	5062	2100	2962	54.7 (8.0)	-	4725	337	PDDS
Smith & Arnett 2005	50	29	21	49.88 (7.6)	10.3 (6.0)	28	22	EDSS, Composite (FIS, FSS)
Strober et al. 2012	101	54	47	46.6 (8.0)	10.7 (7.7)	-	-	EDSS, FSS
Strober et al. 2014	77	40	37	44.9 (8.7)	10.5 (7.8)	52	25	MSFC
Van der Hiele et al. 2014 & 2015*	55	20	35	47.2 (7.6)	12.3 (6.5)	-	-	EDSS

Measure Abbreviations: ADL SFMSS (Activities of Daily Living Self-care Multiple Sclerosis Scale); BP Scale (Bodily Pain Scale); BPI (Brief Pain Inventory); BS-11 (Box-Score 11); EDSS (Extended Disability Status Scale); FIS (Fatigue Impact Scale) ; FQ (Fatigue Questionnaire); FSS (Fatigue Severity Scale); GPB (Grooved Pegboard Test); HUI-3 (Health Utilities Index Mark 3); MFIS (Modified Fatigue Impact Scale); MRRSMC (Maximum Repetition Rate of Syllables and Multisyllabic Combinations); MSFC (Multiple Sclerosis Functional Composite); NARCOMS PS (North American Research Committee on Multiple Sclerosis

Registry Performance Scales); NHPT (Nine-Hole Peg Test); PASAT (Paced Auditory Serial Addition Test); (PDDS (Patient Determined Disease Steps); SRP (Self-Report Pain); SF-36 (36-Item Short Form Survey); T25W (Timed 25-Foot Walk Test); VAS-F (Visual Analogue Scale for Fatigue); WADL (Walking ADL (Activities of Daily Living) Subscale).