Quality of Life in Multiple Sclerosis:

A Meta-analytic Review

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ABSTRACT

Background: Multiple Sclerosis (MS) is a disabling disease that can have a substantial impact on quality of life (QoL). However, use of various assessment instruments to assess QoL, in addition to demographic and MS characteristics, may produce different results. *Aim*: To examine QoL differences between adults with MS and healthy controls as well as the potential moderating role of demographic and disease characteristics (i.e. age, years since diagnosis, disability severity). *Methods*: Thirty-five eligible studies (3,493 MS, 187,296 controls) were identified from a search of the CINAHL, Embase, PsycINFO, PubMed, and Scopus databases. Methodological rigour of the included studies was evaluated using the National Institute of Health Quality Assessment Tool. Group mean differences in QoL were standardised by calculating Hedges' *g*. In addition, 95% confidence intervals, *p* values, fail-safe *N*s, and heterogeneity statistics (Cochran's *Q*, *I*-squared, and tau) were computed, using a random effects model. Sources of between-study variability were examined with a multivariate meta-regression. *Results*: Mean QoL ratings were significantly lower for adults with MS compared to healthy peers (g_w = -0.907, CI -1.168 to -0.654, p <.01), although effect sizes varied markedly across QoL domains (g_w range = -.31 to – 1.15). Older age, years since diagnosis, and disability impairment explained 38% of the variance seen. *Conclusion*: The findings suggest that QoL should be routinely measured in clinical research and practice as a study outcome. Multidisciplinary interventions provided on an ongoing basis can ensure that care needs are met with disease progression.

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.

I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library Search and through web search engines, unless permission has been granted by the School to restrict access for a period of time.

Maryam Pedramkhou

20 September 2020

CONTRIBUTION SECTION

In writing this thesis, my supervisor and I collaborated to generate the research question of interest and to design the appropriate methodology. I collected all data for analysis (i.e., undertook database searches, screened studies, extracted data) and completed all statistical analyses, under the guidance of my project supervisor. I was responsible for the thesis write up. The 'Discussion' chapter was edited for grammar and spelling by a fellow Honours student, Elise Prior.

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CHAPTER 1

Introduction

Multiple sclerosis (MS) is a chronic disease associated with lifelong symptoms that can significantly impact on quality of life (QoL). QoL is a global construct comprising of different dimensions namely, physical, psychological, social, and environmental wellbeing (Kuspinar & Mayo, 2013). While these domains may be differently affected by MS , they can also be improved through multidisciplinary interventions (e.g., physical activities, social support, cognitive behavioural therapies). In addition, individuals living with MS do not experience the same proportion of decline in their health and inevitably their QoL (Chwastiak & Ehde, 2007; McCabe et al., 2009). Indeed, research in this area has produced varying results: some studies suggest that lowered QoL is inevitable after a diagnosis of MS, whilst others suggest that QoL ratings are comparable to healthy peers. These mixed findings may, in part, be due to differences in how QoL is measured with both generic and MS-specific QoL assessment instruments having been applied.

The current project examines and compares QoL ratings among persons with MS to peers without MS to determine whether QoL is, indeed, compromised in this group. The current chapter provides a context to this research by first discussing the nature of MS, followed by its incidence and prevalence, and then its impact on QoL. Methodological and sample considerations, including the use of generic and MS-specific assessment instruments, in addition to the potential role of age, time since diagnosis and MS severity on QoL ratings will then be discussed.

Multiple Sclerosis: Aetiology, Epidemiology, Clinical Courses

Multiple Sclerosis (MS) is a disabling disease of the central nervous system (CNS). The demyelination results from an active inflammatory process, with an abundance of

immune cells (T lymphocytes) targeting the protective myelin sheath that surrounds the nerve fibres in the brain, optic nerves and spinal cord (Gelfand, 2017; Raffel, Wakeley& Nicholas, 2016). The pathology of MS is characterised by plaques or lesions in the brain's white and grey matter (due to autoreactivity of T-cells) as well as axonal loss and slowed nerve conduction (due to damage to the myelin sheath; Raffel et al., 2016). The neurological symptoms that result from this pathology typically include blurry or double vision or blindness in one eye (optic neuritis), sensory impairment (i.e., numbness and paraesthesia), imbalance, bladder and bowel dysfunction, fatigue, and chronic pain. Cognitively, problems with memory, attention span, planning, decision making, and concentration also affect up to 50% of those with MS (Benedict, Cookfair, Gavett et al., 2006). A diagnosis of MS requires clinical evaluation and medical imaging. Known as the McDonald (2001) or Poser (1983) criteria, the key requirement for diagnosis is evidence of at least two or more clinical attacks, as confirmed by two or more MRI lesions in different areas of the brain or spinal cord (Gelfand, 2017).

The average age of onset of MS is between 20 and 40 years old, when people are establishing families and careers (Palmer et al., 2013). Epidemiological studies suggest that the number of people diagnosed with MS, worldwide, has increased from 2.1 million patients in 2008 to 2.3 million in 2013 (Browne, Chandraratna & Angood, 2014). Recent empirical data from the health economic impact of multiple sclerosis in Australia also suggest that the rate of MS prevalence has risen from approximately 23,700 persons in 2012 to currently 25,600 people (Hasnat, Palmer & Campbell, 2018). A significant gender difference has been observed, with women being twice as likely to be diagnosed than men (Hasnat, Palmer & Campbell, 2018). To date, the aetiology of MS remains unknown. Instead, a combination of lifestyle and genetic risk factors have been implicated - namely vitamin D and B12

deficiency, smoking, exposure to Epstein-Barr virus, mononucleosis, and distance from the equator (Ebers, 2013; Tao et al., 2016).

Although the amount of nerve damage, and which nerves are affected, can vary from person to person, four main clinical courses of MS have been identified (Lublin et al, 2014). *Relapsing-remitting* MS (RRMS) is the most common subtype, affecting almost 85% of individuals with MS. Relapses involve episodes of severe neurological deterioration, followed by partial or complete recovery- known as remission (Gelfand, 2017). During remission, persons will experience disease inactivity and symptom improvement. The time interval between attacks is unpredictable, with evidence that relapses may last from 24 hours to anything between a few days to several weeks or months (Gelfand, 2017).

Within almost 10 to 20 years, a relapsing-remitting course may develop into secondary progressive MS (SPMS), manifested by less or no periods of remission and gradual neurological worsening within the brain in addition to CNS deterioration (Ransohoff, Hafler & Lucchinetti, 2015). Neurological studies suggest that symptom patterns for SPMS vary considerably. While neural deterioration and disability may be gradual among some, others with MS will experience quicker and more severe deterioration (Ransohoff, et al., 2015). *Primary progressive* (PPMS) affects approximately 10-15% of persons with MS (Antel et al., 2012). The suggestion is that persons with PPMS do not experience relapses; instead, they suffer from progressively worsening and unremitting neurological deteriorations (Miller & Leary, 2007). Finally, *clinically isolated syndrome* (CIS) is characterised by single episodes of neurological inflammation.

Quality of Life

Definition

Given the broad range impairments associated with MS, it is perhaps not surprising that quality of life (QoL) has been well-researched as a key disability indicator. QoL captures almost every facet of a patient's perception of their treatment and disease progression (Bandari et al., 2010). However, while the definition of QoL is intuitively understood, no universal definitions exists. According to the World Health Organisation (WHO, 2002), QoL encompasses an individual's self-perception of their physical functioning (i.e. subjective experience of bodily function and ability to fulfil one's role), psychological or emotional wellbeing, social activities and relationships, and environmental resources (e.g. financial resources, home environment, service access; see Figure 1; WHO, 2002). The term QoL is often used synonymously in the disability literature with health related QoL (HRQoL). The latter focuses on an individual's expectations and experiences in relation to their health, including how they experience their lifestyle pre and post illness, their intuition and desires, and the extent to which they accept and adapt to their illness or impairment (Calman, 1984; Carr et al., 2001). Importantly, research demonstrates significant overlap between QoL and HRQoL (Karimi & Brazier, 2016). For the purpose of this review, the term QoL will be used hereafter to broadly cover all aspects of health and wellbeing of the MS population (Karimi & Brazier, 2016).

Measurement

QoL is typically measured by tools that examine the extent to which a patient's expectations of an ideal life differs from what they are experiencing in reality (Calman, 1984; Sirgy, 1986). Given that the concept of QoL is subjective, self-reported QoL questionnaires rather than measures completed by significant others (e.g. caregivers, health professionals)

are strongly recommended as they allow for self-evaluation of health and illness (Testa & Simonson, 1996).

There are, however, complexities in quantitatively comparing QoL domains between different patients' groups or populations. This includes QoL comparisons between persons with MS and healthy controls. In particular, conceptual variations in the item-content of available QoL measurements need to be considered (see Table 1, Appendix B). For example, while some measures evaluate a single, broad QoL domain (e.g. Visual Analogue Scale; VAS; WHO-5; FAMS); others contain multiple items, yielding scores for different subscales. One such multi-dimensional measure is the Medical Outcome Study 36-item Short Form Health Survey (SF-36), which comprises of eight subscales: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role emotional (3 items), mental health (5 items), and health transition (1 item) (Ware et al., 1992).

The chronic illness and disability literature has also relied on generic QoL tools which measure wellbeing broadly, rather than specific disease dimensions (e.g., attention and sexual function; Guarnaccia et al., 2006; Nortvedt, Risse, Myher & Nyland, 2000). Examples of such measures include the World Health Organisation Quality of Life measure (WHOQOL-BREF) and the EuroQoL (EQ-5D). However, it is argued that generic measures may not be sensitive to capture QoL changes in persons with MS (Izutsu et al., 2005; Ohaeri & Awadalla, 2009; Opara, Jaracz & Brola, 2010).

In response to this criticism, disease-specific scales have been developed. One such scale is the 54-item Multiple Sclerosis Quality of Life Scale (MSQOL-54; Vickrey et al., 1995). Interestingly, the MSQOL-54 borrows heavily from the SF-36, with 36-items derived from the latter questionnaire in addition to an 18-item module developed for MS-specific issues (e.g., health perception, pain, sexual function, health distress, cognitive function).

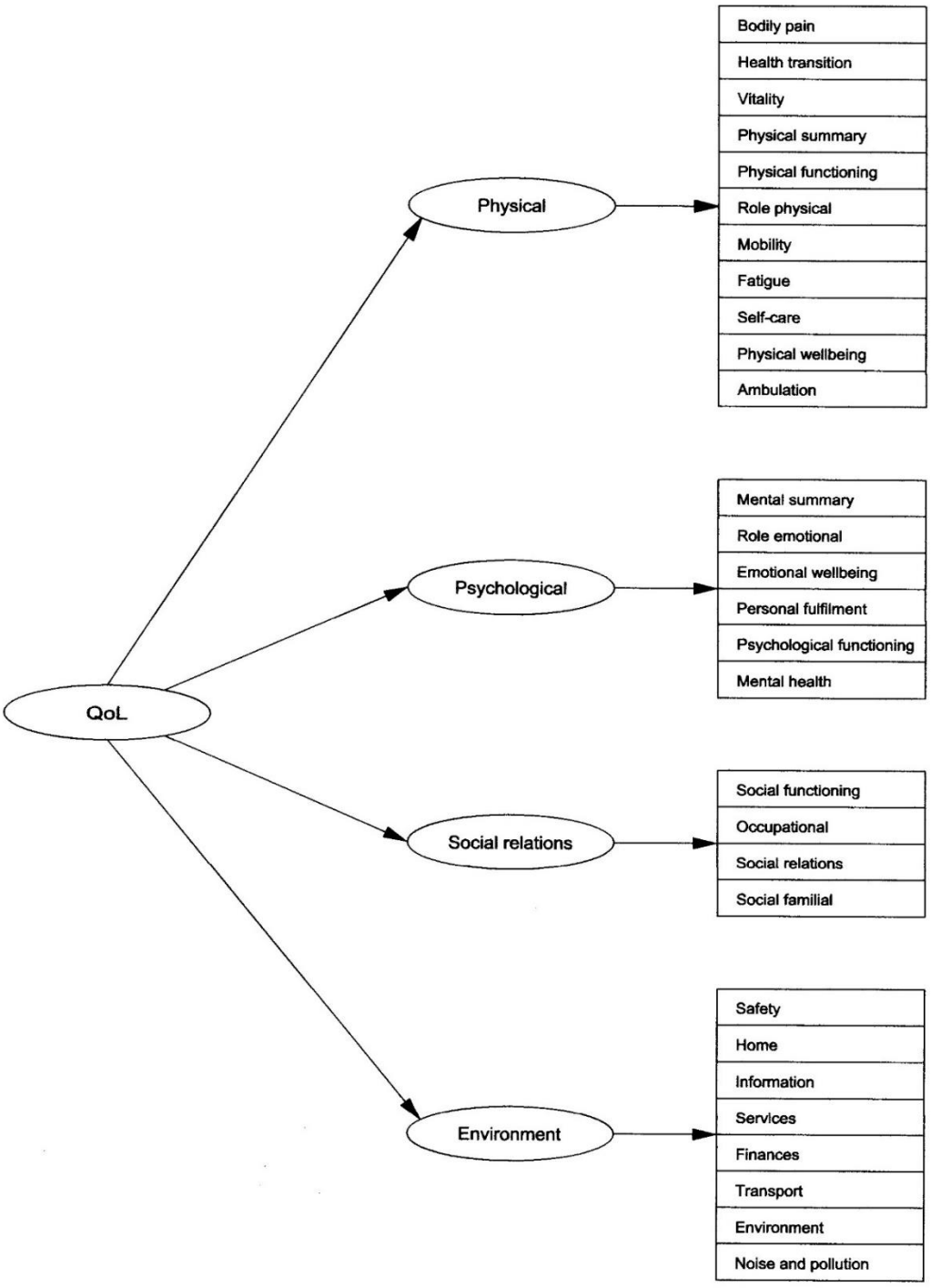


Figure 1: Multidimensional structure of QoL (adopted from WHO, 2002)

The MSQOL-54 has been translated into different languages and evaluated cross-culturally (Ghaem et al., 2007; Solari et al., 1999). The 38-item Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS) is also largely based on the SF-36, although incorporates additional items relating to mobility (upper and lower limbs), social functioning, fatigue and thinking (Brenk et al., 2017). Importantly, these disease-specific tools, while considered valid, reliable, and appropriate for QoL assessment in MS (Gold, Heesen, Schulz et al., 2001), are broadly appropriate and practical when making QoL comparisons between persons with MS and healthy peers.

QoL comparisons with healthy controls

The available evidence suggests that persons with MS rate their QoL much lower when compared to healthy controls. Muhtaroglu et al (2018), for example, found a significant and large difference in physical QoL, as measured by the SF-36, among persons with relapsing remitting MS (RRMS) in comparison to healthy peers. That is, adults with MS identified more role limitations due to physical problems than peers without MS. Glavor et al (2019) and Nyland et al (2019) replicated this finding with the SF-36. However, there is also evidence to suggest that QoL ratings among those with MS are comparable to the community. In particular, Conttenti et al., (2017) reported no significant group differences between persons with MS and healthy counterparts on several SF-36 subscales: bodily pain, social functioning, mental health, physical and role functioning. Similarly, Uccelli et al., (2016), using the World Health Organisation Five Wellbeing Index (WHO-5), identified no statistically significant group differences in QoL among their sample of young adults with MS (mean age 24.2, SD = 2.8 years) and healthy peers (mean age 22.1 ± 2.7 years). The suggestion is that measurements which rely on physical functioning and symptoms (e.g., SF-36) may report greater differences than measures focusing on psychological wellbeing (e.g. WHO-5). Indeed, even though serious mental illness (e.g., depression, and anxiety), have

been reported among individuals living with MS, many do not exhibit these problems (Chwastiak & Ehde, 2007). A growing body of literature even suggests that the majority who are diagnosed with MS can maintain psychological wellbeing (Prakash et al., 2019).

These mixed findings might also be explained by sociodemographic and disease characteristics. For example, Prakash et al (2014) found a non-significant group difference in QoL after controlling for age, gender, and education. Notably, the majority (91%) of their sample had been diagnosed with RRMS and were living with moderate disability which, although affected their daily activities required minimal care assistance (Expanded Disability Status Scale = 4.64; SD = 1.28). In their sample of 61 persons with either RRMS or SPMS and 30 healthy people, Labuz-Roszak et al (2013) reported a negative association between age, years since diagnosis, level of disability and QoL. That is, older persons with a progressive illness course and greater impairment rated their QoL lower in comparison to younger persons diagnosed with RRMS, and minimal or no disability. The younger cohort in this study were, however, using disease modifying medications (i.e. immunosuppressive therapy), which may have helped to promote their QoL (Labuz-Roszak et al., 2013). These findings highlight a need to use case-control study designs or to match study groups on key sample characteristics- such as age and level of MS related disability in order to rule out QoL differences that might result from potential sample confounds.

Current study

Despite a growing body of research, the impact of MS on QoL domains remains unclear. This meta-analysis synthesises the current evidence base to quantify the impact of MS on physical, psychological, social, and environmental QoL, therefore providing an exact and powerful effect estimate than would otherwise be provided by an individual study (Gopalakrishnan & Ganeshkumar, 2013). Using meta-analysis, sources of between-study

heterogeneity can also be explored to construct a cohesive and precise picture of QoL in this chronic disease cohort (Vickrey et al., 1995).

The specific research aims are to:

1) Examine the degree to which QoL scores, including domain scores, differ between adults with MS and healthy controls.
2) Explore the potential moderating role of sociodemographic (i.e., age) and disease characteristics (i.e., years since diagnosis, level of disability) on mean QoL ratings.
3) Examine the findings in relation to study quality, including potential sources of methodological bias.

CHAPTER 2

Method

Literature Search Strategy

Empirical studies that compared Quality of Life (QoL) ratings in adults with multiple sclerosis (MS) and healthy control groups were identified from five electronic databases (Embase, CINAHL, PsycINFO, Scopus, PubMed), in addition to the Google Scholar search engine. Search terms were developed with the assistance of an expert research librarian and included a combination of words specific to the MS population (e.g., 'multiple sclerosis', 'disseminated sclerosis'), and QoL outcomes (e.g. 'quality of life', 'life quality'; see Appendix A for complete logic grids). Databases were searched from inception until March 1st, 2020 with weekly alerts activated until July 1st, 2020 to ensure that all current studies were captured. In addition, the reference lists of two meta-analyses on QoL interventions in MS (Alphonsus et al., 2019; Dauwan et al., 2019) were hand-searched to identify any potentially relevant studies that may have been missed in the initial electronic search strategy. No further unique articles were identified through this process indicating that the original search criteria were effective.

Study Eligibility and Screening

Studies of any design were included if they prospectively recruited: (a) adults (aged >18 years) diagnosed, or reported having been diagnosed with MS (as per McDonald, 2001 or Poser, 1983 criteria) and (b) a healthy control group (also referred to as the 'general population' or a 'non-clinical-group'). Studies also had to (c) measure QoL, as a primary or secondary outcome, using a well-validated generic or MS-specific scale (see Appendix B for a list of eligible measures). Only studies that (d) provided quantitative data (e.g. means, standard deviations) to allow for the calculation of standardised mean group differences were

eligible, as were (e) journal articles published in the English language, or with English translation (Balshem et al., 2013; Juni et al., 2002).

MS studies were excluded if they (a) used normative QoL data as a comparison, given that a population's perception of QoL may change over time, thereby compromising data validity, reliability, and representativeness (Calman, 1984; Pristed et al., 2013). Studies which (b) included different chronic illness or disability groups but did not provide the data for participants with MS separately were also ineligible. Finally, studies with (c) a design that lacked synthesisable data (e.g. qualitative research protocols, reviews, commentaries) in addition to (d) conference proceedings, which typically lack detailed information about recruitment and research methods necessary for critical appraisal (Balshem et al., 2013), were excluded.

Potentially eligible records were imported into Covidence systematic review software (Veritas Health Innovations) and screened by the student researcher (M.P). To detect selection bias, a random subset of 30 full-text records were screened by a second reviewer (postgraduate psychology student, A.W.) Inter-rater reliability was high, with reviewers greening in 93% of cases (k = .81, Viera & Garret, 2005). The two discrepant papers were discussed, and full agreement was reached.

Data Extraction, Preparation and Organisation

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (see Appendix D; PRISMA; Moher, Liberati, Tetzlaff & Altman, 2009) were followed in this review. A purposely designed Microsoft Excel spreadsheet was used to extract the following key information from each included study.

(a) Study characteristics (e.g. lead author, country, recruitment source, etc).

(b) Sample demographics: gender, marital status (married, single, divorced/widow), educational achievement (primary, secondary/high school, post-secondary, university), employment status (employed, unemployed, medically retired due to MS-related disability).

(c) MS information: disease subtype (RRMS, PRMS, SPMS, progressive MS, unknown), duration (in years), disability severity (i.e., Extended Disability Status Scale, [EDSS]), and use of disease-modifying treatment or medication (dichotomised as 'Yes' or 'No').

(d) Effect size data. Although most studies provided sufficient data for the calculation of standardised mean differences (i.e. group *M*s, SDs, sample size *N*, *t*-tests, one-way ANOVAs, or exact *p* values) some data conversion was necessary. Two studies (Barry et al., 2018; Jones et al., 2008) provided 95% confidence intervals or standard errors, which were converted to standard deviations, as per the formulae provided by the Cochrane Collaboration (Higgins & Green, 2008). A further two studies provided QoL data for different subgroups (e.g. across different countries and high versus low health anxiety; Hayter et al., 2016; Murphy, 1998): these data were averaged to provide an overall QoL score for the MS and healthy control groups.

To simplify data interpretation and presentation, individual QoL subscales were grouped under four life domains, as defined by WHO (1998): *physical* (i.e., the ability to fulfil one's normal role to the extent that a physical impairment allows), *psychological* (i.e., feelings, mood and self-perception about disease and health), *social* (i.e., personal and social relationships and supports), and *environmental* or the physical and psychological environments that individuals live within, and form connections with (e.g., financial resources, health and social care, transport).

Assessment of Study Reporting Quality

The National Institute of Health Quality Assessment Tool (NIH, 2014) was adopted to evaluate the methodological rigour, power, reliability, and validity of the included studies, while simultaneously weighing the risk of bias in QoL reporting (National Institute of Health, 2014). Each study was rated by the student researcher (M.P) based on 10 criteria, referred to as the 'ideal functional tool' suitable for use across different study designs. Four criteria specific to intervention studies were deemed 'not applicable' for the observational data that characterised most studies in this review (e.g., items related to blinding of participants or research personnel, intervention duration, follow-up, time interval, and use of repeated measurement). For each criterion, a study was rated as '*meet'* (score = 2), '*partially met'* (score = 1), or '*did not met'* (score = 0; see Appendix E). The total number of studies (or percentage) that met each criterion was then calculated. After eight weeks, the same person (M.P) re-rated a random sample of 31 studies to determine the intra-rater reliability of these quality scores. The percentage of agreement between the scores assigned to the 10 criteria, on each occasion, was high (90% agreement).

Statistical Analyses

Effect size data were entered, and analysed using Comprehensive Meta-Analysis Software (CMA, Version 3.0, Englewood, NJL Biostat Inc). Given the use of various QoL tools across the included studies, in addition to clinical heterogeneity within the MS population (e.g. different subtypes, time since diagnosis) a random-effects model was used for all meta-analyses (Cumming, 2012). Hedges' *g* was selected as the effect size estimate, to reflect standardised group mean differences in self-reported QoL scores between participants with MS and healthy controls (Hedges & Olkin, 1985). This measure of effect size, which performs a pooled SD weighted to sample size, was suitable, given that some included studies were characterised by very small (i.e. $N < 20$) samples (Borenstein, Hedges, Higgins &

Rothstein, 2009). The guidelines proposed by Cohen (1988) were followed to interpret *g* with .20, .50, and ≥ 80 representing small, medium, and large to very large group differences, respectively.

Individual effect size estimates, for each study, were first averaged and an overall effect calculated across the included studies. Effect size estimates for QoL domains were then examined separately, with QoL scales or subscales grouped according to the domain they represented: physical, psychological, social, or environmental. Studies which used the same QoL measure were pooled and weighted based on their inverse variance (g_w). This weighting gives greater preference to studies with a larger *N*, thereby minimising the probability of bias which typically accompanies effect estimates that are based on studies with a small sample size (Higgins & Green, 2008). If a study provided multiple effect sizes for a single domain the effect estimates for that study were averaged beforehand, so that each study contributed a single effect estimate to any meta-analysis. Likewise, to ensure data independence, only baseline data were extracted and analysed from the four longitudinal studies included (Barry et al., 2018; Brenk et al., 2007; Kerling et al., 2014; Rosti, 2007). The direction of *g* was standardised so that a negative value reflected lower QoL ratings among persons with MS compared to healthy peers. To examine the precision of *g*, 95% confidence intervals (CIs) were calculated for both individual and pooled effect estimates. If a CI does not include the value of zero, it represents a significant group difference, with 95% confidence (Cumming, 2012). Statistical significance was then examined with (*p*) values (Cumming, 2012)

Between-study variation in effect estimates, or heterogeneity, was estimated with three statistics. The *Q*-statistic, which analyses the proportion of observed variation to within study error was first calculated. A statistically significant result (i.e. $p < .05$) suggests there may be a problem with heterogeneity (Borenstein et al., 2009). Tau (*T*), analogous to the standard deviation of *g* then helped to identify the distribution of effect sizes about the mean

effect (Borenstein et al., 2009). Finally, I^2, which is expressed as a percentage of total difference across studies due to heterogeneity rather than chance, was used (Borenstein et al., 2009). I^2 values of 25%, 50%, and 75% represent small, moderate, and high amounts of variance (Higgins, Thompson, Deeks, and Altman, 2003).

A funnel plot was generated to visually inspect potential publication bias for meta-analyses that were sufficiently powered (i.e., $N_{studies}$ >10; Fu et al., 2011; Higgins & Green, 2008). Funnel plots display the association between effect size estimates and the precision of each estimate (i.e. the inverse sampling variance). In the absence of publication bias, effect sizes concentrate around a precise estimate with increasing sample size, forming a symmetric funnel shape (Duval & Tweedie, 1998). Funnel plot analysis was supplemented with the trim-and-fill method, a statistical method whereby studies that cause asymmetry are 'trimmed' from the analysis, and hypothetical studies which then create a symmetric funnel plot are added (Duval & Tweedie, 1998). Additionally, Orwin's (1983) fail-safe *N* (N_{fs}) statistic was calculated for both individual and pooled *g*'s. The fail-safe *N* (N_{fs}) determines the number of hypothetical non-significant studies that would be required to reduce a given *g* to a small and non-significant effect (i.e. $g \leq 0.2$; Lipsey & Wilson, 2001). Typically, the larger the N_{fs} value, the more likely that *g* or g_w is robust (i.e. $N_{fs} > N_{studies}$).

A combination of these statistics was considered when interpreting the results of each meta-analysis. That is, differences in QoL ratings between individuals with MS versus healthy controls (g/g_w) were considered to be significant if: (1) the associated 95% CI did not include the value of zero, (2) the *p* value was < .05, and (3) the funnel plot and/or N_{fs} score suggested that the results were not affected by publication bias. These results were considered in the context of study heterogeneity.

Sensitivity and Moderator Analyses

A one-study removed sensitivity analysis was performed for each QoL domain. This analysis is highly recommended as a robustness check to identify potential outlier effects (Borenstein et al., 2009). Results were considered meaningful, if the associated *p* value or the magnitude of an effect size changed significantly following the removal of any one study (Borenstein et al., 2009; Cohen, 1988).

Subgroup analysis was then used to examine if the observed heterogeneity in Hedges' *g* was influenced by the type of QoL instrument (generic vs. MS-specific). Studies which used both generic and MS-specific QoL measurements were excluded from this analysis to ensure data independence. This analysis involved a *Q*-test, where the null hypothesis states that the effect size is not related to either subgroup (i.e., use of generic or disease-specific instruments; Borenstein et al., 2009).

Finally, a multivariate meta-regression was conducted to examine the potential effects of three covariates considered to be critical to QoL following a diagnosis of MS (Giovagnoli et al., 2019; Glavor, 2019): (a) mean age of adults with MS ($N_{studies}$ = 35), (b) years since diagnosis ($N_{studies}$ = 27), and (c) EDSS ($N_{studies}$ = 23). As age and time since diagnosis among the included studies were moderately correlated (r = 0.6), these two variables were linked in the regression equation.

CHAPTER 3

Results

Study Selection

Of the 19,977 records initially identified through database searching, 9,660 unique records were screened (see Figure 2). The titles and abstracts of 7,664 potentially relevant records were then rescreened against the inclusion criteria and 319 full texts retrieved. Authors from seven studies were emailed with requests for additional data, with two responding. During the screening six studies with overlapping samples were identified. To ensure no study contributed to more than one effect size in any pooled effect, the overlapping studies were combined and treated as three independent studies. The article that provided the most comprehensive dataset (e.g. largest sample size) was included (see Appendix F). Three additional articles were identified from the automatic email alerts set up for each database. This resulted in a final sample of 35 independent studies.

Study Characteristics

Thirty-five independent studies comparing mean quality of life (QoL) ratings between persons with MS and healthy controls over the last 20 years (publication date range: 1998 to 2019) were identified. Most studies were cross-sectional in design ($N_{\text{studies}} = 29$), with four longitudinal and two case control studies identified (see Table 2; Appendix C). Most studies were from Westernised countries ($N_{\text{studies}} = 29$), with several from Asia ($N_{studies} = 5$) and a single study from the Mediterranean ($N_{studies} = 1$). Five studies contributed to approximately 48% of the entire MS sample (Gupta, 2014; McCabe, 2009; Jones, 2008; Murphy, 1998; Jarcaz, 2010). Persons with MS were recruited from single sites (e.g., outpatient clinics; Solmaz et al., 2018), national health and wellness surveys (Lightspeed Research, Gupta, et

al., 2014; Canadian Community Health Survey Cycle, Jones et al., 2008), and local MS groups (e.g. MS Society of Victoria; McCabe et al., 2009).

Quality of life was typically measured with generic instruments, including the Short-Form 36 Health Status Survey (SF-36; $N_{studies}$ = 15; Ware & Sherbourne, 1992) and the World Health Organisation Quality of Life scales (WHOQOL, $N_{studies}$ = 6; WHOQOL Group, 1998). Six studies adopted MS-specific measures: The Functional Assessment of Multiple Sclerosis (FAMS; Goverover et al, 2016); Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS; Brenk et al., 2007), RAYS scale (Rostein e t al., 2000), and the Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54, Barry et al., 2018; Jarcaz et al, 2010; Postigo-Alonso, 2019; see Appendix B). Although Barry et al (2018) incorporated the MSQOL-54, they only used the generic items adopted from the SF-18, to compare QoL between their two groups.

Sample Characteristics

MS

A pooled sample of 3,493 persons with MS, with a mean age of 42.14 years (SD = 5.54; Table 3) contributed to this meta-analysis. There was a higher proportion of females (67.4%) than males (32.6%), consistent with a known bias in MS diagnosis toward women (Charles, Valenti & Britt, 2011). On average, 80% of the MS sample were living with minimal to moderate disability (EDSS mean 3.2, SD = 1.3), that is, they were not severely impaired physically but did experience muscle weakness, limitations in daily activities, loss of balance, alongside problems with speech, swallowing, bowel and bladder function, vision, and cognition (Kurtzke, 1983).

Healthy Controls

The comparison group comprised of 187,296 peers with a mean age of 41.61 years (SD = 5.65; see Table 3). These participants were usually described as ‘healthy controls’ (N_{studies}

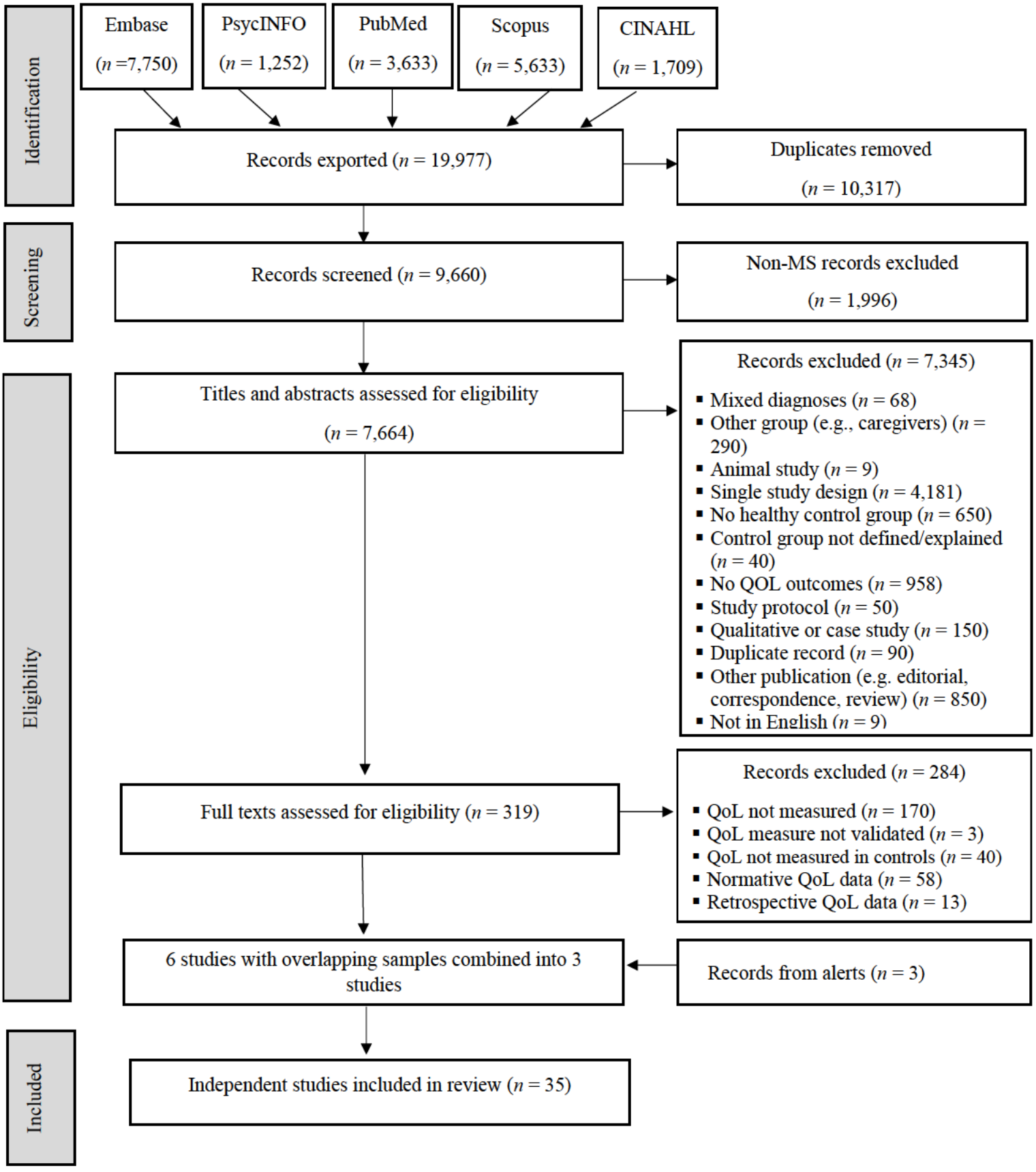


Figure 2. PRISMA flowchart for study selection process (Moher et al., 2009).

=29), although the terms 'age matched' ($N_{studies}$ = 2), 'general population' ($N_{studies}$ = 2), 'community control' ($N_{studies}$ = 1) and 'non-MS respondents' ($N_{studies}$ =1) were also used. The MS and healthy control groups were comparable in age (t (68) = 0.39, p = 0.69), likely because most studies controlled for this potential confound (Nstudies = 25). A higher proportion of females was, however, noted among the MS group (X^2 (1) = 353.95, p < .001).

Study Reporting Quality

The reporting quality of all included studies, as assessed by the adapted National Institute of Health Quality Assessment Tool (2014), is shown in Figure 3. Most studies at least partially met more than half of the 10 criteria. Specifically, all identified their key research question(s) and defined their eligibility criteria prior to the recruitment of participants (*items 1 to 4*: 100% fulfilled). However, study power was problematic with 61% of studies not having a sufficiently powered sample to identify a statistically significant group difference (i.e., $N > 26$ with power at .80 and alpha at .05, Cohen, 1992, *item 5*). Studies assessed one or more QoL domains with valid, reliable, and multi-lingual generic or MS-specific questionnaires, in addition to providing an adequate description of their QoL outcome(s) (*items 6* - 9, 100% fulfilled). More than half of the studies also adjusted for age and/or gender as potential sample confounds in their statistical analyses (*item 10*: 58 % fulfilled).

Effect Size Estimates

The pooled effect size across all 35 studies was negative, large, and statistically significant (see Figure 4), persons with MS reported significantly reduced QoL compared to healthy controls. This finding was unlikely to be characterised by publication bias, as evident by the substantial N_{fs} value and the unchanged, combined effect calculated by the trim-and-

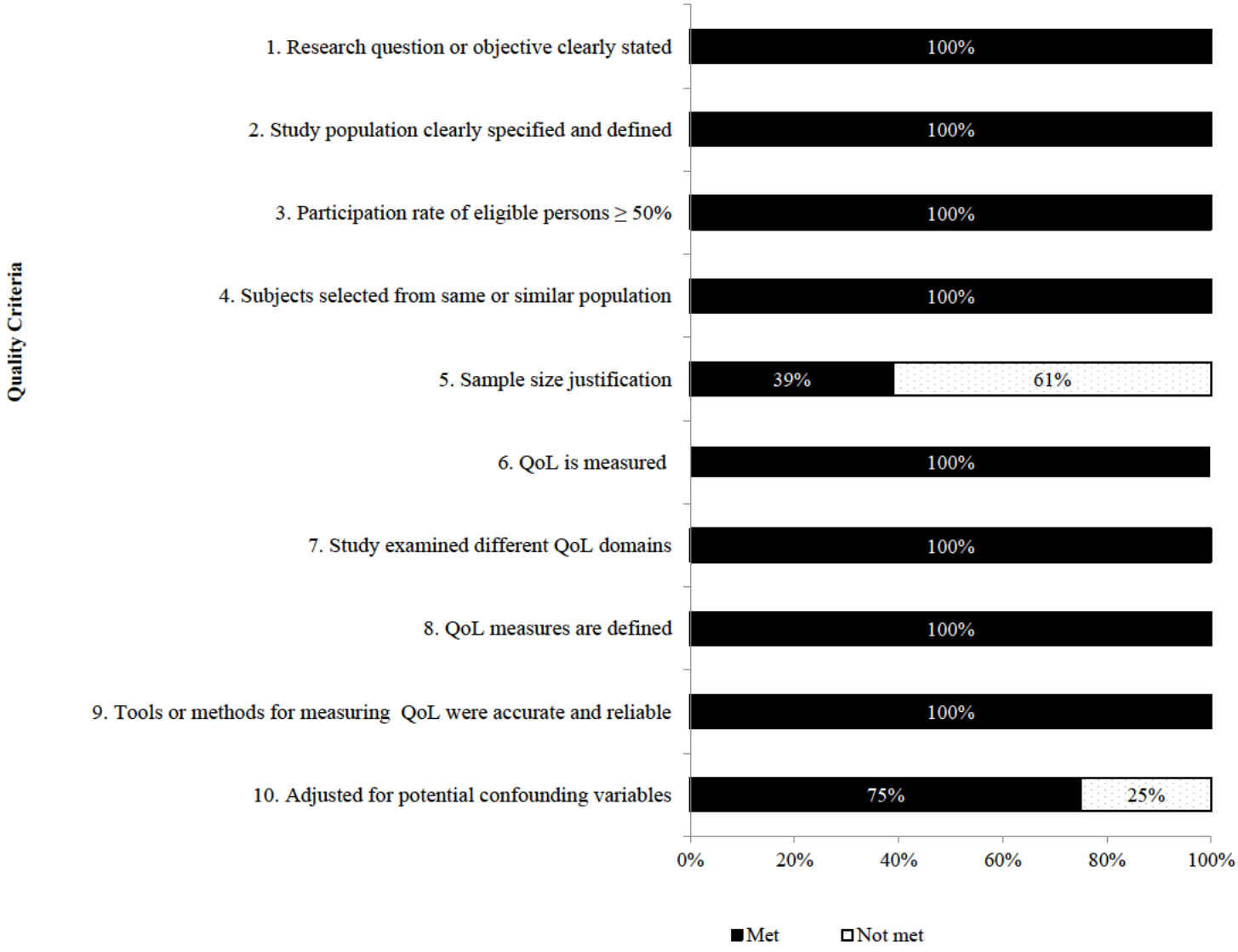


Figure 3: Percentage of studies meeting each NIH criteria (2014, $N_{studies}$ = 35)

Table 3.

Sample Characteristics ($N_{studies}$ = 35)

Variable	MS			Control		
	$N_{studies}$	$N_{participants}$ (%)	Mean ± SD	$N_{studies}$	$N_{participants}$ (%)	Mean ± SD
Total sample size	35	3493		35	187296	
Mean age (SD) in years			42.14 ± 5.54			41.61± 5.65
Gender						
Male	35	1139 (32.6)		35	91145 (48.7)	
Female	35	2354 (67.4)		35	96151 (51.3)	
Total (%)		3493 (100)			187296(100)	
Employment status						
Employed	14	847 (64)		12	128510 (99.7)	
Unemployed	10	210 (16)		7	357 (0.28)	
Disability pension/retired	6	262 (20)		2	56 (< .05)	
Student	3	14 (1)		4	33 (< .05)	
Total (%)		1333 (100)			128956 (100)	
Education						
Primary	6	112 (5)		3	25765 (14)	
Highschool	10	502 (24)		6	40252 (21)	
Post-secondary	7	501 (24)		5	41951 (22)	
≥University	14	995 (47)		13	82184 (43)	
Total (%)		2110 (100)			190152 (100)	
Relationship status						
Married	10	774 (72)		9	73719 (99.5)	
Partner	1	23 (2)		1	11 (< .05)	
Single	8	235 (22)		7	368 (< 0.5)	
Widowed/Divorced/Separated	5	38 (4)		4	17 (< .05)	
Total (%)		1070 (100)			74115 (100)	
MS details				-	-	-
Disease duration (in years)	25		9.04 ± 6.2	-	-	-
EDSS score	16		3.2 ± 1.3	-	-	-
Subtype				-	-	-
RRMS	23	1270 (80)		-	-	-
PPMS	10	109 (7)		-	-	-
SPMS	10	206 (13)		-	-	-
Progressive MS	1	4 (< .05)		-	-	-
Unknown	1	4 (< .05)				
Total (%)		1593 (100)				
Disease modifying treatments						
Currently receiving treatment	8	230 (57)		-	-	-
No treatment	2	177 (43)		-	-	-
Total (%)		407 (100)				

Abbreviations: $N_{participants}$= number of participants providing these data; $N_{studies}$= number of studies included; MS = Multiple Sclerosis; M= Mean; SD= Standard Deviation; EDSS, Expanded Disability Status Scale; RRMS = Relapsing Remitting Multiple Sclerosis; PPMS = Primary Progressive Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis; (-) not applicable or data not provided.

fill method (see Figure 5, Appendix F). Effect estimates did, however, vary across studies (g_w range: -6.18 to -0.14), highlighting a need to explore potential sources of heterogeneity.

Group Differences across QoL Domains

Physical domain

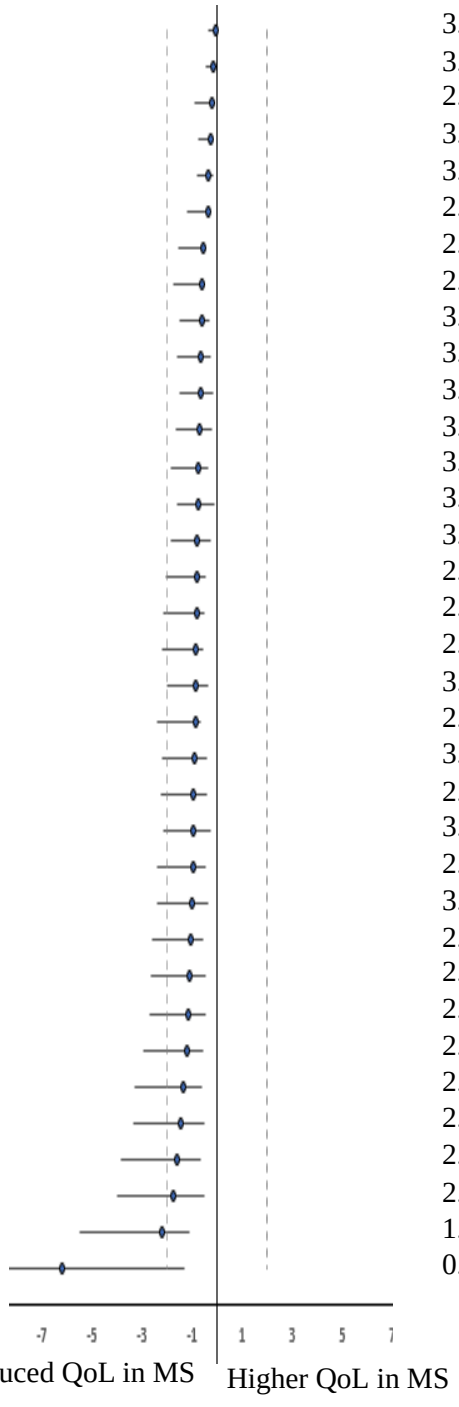
Thirty independent studies, utilising 11 individual QoL measures and 26 subscales, examined mean differences in various aspects of physical functioning between adults with MS (n = 3,203) and healthy controls (n = 187,056; see Table 4). The overall pooled estimate was very large: MS negatively impacted on physical health, in general (g_w range: 2.13 to -.09). The N_{fs} value suggests that 98 studies would be needed to overturn this finding. This robust finding was confirmed by funnel plot analysis (see Figure 6, Appendix G). There was, however, substantial between study heterogeneity (total I^2 > 90%). The largest group differences were associated with the impact of physical health on ability to engage in daily activities (e.g., SF-36 role physical subscale) as well as physical functioning (SF-36; SF-12; MSQOL-54; RAYS, SIP). However, five studies identified no significant group differences in self-perceived health (MSQOL-54 energy), self-care and physical independence (QLI, WHOQOL-100), mobility (HAQUAMS), vision and dexterity (HUI-3).

Psychological domain

Twenty-nine studies, using 10 individual QoL scales and 15 subscales, measured the extent to which persons with MS differed from healthy controls in psychological functioning. The overall pooled and weighted g indicated a negative and moderately significant group difference (see Table 5): those with MS (n = 3,067) consistently reported more psychological and emotional difficulties than non-MS peers (n = 187,025). Funnel plot analysis, in addition to the trim-and-fill method, detected no missing (unpublished) studies in this analysis (see Figure 7; Appendix G). Heterogeneity was, however, substantial, despite studies using the

Figure 4: Forest plot depicting overall QoL differences between MS and controls ($N_{studies}$ = 35)

Lead author (date)	*N* MS	*N* Control	Hedges' *g*	95% CI LL	95% CI UL	*p*	Forest plot of g with ± 95% CI	Weight (random)
Uccelli, 2016	89	109	-0.041	-0.320	0.238	.772		3.36
Jones, 2008	302	109741	-0.160	-0.273	-0.047	.006		3.74
Goverover, 2016	41	32	-0.208	-0.667	0.250	.373		2.78
Klevan, 2013	93	96	-0.243	-0.529	0.042	.095		3.34
McCabe, 2009	382	291	-0.331	-0.485	-0.177	.000		3.67
Giovagnoli, 2019	22	66	-0.369	-0.853	0.115	.135		2.69
Glavor, 2019	30	30	-0.526	-1.042	-0.011	.045		2.59
Muhtaroglu, 2018	24	24	-0.591	-1.170	-0.013	.045		2.39
Prakash, 2019	10	98	-0.597	-0.882	-0.312	.000		3.34
Murphy, 1998	267	90	-0.666	-0.914	-0.418	.000		3.44
Nicholas, 2019	196	784	-0.671	-0.830	-0.511	.000		3.66
Nohara, 2017	96	480	-0.709	-0.933	-0.486	.000		3.51
Fruehwald, 2001	60	60	-0.729	-1.102	-0.356	.000		3.06
Gupta, 2013	536	74451	-0.767	-0.852	-0.682	.000		3.77
Papuc, 2012	173	86	-0.778	-1.049	-0.507	.000		3.38
Labuz-Roszak, 2013	61	30	-0.801	-1.252	-0.350	.000		2.80
Philips, 2014	31	31	-0.804	-1.323	-0.285	.002		2.58
Hayter, 2016	42	21	-0.829	-1.366	-0.292	.002		2.52
Contentti, 2017	74	87	-0.841	-1.168	-0.513	.000		3.21
Brenk, 207	27	14	-0.861	-1.526	-0.197	.011		2.13
Nyland, 2019	43	96	-0.906	-1.281	-0.530	.000		3.05
Kerling, 2014	60	48	-0.926	-1.325	-0.527	.000		2.97
Jarcaz, 2010	210	108	-0.957	-1.201	-0.713	.000		3.45
Newland, 2009	40	40	-0.965	-1.431	-0.499	.000		2.75
Odabas, 2018	64	60	-1.061	-1.388	-0.643	.000		3.06
Isernia, 2019	42	26	-1.031	-1.565	-0.497	.000		2.53
Rotstein, 2000	50	50	-1.098	-1.528	-0.668	.000		2.87
Hoogs, 2011	132	26	-1.133	-1.570	-0.969	.000		2.85
Fritz, 2016	29	29	-1.192	-1.749	-0.636	.000		2.46
Meeus, 2014	19	39	-1.345	-1.941	-0.749	.000		2.34
Solmaz, 2018	42	41	-1.428	-1.915	-0.942	.000		2.69
Postigo-Alonso, 2019	23	24	-1.606	-2.257	-0.956	.000		2.18
Rosti, 2007	45	48	-1.760	-2.236	-1.284	.000		2.72
Barry, 2018	9	10	-2.184	-3.299	-1.068	.000		1.18
Hassan, 2014	30	30	-6.198	-7.493	-4.902	.000		0.95



Abbreviations: N = sample size, MS = multiple sclerosis, CI = 95% confidence interval, LL = lower limit, UL = upper limit, *p* = significance level

Table 4.

Standardised Mean Group Differences in Physical QoL

Measure	Subscale	$N_{studies}$	$N_{participants}$		g_w	95% CI		p	N_{fs}	Heterogeneity statistics			
			MS	Control		Lower	Upper			Q	p	I^2	T
SF-36	Bodily pain	8	405	473	**-0.734**	-1.218	-0.251	<.003	12	79.922	<.001	91.241	0.429
	Health transition	1	42	41	**-0.939**	-1.389	-0.490	<.001	4				
	Vitality	9	447	514	**-1.039**	-1.551	-0.527	<.001	23	107.349	<.001	92.548	0.547
	Physical summary	7	513	1546	**-1.200**	-1.409	-0.991	<.001	31	13.530	.035	55.655	0.038
	Physical functioning	8	354	418	**-1.504**	-1.967	-1.040	<.001	43	55.978	<.001	87.495	0.376
	Role physical	8	354	418	**-1.839**	-2.547	-1.130	<.001	40	122.211	<.001	94.272	0.920
	Total SF-36	15	890	1,934	**-1.169**	-1.441	-0.898	<.001	58	109.184	<.001	87.178	0.229
SF-12	Physical summary	2	578	74477	**-1.486**	-2.186	-0.786	<.001	13	8.856	.016	82.923	0.217
MSQOL-54	Pain	2	219	118	**-1.037**	-1.759	-0.315	<.005	8	2.324	.127	56.975	0.181
	Role physical	1	210	108	**-1.179**	-1.428	-0.930	<.001	5				
	Physical function	1	9	10	**-1.268**	-1.520	-1.017	<.001	5				
	Energy	2	219	118	-1.514	-3.383	0.356	.113	13	9.661	<.002	89.649	1.646
	Physical summary	1	9	10	**-2.130**	-2.929	-1.331	<.001	10				
	Total MSQOL-54	3	242	142	**-1.583**	-2.402	-0.763	<.001	14	9.959	<.007	79.917	0.398
HAQUAMS	Mobility upper	1	27	14	**-0.700**	-1.351	-0.049	<.035	3				
	Mobility lower	1	27	14	**-0.991**	-1.659	-0.332	<.004	4				
	Fatigue	1	27	14	**-1.392**	-2.093	-0.691	<.001	6				
	Total HAQUAMS	1	27	14	**-1.028**	-1.701	-0.354	<.003	4				

Table 4. *Continued*

Measure	Subscale	$N_{studies}$	$N_{participants}$		g_w	95% CI		p	N_{fs}	Heterogeneity statistics			
			MS	Control		Lower	Upper			Q	p	I^2	T
QLI	Self-care	1	60	60	-0.807	-1.177	-0.437	<.001	3				
	Physical wellbeing	1	60	60	-1.148	-1.532	-0.764	<.001	5				
	Total QLI	1	60	60	**-0.977**	-1.355	-0.600	<.001	4				
WHOQOL-100	Physical	3	577	443	-0.567	-1.333	0.200	.147	2	46.133	<.001	95.665	0.431
	Independence	3	577	443	-1.063	-2.263	0.137	.082	6	99.733	<.001	97.995	1.092
	Total WHOQOL-100	3	577	443	-0.815	-1.797	0.168	.104	4	71.159	<.001	97.189	0.724
WHOQOL-BREF	Physical	2	131	129	**-1.291**	-1.913	-0.669	<.001	14	3.827	.050	73.869	0.152
RAYS	Physical	1	50	50	**-1.496**	-1.937	-1.056	<.001	6				
SIP	Physical summary	1	132	26	**-1.092**	-1.527	-0.656	<.001	4				
FSQ	Physical functioning	1	264	90	**-0.916**	-1.164	-0.668	<.001	4				
HUI-3	Ambulation	1	302	109741	**-0.259**	-0.372	-0.146	<.001	0				
	Vision	1	302	109741	-0.085	-0.198	0.028	.142	0				
	Dexterity	1	302	109741	-0.094	-0.207	0.019	.102	0				
Total Physical QoL		30	3203	187056	**-1.145**	-1.354	-0.937	<.001	98	470.058	<.001	93.831	0.283

Abbreviations. $N_{studies}$= number of studies included in analysis; $N_{participants}$= number of participants providing this data; 95% CI = confidence interval (with lower and upper limits); MS = Multiple Sclerosis; g_w = pooled Hedges' g with inverse variance weighting (note: weighting only applies to total effect sizes involving 2 or more studies); p = significance value associated with effect estimate; N_{fs} = fail safe N; Q= chi-squared test of heterogeneity; I^2= proportional estimate of true effect variance over sampling error observed; T = SD of g_w. QoL measures: WHOQOL-100 = World Health Organisation Quality of Life-100; WHOQOL-BREF = Health-Related Quality of Life Assessment; RAYS = RAYS scale; SF-12 = Short Form 12; SIP = The Sickness Impact Profile; FSQ = Functional Status Questionnaire; HUI3 = The Health Utilities Index Mark 3

Bold font indicates significant group difference

Table 5.

Standardised Mean Group Differences in Psychological QoL

Measure	Subscale	$N_{studies}$	$N_{participants}$		g_w	95% CI		p	N_{fs}	Heterogeneity statistics			
			MS	Control		Lower	Upper			Q	p	I^2	T
SF-36	Mental summary	7	470	1450	**-0.416**	-0.597	-0.234	<.001	5	11.718	.069	48.798	0.026
	Mental health	9	450	514	**-0.946**	-1.461	-0.431	<.001	17	109.710	<.001	92.708	0.550
	Role emotional	8	357	418	**-1.396**	-2.023	-0.768	<.001	31	106.115	<.001	93.403	0.743
	Total SF-36	15	890	1934	**-0.806**	-1.101	-0.511	<.001	22	139.851	<.001	89.989	0.284
SF-12	Mental summary	2	578	74477	**-0.345**	-0.429	-0.261	<.001	6	0.611	.434	0.000	0.000
MSQOL-54	Emotional wellbeing	1	210	108	**-0.596**	-0.832	-0.360	<.001	2				
	Role emotional	1	210	108	**-0.739**	-0.978	-0.501	<.001	3				
	Mental summary	2	32	34	**-1.633**	-2.180	-1.085	<.001	14	0.255	.614	0.000	0.000
	Total MSQOL-54	3	242	142	**-1.257**	-2.043	-0.470	<.002	10	10.301	<.006	80.585	0.371
HAQUAMS	Mood	1	27	14	**-0.958**	-1.624	-0.291	<.005	4				
QLI	Personal fulfilment	1	74	87	**-0.939**	-1.314	-0.564	<.001	4				
	Emotional wellbeing	1	74	87	**-1.206**	-1.593	-0.819	<.001	5				
	Total QLI	1	74	87	**-1.073**	-1.454	-0.692	<.001	4				
WHOQOL-100	Psychological	3	577	443	**-0.351**	-0.479	-0.224	<.001	3	0.775	.679	0.000	0.000
WHOQOL-BREF	Psychological	2	131	129	**-0.534**	-0.780	-0.288	<.001	3	0.002	0.961	0.000	0.000

Table 5. *Continued*

Measure	Subscale	$N_{studies}$	$N_{participants}$		g_w	95% CI		p	N_{fs}	Heterogeneity statistics			
			MS	Control		Lower	Upper			Q	p	I^2	T
RAYS	Psychological	1	50	50	**-0.809**	-1.213	-0.404	<.001	3				
FSQ	Psychological functioning	1	265	90	**-0.384**	-0.624	-0.144	<.002	1				
HUI3	Emotion	1	302	109741	-0.090	-0.203	0.023	.117	0				
Total Psychological QoL		29	3067	187025	**-0.649**	-0.798	-0.501	<.001	29	222.120	<.001	87.394	0.122

Abbreviations. $N_{studies}$= number of studies included in analysis; $N_{participants}$= number of participants providing this data; 95% CI = confidence interval (with lower and upper limits); MS = Multiple Sclerosis; g_w = pooled Hedges' g with inverse variance weighting (note: weighting only applies to total effect sizes involving 2 or more studies); p = significance value associated with effect estimate; N_{fs} = fail safe N; Q= chi-squared test of heterogeneity; I^2= proportional estimate of true effect variance over sampling error observed; T = SD of g_w

QoL measures: MSQoL-54 = Multiple Sclerosis Quality of Life-54 Questionnaire; HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis; SF-36 = Short-Form 36 Health Status Survey; QLI = Quality of Life Index; WHOQOL-100 = World Health Organisation Quality of Life-100; WHOQOL-BREF = Health-Related Quality of Life Assessment; RAYS = RAYS scale; SF-12 = Short Form 12; FSQ = Functional Status Questionnaire; HUI3 = The Health Utilities Index Mark 3

Bold font indicates significant group difference

same QoL measure. This dispersion was further evident by the wide confidence intervals and high I^2 values. Notably, three single studies reported no significant group differences in relation to the impact of emotional problems on one's ability to participate in daily activities (MSQOL-54), self-perceived mood (HAQUAMS) and general emotional wellbeing (HUI-3).

Social domain

Seventeen studies evaluated perceived differences in various aspects of social functioning between MS (n = 1,627) and healthy control (n = 2,899) groups, using eight different QoL scales and 11 subscales. The overall pooled effect size was statistically significant and robust (see Table 6; Figure 8; Appendix G). There were, however, mixed findings. Social functioning contributed to the largest group difference: adults with MS reported a reduced ability to participate in normal social activities with family, friends and social groups (SF-36; MSQOL-54), and more difficulties in meeting occupational or work demands (QLI). Social familial activities and interpersonal relations were also negatively affected by MS symptoms (RAYS; QLI). Two small-scale studies reported similar ratings when examining communication or interactions with others, regardless of whether disease-specific (HAQUAMS) or generic (QLI) measures- were used. These findings were associated with very low N_{fs} values ($N_{fs} < N_{studies}$).

Environmental domain

Five studies evaluated group differences between MS (n = 708) and healthy controls (n = 572) groups in environmental QoL, or access to social and physical services, as measured by the WHOQOL. The overall effect size was small to moderate, albeit significant (see Table 7; Figure 9; Appendix G): those with MS reported experiencing more difficulties and less satisfaction within their environment (e.g. financial resources, physical safety, social and

Table 6

Standardised Mean Group Differences in Social QoL

Measure	Subscale	$N_{studies}$	$N_{participants}$		g_w	95% CI		p	N_{fs}	Heterogeneity statistics			
			MS	Control		Lower	Upper			Q	p	I^2	T
SF-36	Social functioning	8	354	418	**-1.259**	-1.910	-0.608	<.001	31	115.878	<.001	93.959	0.815
MSQOL-54	Social functioning	1	210	108	**-1.092**	-1.339	-0.845	<.001	4				
HAQUAMS	Communication	1	27	14	-0.267	-0.903	0.369	.410	0				
QLI	Social emotional	1	60	60	0.000	-0.356	0.356	1.000	0				
	Community & service	1	60	60	-0.350	-0.708	0.008	.055	1				
	Interpersonal	1	60	60	-0.691	-6.584	5.202	.818	2				
	Occupational	1	60	60	**-1.298**	-1.690	-0.907	<.001	5				
	Total QLI	1	60	60	**-0.585**	-0.953	-0.217	<.002	2				
WHOQOL-100	Social relations	3	577	443	**-0.282**	-0.409	-0.155	<.001	2	0.480	.787	0.000	0.000
WHOQOL-BREF	Social relations	2	131	129	**-0.379**	-0.623	-0.135	<.002	2	0.387	.534	0.000	0.000
RAYS	Social familial	1	50	50	**-0.666**	-1.066	-0.266	<.001	2				
FSQ	Social functioning	1	265	90	**-0.342**	-0.582	-0.102	<.005	1				
Total Social QoL		17	1627	1262	**-0.713**	-0.959	-0.468	<.001	30	139.202	.000	88.506	0.220

Abbreviations. $N_{studies}$= number of studies included in analysis; $N_{participants}$= number of participants providing this data; 95% CI = confidence interval (with lower and upper limits); MS = Multiple Sclerosis; g_w = pooled Hedges' g with inverse variance weighting (note: weighting only applies to total effect sizes involving 2 or more studies); p = significance value associated with effect estimate; N_{fs} = fail safe N; Q= chi-squared test of heterogeneity; I^2= proportional estimate of true effect variance over sampling error observed; T = SD of g_w

QoL measures: MSQoL-54 = Multiple Sclerosis Quality of Life-54; HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis; SF-36 = Short-Form 36 Health Status Survey; QLI = Quality of Life Index; WHOQOL-100 = World Health Organisation Quality of Life-100; WHOQOL-BREF = Health-Related Quality of Life Assessment; RAYS = RAYS scale; FSQ = Functional Status Questionnaire

Bold font indicates significant group difference

Table 7.

Standardised Mean Group Differences in Environmental QoL

Measure	Subscale	$N_{studies}$	$N_{participants}$		g_w	95% CI		p	N_{fs}	Heterogeneity statistics			
			MS	Control		Lower	Upper			Q	p	I^2	T
WHOQOL-100	Environmental	3	577	443	**-0.274**	-0.402	-0.147	<.001	2	0.296	.863		
WHOQOL-BREF	Environmental	2	131	129	**-0.423**	-0.668	-0.179	<.001	2	0.172	.678		
Total Environmental QoL		5	708	572	**-0.306**	-0.419	-0.193	<.001	3	1.587	.811		

Abbreviations. $N_{studies}$= number of studies included in analysis; $N_{participants}$= number of participants providing this data; 95% CI = confidence interval (with lower and upper limits); MS = Multiple Sclerosis; g_w = pooled Hedges' g with inverse variance weighting (note: weighting only applies to total effect sizes involving 2 or more studies); p = significance value associated with effect estimate; N^{fs} = fail safe N; Q= chi-squared test of heterogeneity; I^2= proportional estimate of true effect variance over sampling error observed; T = SD of g_w

QoL measures: WHOQOL-100 = World Health Organisation Quality of Life-100; WHOQOL-BREF = Health-Related Quality of Life Assessment.

Bold font indicates significant group difference

health accessibility, noise, and transport). Effect estimates were relatively consistent across studies (I^2 = 0%), although more research is needed to confirm these findings ($N_{studies} < N_{fs}$).

Sensitivity Analysis

Examination of the forest plot for all 35 studies identified a single outlier effect from the study by Hassan et al (2014), as characterised by a large SD > ±2 (see Figure 4). Meta-analyses for physical functioning (i.e. physical daily activities, role physical, bodily pain, and vitality), psychological (role emotional and mental health), and social functioning (social interactions) QoL domains (Hassan et al., 2014) were subsequently re-run with the removal of this study. However, given that the contribution (i.e., weight) assigned to this study was small, its removal did not significantly change the overall effect size estimate or associated *p* value of any of these meta-analyses.

Subgroup Analysis

A subgroup analysis involving all 35 studies revealed large to very large *g* values, regardless of whether a generic (*g* = -0.824, 95% CI = -0.982 to -0.666, *p* <.001) or MS-specific measurement was used (*g* = -1.007, 95% CI, -1.434 to -0.580, *p* < .001). Differences in QoL ratings between these two subgroups were not statistically significant (*Q* (1) = .62, *p* = .431).

Multivariate Meta-Regression

A multivariate meta-regression to examine the combined contribution of mean age, years since diagnosis, and EDSS was statistically significant (Q_{model} = 8.84, *df* = 3, *p* = .03). The final model explained 38% of the overall variance in group QoL differences (see Table 8 & Appendix H). This suggests that a reduction in QoL among those with MS could, potentially, be explained by study-level covariates. More specifically, QoL following a diagnosis of MS may be associated with older age, longer disease duration, and physical impairment.

Table 8.

Multivariate meta-regression model

Covariate	Coefficient	Standard Error	95%CI		z-value	*p*
			Lower	Upper		
Intercept	0.518	0.600	-0.658	1.695	0.86	0.388
Years since diagnosis	-0.022	0.032	-0.084	0.039	-0.70	0.484
Mean age	-0.458	0.011	-0.085	-0.007	-2.32	0.020
EDSS	0.207	0.121	-0.029	0.443	1.72	0.086

CHAPTER 4

Discussion

Key Findings

Thirty-five empirical studies comparing QoL self-ratings of 3,493 persons with MS and 187,296 healthy controls were identified and included in this meta-analysis. The results were structured within four broad QoL domains: physical, psychological, social, and environment. Overall findings revealed that persons with MS perceived their global QoL to be significantly lower than that of peers without MS. There were, however, mixed results. The present findings highlight a need for further research, particularly the need to examine the interventional resources that contribute to QoL. The findings also highlight a need to conceptualise QoL as a multifaceted construct and to consider the potential role of demographic and clinical characteristics in maintaining QoL. The clinical implications of these findings, along with methodological limitations, are discussed below.

QoL domains

Given the underlying neurological impairments that occur to the central nervous system, it is not surprising that persons with MS perceive both their global and domain-specific QoL as being severely affected by their illness. Everyday activities for persons with MS become restricted due to their MS symptoms which negatively impacting on a person's perception of their ability to engage in activities that they used to. The largest groups differences were observed in the physical QoL domain, with physical summary scores (as measured by the SF-36) significantly reduced in persons with MS. This finding is consistent with previous QoL research, where persons with MS consistently report that their physical functioning (e.g., everyday activities) has been impacted during the course of MS (Gupta et al., 2013; Kerling et al., 2014; Newland et al., 2009; Postigo-Alonso, 2019). Persons with MS reported poor physical functioning, including difficulty engaging

in activities of daily living (e.g., self-care, walking indoors, and lifting heavy objects), role limitations (i.e., difficulty or limited ability to complete work or other everyday activities) often due to pain frequency and low physical and/or mental energy to engage in physical or social functions. However, it is important to note that this finding was, in part, based on the SF-36 which includes a composite physical summary score comprising physical functioning, role limitation due to physical difficulties, bodily pain, and general health. Interpreting physical summary scores in their present form is difficult due to possible overlapping effects from comorbid difficulties in the physical, mental, and social domains (Nortvedt et al., 2000). For example, when effect size estimates of bodily pain in persons with MS were compared with those of healthy controls, differences in scores were negative and significant. This is consistent with the underlying symptoms/outcomes of disease progression in persons with MS (Newland et al., 2009). The construct validity and reliability of the SF-36 instrument for identifying population differences in physical and psychological status, the health burden of chronic disease such as MS, and QoL in persons with inflammatory diseases such as MS has shown floor and ceiling effects in subsets of persons with MS (Bandari et al., 2010; Vickrey et al., 1995). Despite the noted floor and ceiling effects of the SF-36, the findings from the physical functioning scale in this meta-analysis supports the role limitations due to physical or psychological difficulties in persons with MS. The low sensitivity in the SF-36 instrument to detect the severity of change in physiological impairment and to measure MS-specific symptoms (i.e., chronic pain, sensory impairment, balance, and walking, and sexual dysfunction due to pain) are limitations that highlight a need for future studies to use the SF-36 instrument with a complemented diagnostic-specific instrument or symptoms checklist whenever it is possible and whenever the focus is on the impact of specific symptoms on QoL (e.g., the association between chronic pain and sexual dysfunction). Regardless of the subscale name, the mean difference in fatigue was significant when measured by the SF-36 (Contentti et al., 2017; Klevan, 2013; Nyland et al., 2019), but not significant when it was measured by the MSQOL-54

(Barry et al., 2018; Jarcaz et al., 2010). Given that the MSQOL-54 shares 36 items (i.e., vitality/energy) with the SF-36, this difference in result highlights a need for further investigation. Notably, fatigue or lack of energy is nominated as a physical and/or mental energy subscale in various QoL scales instruments (e.g., the SF-36 and the MSQOL-54): therefore, it is important to consider this difference when interpreting the results. To summarise, the findings in this meta-analysis confirm the unfavourable consequences of MS; a disease that has a negative impact on physical functioning. It is understandable, then, that persons with MS perceive their disrupted physical health as a major impediment to their daily functioning (Glavor et al., 2019; Jarcaz et al., 2010; Muhtaroglu et al., 2018).

Given the underlying neuropathologic alterations that occur to the central nervous system, and the unpredictability, fear, and physiological changes associated with MS, it is not surprising that persons with MS perceive more difficulties in their psychological domain. Overall mean differences were negative and statistically significant in this domain, namely when measured with composite QoL scales including role emotional (SF-36), mental health composite (MSQOL-54), and emotional wellbeing (QLI). In the majority of the included studies, the role emotional scores due to psychological difficulties, as measured by the SF-36, were significantly lower in persons with MS. That is, persons with MS rated higher incidence of emotional problems which impacted their daily activities (e.g., accomplished less work/tasks, and have not been careful when performed a task). The mental health composite score, as measured by the MSQOL-54, was negative and significant. It is important to be cautious when interpreting the mental health composite score since this score is a total score for five items: (a) anxiety, (b) depression, (c) loss of behavioural control, (d) loss of emotional control, and (e) psychological well-being. After validating the MSQOL-54 scale for MS, Vickrey et al. (1992) found that the psychological QoL domain in persons with MS was an overlap of different QoL domains such as physical well-being. The overall effect size estimates in psychological domains indicated a significant difference in emotional wellbeing

between persons with MS and healthy controls (Fruehwald et al., 2001). Persons with MS reported more depression, anxiety, and fatigue symptoms, poorer emotional wellbeing in general, and more difficulties with emotion regulation than did healthy controls. In contrast to the composite QoL scales (the SF-36 and the MSQOL-54), no significant differences were found between self-esteem, self-efficiency, mood, and global QoL between persons with MS and peers without MS (as measured by the WHO-5; Uccelli et al., 2016). Additionally, the FAMS scale includes 44 scored items in mobility, symptoms, emotional well-being, general contentment, thinking/fatigue, and family or social well-being. Similarly, in an empirical study where the FAMS was used to compare the mean difference in psychological QoL, no significant difference was found in emotional well-being and QoL in persons with MS and controls (Giovagnoi et al., 2019). The findings from later studies are consistent with psychological resilience and high self-esteem in persons with MS being associated with better coping with MS and, in turn, positive QoL (Black & Dorstyn, 2018; Chwastiak & Ehde, 2007). To summarise, although findings confirmed that MS negatively affected the psychological domain in persons with MS, it is crucial to interpret the results very carefully, given that the content of the QoL assessment instruments and the context in which the QoL is measured are highly influential. Future QoL research needs to regularly follow up their assessments of psychological domains in persons with MS. A possible result from this regular assessment might be early interventional programs such as those that target positive psychological factors (i.e., self-esteem and self-efficacy) to prevent or to decrease the amount of psychological impairment and to increase QoL in persons with MS.

The subjective impact of MS on the social QoL domain was large, negative, and significant. This suggests that persons with MS rate their global social activities (including participation in activities with friends, family, and community activity groups) as significantly compromised when compared to healthy controls (Fruehwald et al., 2001; Nyland et al., 2019; Solmaz et al., 2018). A range of factors may explain social impairments among persons with MS. The QoL domain

relating to social and occupational functioning was significantly affected. Particularly large differences in scores were observed for occupational impairment (as measured by the QLI instrument). Work impairment and long-term sick-leave have been shown to be more evident among persons with relapsing remitting MS rather than persons with progressive MS, possibly because a higher proportion of persons with relapsing remitting MS are still continuing their paid work (Nicholas et al. 2019; Nyland et al., 2019). Persons with MS have reported concerns about diminished work hours (e.g., doing less work compared to healthy controls performing similar jobs), fear of losing one's job, and financial instability, in addition to concerns about the impact of cognitive impairment on their occupational functioning (Nicholas et al., 2019; Nohara et al., 2019). While the loss of a job can significantly threatens a person's sense of identity and contribution to the social community, there is little evidence to determine whether occupational impairment is associated with greater disability severity, role limitations, or psychological factors such as cognitive impairment and depression (Halper, 2007; Rumrill, 2000; Nyland et al., 2019).

The overall effect size estimate for the environmental domain was negative, small to moderate, but significant. This suggests that the subjective perception of the environment may change, to some extent, for a person with MS. Notably less research was dedicated to the impact of MS on the environment where a person with MS lives in or makes a connection with, with only five studies contributing to this meta-analysis. The WHO-100 and the WHO-BREF were the QoL instruments that explicitly examined the environmental domain in persons with MS. Notably, the environmental domain in the WHO instruments centres around financial resources (Group, 1994). According to the Group (1994), regardless of whether a person with MS is employed or is unemployed, it is essential for QoL research to assess the extent to which a patient's financial resources can enable them to afford a healthy and comfortable life that could result in enhancing his/her QoL. Physical safety and security of the home and surrounding environment (e.g., level of freedom and feeling safe and secure in environment) were among the QoL items that were assessed

by the WHO instruments. QoL items also focused on how persons with MS rated the availability and quality of, and satisfaction with, health and social care providers; the support and encouragement that they received from health professionals, family, and friends; and the accessibility of transport services. Participation in leisure activities and a feeling of being understood even during temporary absence of MS symptoms, as well as their ability to communicate with others were rated. The significant impact of MS on the environmental QoL highlighted a need for further study, since the extent to which the environmental domain could have a role in QoL of a person with MS remains under-investigated to date.

Taken at face value, the combined findings from this meta-analysis could be interpreted to mean that all four QoL domains examined were overlapping. This is not surprising given that MS has heterogenous impacts on different aspects of heath. Indeed, MS has a large impact on how individuals perceive their quality of life within specific domains (i.e., physical, psychological, and social), but it can also alter the way that a person perceives and interacts with their environment. Previous studies have indicated that a higher quality of social relations helps to promote a better living environment for the person with MS, with subsequent improvements to their mood and energy levels in general (Rotstein et al., 2000).

Notably, the findings from the subgroup analysis indicated significant group differences in QoL, regardless of whether generic or MS-specific QoL assessment instruments were used. This is consistent with previous literature that suggests that both generic and MS-specific QoL instruments are appropriate to use in clinical and research practice (Papuc et al., 2012; Rotstein et al., 2000). Furthermore, the present findings revealed that while some of the composite scales were less sensitive to a QoL domain, namely the environmental domain (i.e., SF-36), other QoL instruments were highly sensitive to this domain (i.e., WHO-100 and WHO-BREF). These findings suggest that the importance of the environmental domain in QoL should not be underestimated and should be used, wherever possible, in future MS research. The SF-36 scale has demonstrated less

sensitivity to MS-specific symptoms, such as cognitive impairment, chronic pain, fatigue, imbalance, and visual impairment due to chronic disease (Busija et al., 2011; Kuspinar & Mayo, 2013). Indeed, generic QoL assessment instruments such as the SF-36 may be more sensitive to global QoL, but are less sensitive to hidden factors (i.e., sexual dysfunction, cognitive difficulties, muscle stiffness; Busija et al., 2011). The suggestion is that regardless of the validity and reliability of the SF-36, when the research interest is centred on specific clinical symptoms, the MS-specific QoL instrument is preferred.

Results of a multivariate meta-regression analysis confirmed the role of moderator variables including age, years since diagnosis, and severity of disability on QoL in persons with MS. Factors specific to individual QoL domains can help to explain the observed contribution of these moderator variables to reduced QoL. In terms of physical domain, studies have shown that level of self-care, independence, and physical exercise is higher among young persons with MS, but physical ability may reduce with age, as does the ability to carry out everyday activities (WHO, 1998). Moreover, pain and distress also increase with age, since there is a high rate of comorbidity of health dysfunction with older age (Busija et al., 2011; Labuz-Roszak et al., 2013). However, psychological risk factors, such as anxiety and depression level, have shown a U-shaped curve: they are high in young persons with MS who were diagnosed in younger age when they were planning for their future, but decrease in the group aged 45-54, and increase again after age 55 (WHO, 1998).

Clinical Implications and Future Research

The results from this meta-analysis have important clinical implications. In terms of QoL assessment, it is critical to select a QoL scale that is the most appropriate and sensitive to change in all domains of QoL. This decision can be particularly challenging for clinicians and researchers when there are a variety of reliable QoL assessment instruments available (Bandari et al., 2010).

For example, although the SF-36 (Ware, 2000) is the most commonly used scale among studies within this meta-analysis, it does not assess the impact of MS on cognition, sexual impairment due to pain, and environmental QoL that have been shown to have substantial effects on general QoL within the MS population. In contrast, MS-specific QoL scales such as MSQOL-54 (Vickrey et al., 1995) provide domain-specific information related to persons with MS (e.g., physiological symptoms such as bladder and bowel incontinence and sexual impairment). Therefore, it is recommended that future MS research includes a combination of both generic and disease-specific instruments in order to equally examine individual QoL domains.

Given that MS has a large and negative impact on global and individual QoL domains, it is important that evidence-based treatments that are multidisciplinary and provide specific and tailored support for persons with MS are provided soon after diagnosis. When the focus is on helping a person with MS to enhance his/her QoL, as well as to have a better perception of their QoL, it is important to formulate an intervention and care plan that is systematic and targets relevant QoL domains. This can be achieved by following the population, intervention, comparison, and outcome (PICO) approach. This approach emphasises the importance of the person-centred approach, which targets body functions, activities, and participation, as well as a person's interaction with the environment. There is sufficient evidence, from a systematic review and meta-analysis, that reducing sedentary time and increasing light to moderate physical activities in the form of walking, jogging, swimming, aerobic, resistance, or neuromotor exercise (e.g., yoga) is essential for promoting physical and psychological QoL in persons with MS (Alphonsus et al., 2019; Dauwan et al., 2019). This type of physical intervention, when provided as an add-on to medical treatments, can have a substantial positive effect on not only physical functioning, but also cognition and mood (Barry et al., 2018). It has even been recommended that exercise training would be more beneficial if done weekly or over a minimum eight-week period. Such physical activities could involve a structured or unstructured exercise program integrated within a

community or home setting, in order to promote the integration of physical activity into daily lifestyle and improve physical health and psychological wellbeing (Alphonsus et al., 2019; Barry et al., 2018; Dauwan et al., 2019).

Longitudinal studies have suggested that the use of attentional tasks or short-term cognitive training can also improve mental efficiency and mood in persons with MS (Brenk et al., 2007; Rosti et al., 2007). Indeed, the strong relationships noted between lower QoL, poor cognitive functioning, and depression warrants consideration of external remediation strategies, such as training of impaired and unimpaired abilities within selected cognitive tasks (Brenk et al., 2007). Additionally, psychological-based therapies, such as mindfulness and cognitive behavioural therapy, together with psycho-educational information have shown significant benefits by helping persons with MS to accept their current situation and to learn proactive positive coping strategies to promote QoL (Brenk, et al., 2007, McCabe et al., 2009; Rosti et al., 2007).

Strength and Limitations

The greatest strength of the current study is that it provides a substantial and a new quantitative overview of literature comparing global QoL between persons with MS and healthy controls. Incorporating individuals without MS is important as it allows the researcher to have a baseline to compare the effect of MS on QoL. Furthermore, in contrast to previous studies that mostly focused on measuring the impact of MS on three domains of QoL (i.e., physical, psychological, and social), the current study expanded this scope and included the fourth domain of QoL, namely the environmental domain. Thus, the current study expands the knowledge base regarding the importance of all domains of QoL.

However, the results from this meta-analysis must be considered in light of several limitations. Firstly, the findings were mainly focused on persons with relapsing remitting MS with a mild to moderate disability (EDSS < 3.2); therefore, findings cannot be generalised to a broader

MS population. This is a typical bias found within the inclusion criteria of much of the MS literature. It is crucial, then, that future research is more inclusive of persons with progressive MS (e.g., more physical and psychological impairment), so that the results can be broadly generalised.

Secondly, while grouping outcomes into four individual QoL domains was more efficient in terms of data analysis and captured the potential factors related to lower QoL in persons with MS, it was also problematic due to a significant overlap between MS clinical symptoms (e.g., physical and mental composite summaries, social functioning, and environmental wellbeing). Moreover, categorisation of subscales within this review under broad QoL domains was a challenge. For example, the role limitation due to physical health subscale of the SF-36 was operationalised as an impairment to physical health, but could equally be studied as an impairment to the role limitation due to emotion, environmental well-being, and/or social functioning, given that individuals were required to rate the degree to which their physical functioning slowed or stopped their physical activity within their surrounding environment or reduced social participation.

Thirdly, the results from this meta-analysis were mainly obtained from cross-sectional studies, which restricted the detection of QoL to a single point in time (Gupta et al., 2014). Consequently, no inferences can be made about causality between lower QoL in persons with MS and the longitudinal effects of MS on QoL over time (Nohara et al., 2017). Longitudinal studies should be conducted in the future, in order to better understand QoL domains and their trajectories over time, particularly in response to changing symptom profiles.

Finally, it is important to highlight that low-income countries were not well represented in sample studies. Future studies need to recognise (a) international differences in health, health care, and health care delivery models, (b) that patient health outcomes could be influenced by urban-rural geographic status, (c) potential environmental barriers (e.g., physical, financial, and social) that

could impact health and quality of life of individuals with MS in the long-term, and (d) the potential international differences in priorities for functional recovery among individuals with MS.

Conclusions

The findings from this meta-analysis highlight the most important and affected domains of QoL, from the perspective of persons with MS themselves. MS has a significant and substantial impacts across all domains. While the proportion of persons with MS is relatively smaller than healthy controls, the importance of QoL in persons with MS is highly important from patient, clinical practice, and policy decision perspectives. The findings necessitate the need for QoL to be routinely measured in clinical research and practice as a study outcome, with multidisciplinary interventions provided on an ongoing basis to ensure that care needs are met during all stages of disease progression.

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Appendices

Appendix A

Logic Grids

Quality of life **AND** **Multiple sclerosis**

Database	Quality of life	Multiple Sclerosis
PsycINFO	Quality of life.sh OR Quality of work life.sh OR Quality of life. Tw OR Quality of work life. Tw OR Quality of working life.tw OR Quality of work$ life. Tw OR QOL.tw	Multiple sclerosis.sh OR Multiple scleros*.tw OR Disseminated sclerosis.sh OR Disseminat$ scleros*.tw
Embase	'Quality of life'/de OR 'Quality of life':ti,ab OR 'Quality of work life':ti,ab OR 'Quality of working life':ti,ab OR 'life quality':ti,ab OR QOL:ti,ab	'Multiple sclerosis'/de OR 'Multiple scleros*':ti,ab OR 'disseminated scleros*':ti,ab
PubMed	"Quality of life"[mh] OR Quality of life[tw] OR life quality[tw] OR Quality of work life[tw] OR Quality of working life[tw] OR QOL[tw]	"Multiple sclerosis"[mh] OR Multiple scleros*[tw] OR disseminated scleros*[tw]
CINAHL	MH"Quality of life" OR TI"Life quality" OR AB"Life quality" OR TI"Quality of life" OR AB"quality of life" OR TI"quality of working life" OR AB"quality of working life" OR TI QOL OR AB QOL	MH"multiple sclerosis" OR TI"multiple scleros*" OR AB"multiple scleros*" OR TI"disseminated scleros*" OR AB"disseminated scleros*"
Scopus	"Quality of life" OR "life quality" OR "quality of working life" OR "Quality of work life" OR QOL	"Multiple sclerosis" OR "Multiple scleros*" OR "disseminated scleros*"

Appendix B

Table 1.

Validated Generic and MS-specific Measures

	No items	Domains	Lead author(s)
Generic ($N_{studies}$ = 31)			
SF-36	36	Physical HRQoL Composite (PCS): Physical function, Role-physical, Bodily Pain, General Health Perceptions. Mental HRQoL Composite (MCS): Vitality, Mental Health, Social Functioning, Role Emotional.	Ware & Sherbourne, 1992
WHOQOL-100	100	Overall HRQoL: Physical health, psychological, level of independence, social relations, environment, spirituality/ personal beliefs	Power, 1999
SF12V2	12	Physical HRQoL Composite (PCS): General health rating, moderated activities, climb several flights, accomplished less tasks than would like, limited in kind of work or other activities, pain interference in daily Mental HRQoL Composite (MCS): Accomplished less than would like, did work or activities less carefully than usual, felt Peaceful, felt Energetic, felt blue/sad, problems interfered in social activities	Ware, 2002
EuroQoL 5D	5	EQ-5D: motor skills, taking care of self, normal daily activities, presence and severity of pain, mood disorders EQ-VAS is an analogue visual scale: Assessing the general health status and disease activity.	Brooks & the EuroQol Group, 1996
WHO-5	5	Subjective quality of life based on positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested), and general interest (being interested in things)	WHO, 1998
SIP	136	Physical dimension: Ambulation, mobility, body care and movement, sleep and rest, eating, work, home management, recreation, and pastimes. Psychological dimension: Social interaction, alertness behaviour, emotional behaviour, communication	Bergner, 1981

Table 1. *Continued*

	No items	Domains	Lead author(s)
QLI	10	Physical and Emotional Well-being, Self-care and Independence, Occupational and Interpersonal Functioning, Social Emotional and Community Support, Personal and Spiritual Fulfilment and overall QOL	Ferrans & Powers, 1992
HUI3	46	Vision, hearing, speech, ambulation, dexterity, emotion, cognition, pain	Feeny, 1996
WHOQoL-BREF	24	Physical health function: pain and discomfort, sleep and rest, energy and fatigue, mobility, activity of daily living, dependence on medicinal substances and medical aids, work capacity Psychological function: positive feelings, thinking, learning, memory and concentration, self-esteem, bodily image and appearance, negative feelings, spirituality/religion/personal belief Social relationships: Personal relationships, social support, sexual activity Environment: Freedom, physical safety and security, home environment, financial resources, health, and social care: accessibility and quality, opportunities for acquiring new information and skills, participation in and opportunities for recreation/leisure activity, physical environment (pollution/noise/traffic/climate) transport.	WHOQOL Group, 1998
FSQ	34	Physical function, basic activities of daily living (ADL), intermediate ADL.	Jette, 1986
15D	15	Physical health function: breathing, speech, vision, mobility, usual activities, vitality, hearing, eating, eliminations, sleeping, sexual activities, discomfort and symptoms. Psychological function: mental function, distress, depression	Sintonen 2001
Specific ($N_{studies}$=6)			
FAMS		*Overall QOL:* symptoms, mobility, family/social wellbeing, general contentment, thinking/fatigue, emotional well-being.	Cella, 1996
HAQUAMS	38	Fatigue/cognitive functioning, mobility/lower extremities, mobility/upper extremities, social function, mood, sensory symptoms, vision, bladder/Bowel/Sexuality, communication, handicap.	Gold, 2001

Table 1. *Continued*

	No item	Domains	Lead author(s)
MSQOL-54	54	All included SF-36 scales plus cognitive function, sexual function, health distress. Three original SF-36 subscales (vitality or energy/fatigue, social role function, bodily pain) modified by supplementing one additional question relevant to MS for each.	Vickrey, 1995
RAYS QOL	50	Physical, Psychological, Social familial.	Rostein, 2000

Abbreviations: SF-36 = Short-Form 36 Health Status Survey; WHOQOL-100 = World Health Organisation Quality of Life-100; SF-12v2 = Short Form 12 Version 2; EQ-5D = Europe Quality of life-5D; EQ-VAS = Europe Quality of Life Visual Analogue Scale; WHO-5 = WHO-Five Well-being Index; SIP = The Sickness Impact Profile; QLI = Quality of Life Index; HUI3 = The Health Utilities Index Mark 3; WHOQOL-BREF = The Health-Related Quality of Life Assessment;
FSQ = Functional Status Questionnaire; FAMS = Functional Assessment of Multiple Sclerosis; HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis; MSQoL-54 = Multiple Sclerosis Quality of Life-54 Questionnaire; RAYS= RAYS scale; 15D = Self-reported quality of life questionnaire

Appendix C: Study Characteristic

Table 2.

Characteristics of included studies ($N_{studies}$ = 35)

Lead author (citation)	Country	Years since diagnosis (Mean ± SD)	Sample size		Age (Mean ± SD)		QOL measure(s)	MS recruitment	Design
			MS (F:M)	HC (F:M)	MS	HC			
Barry (2018)	Ireland	5.9 ± 1.2	9 (8:1)	10 (8:2)	35.3 ± 2.1	36.00 ± 2.04	MSQOL-54	MS society	Longitudinal
Brenk (2007)	Germany	3-10	27 (15:12)	14 (7:7)	43.5 ± 8.9	39.6 ± 10.2	HAQUAMS	Outpatient clinic	Longitudinal
Contentti (2017)	Argentina	5.2 ± 4.3	74 (46:28)	87 (57:30)	37.5 ± 8.9	34.6 ± 10.4	SF-36	Neurology clinic	Cross-sectional
Fritz (2016)	USA	11.9 ± 8.7	29 (17:12)	29 (20:9)	48.7 ± 11.5	50.8 ± 11.6	MSQOL-54 SF-36	Neurology clinic	Cross-sectional
Fruehwald (2001)	Austria	7.6 ±6.2	60 (40:20)	60 (35:25)	38.5 ± 7.8	36.5 ± 9.8	QLI	Hospital	Longitudinal
Giovagnoli (2019)	Italy	8.7 ± 6.2	22 (6:16)	66 (38:28)	39.00 ± 9.3	49 ± 15.1	WHOQOL-100	Hospital	Cross-sectional
Glavor (2019)	Croatia	-	30 (22:8)	30 (22:8)	37 ± 9.7	38 ± 6.8	SF-36	Outpatient clinic	Cross-sectional
Goverover (2016)	USA	12.6 ± 8.2	41 (38:3)	32 (23:9)	46.7 ± 8.6	43.8 ± 9.5	FAMS	Support groups	Cross-sectional
Gupta (2014)	USA	12.50	536 (349:187)	74,451 (38,161:36,290)	49.0 ± 12.0	47.9 ± 16.4	SF12v2	National survey	Cross-sectional
Hassan (2014)	Egypt	-	30 (20:10)	30 (20:10)	31.7 ± 6.8	35.3 ± 9.1	SF-36	Neurology clinic	Cross-sectional
Hayter (2016)	UK	5.1 ± 3.2	42 (34:8)	21 (17:4)	42.7 ± 10.3	40.5 ± 10.7	QLI	Neurology clinic	Cross-sectional
Hoogs (2011)	USA	11.7 ± 8.3	132 (96:36)	26 (15:11)	46.4 ± 10.3	43.6 ± 11.5	SIP	MS care centre	Cross-sectional
Isernia (2019)	Italy	21.2 ± 10.9	42 (24:18)	26 (19:7)	52.4 ± 10.3	51.4 ± 12.4	MSQOL-54	Outpatient clinic	Cross-sectional
Jaracz (2010)	Poland	6.9 ± 6.0	210 (150:60)	108 (74:34)	37.4 ± 10.2	37.3 ± 9.2	MSQOL-54	Neurology clinic	Cross-sectional

Table 2. *Continued*

Lead author (citation)	Country	Years since diagnosis (Mean ± SD)	Sample size		Age (Mean ± SD)		QOL measure(s)	MS recruitment	Design
			MS (F:M)	HC (F:M)	MS	HC			
Jones (2008)	Canada	-	302 (206:96)	109741 (55,858:55,883)	48.7 ± 18.6	44.8 ± 8.5	HUI3	Community survey	Cross-sectional
Kerling (2014)	Germany	-	60 (44:16)	48 (36:12)	44.0 ± 10.4	40.0 ± 13.7	SF-36 HAQUAMS	MS society & Neurology clinic	Cross-sectional
Klevan (2014)	Hordaland	2.32	93 (64:29)	96 (69:27)	41.8 ± 9.6	44.4	SF-36	Neurology clinic	Cross-sectional
Labuz-Roszak (2013)	Poland	7.1 ± 6.1	61 (45:16)	30 (20:10)	38.6 ± 11.4	32.5 ± 10.3	EQ-5D EQ-VAS	Neurology clinic	Cross-sectional
McCabe (2009)	Australia	-	382 (238:144)	291 (190:101)	45.3	45.5	WHOQOL-100	MS society	Longitudinal
Meeus (2014)	Belgium	6.9 ± 5.8	19 (13:6)	39 (24:15)	38.1 ± 15	42.4 ± 11	SF-36	Neurology clinic	Cross-sectional
Muhtaroglu (2018)	Cyprus	12.6 ± 7.9	24 (16:8)	24 (16:8)	43.5 ± 10.5	43.1 ± 10.3	SF-36	Neurology clinic	Cross-sectional
Murphy (1998)	France Germany UK	11.8 ± 7.7	267 (172:95)	90 (60:30)	43.2 ± 10.9	43.4 ± 10.9	FSQ	Hospital	Cross-sectional
Newland (2009)	USA	8.7 ± 7.3	40 (40:00)	40 (40:00)	43.8 ± 9.2	43.4 ± 10.3	SF-36	University clinic	Cross-sectional
Nicholas (2019)	USA	-	196 (137:59)	784 (553:231)	45.2 ± 11	45.3 ± 11.2	SF-36v2 EQ-5D	National survey	Cross-sectional

Table 2. *Continued*

Lead author (citation)	Country	Years since diagnosis (Mean ± SD)	Sample size		Age (Mean ± SD)		QOL measure(s)	MS recruitment	Design
			MS (F:M)	HC (F:M)	MS	HC			
Nohara (2017)	Japan	-	96 (59:37)	480 (319:161)	47.5 ± 14.2	46.2 ± 17.1	SF-36v2 EQ-5D	National survey	Cross-sectional
Nyland (2019)	Norway	8.5 ± 1.0	43 (33:10)	96 (69:27)	47 ± 10	44 ± 9	SF-36	MS society	Cross-sectional
Odabas (2018)	Turkey	8.62	64 (00:64)	60 (00:60)	37.2 ± 8.8	37.5 ± 6.4	SF-36	University clinic	Cross-sectional
Papuc (2012)	Poland	8.9 ± 6.6	173 (121:52)	86 (59:27)	36.9 ± 8.9	38.4 ± 11.1	WHOQOL-100	Neurology clinic	Cross-sectional
Philips (2014)	Scotland	7.9 ± 5.5	31 (23:8)	31 (25:6)	44.0 ± 9.3	44.5 ± 9.7	WHOQOL-BREF	Research database	Cross-sectional
Potsigo-Alonso (2019)	Spain	8.3 ± 6.4	23 (18:5)	24 (16:8)	46.03 ± 8.1	41.4 ± 11.4	MSQOL-54	Neurology clinic	Case-controlled
Prakash (2019)	USA	9.4 ± 7.8	100 (85:15)	98 (86:12)	45.5 ± 9.5	46 ± 9.4	WHOQOL-BREF	Online	Cross-sectional
Rostein (2000)	Israel	8.2 ± 3.6	50 (27:23)	50 (27:23)	44.1 ± 8.3	45.2 ± 6.9	RAYSs QoL SF-36	Hospital	Cross-sectional
Rosti (2007)	Finland	9.1 ± 5.9	45 (33:12)	48 (33:15)	42.7 ± 8.3	42.3 ± 7.4	15D	Hospital	Longitudinal
Solmaz (2018)	Turkey	8.9	42 (42:00)	41 (41:00)	41.9 ± 8.1	39.7 ±7.3	SF-36	Neurology clinic	Cross-sectional
Uccelli (2016)	Italy	5.3 ± 3.2	89 (75:14)	109 (94:15)	24.2 ± 2.8	22.1 ± 2.7	WHO-5	Online	Case-controlled

Abbreviations: (-) data not provided or reported; SD, Standard Deviation; MS, Multiple Sclerosis; HC, Healthy Control; MSQOL-54 = Multiple Sclerosis Quality of Life 54-item; SIP = Sickness Impact Profile; SF-36 = Short-Form 36-item Health Status Survey; QLI = Quality of Life Index; WHOQOL-100 = World Health Organisation Quality of Life-100; FAMS = Functional Assessment of Multiple Sclerosis; SF-12v2 = Short Form 12 Version 2; HUI3 = Health Utilities Index Mark 3; HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis; EQ-5D = Europe Quality of life-5D; EQ-VAS = Europe Quality of life with Visual Analogue Scale; WHO-5 = WHO-Five Well-being Index; FSQ = Functional Status Questionnaire; RAYS = RAYS scale; MSIS29 = Multiple Sclerosis Impact Scale 29; WHOQOL-BREF = Health-Related Quality of Life Assessment.

Appendix D : PRISMA Checklist

Table D1.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Checklist (Moher et al., 2009).

Section/topic	#	Checklist item	Reported on page
TITLE	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	iv
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8-9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	10-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	58
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10-11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11,12; 59, 60, 61
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	13

Table D1. Continued

Section/topic	#	Checklist item	Reported on page
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11-12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) if done, indicating which were pre-specified	13-16
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	17-19
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	17, 18; 62, 63, 64
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	67-68
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	20; 23-31
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	20; 23-31
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	21, 24
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	32-33
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	34-41
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	42-43
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	44
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	N/A

Appendix E: Assessment of Study Reporting Quality

Table E1.

NIH Assessment Tool for Observational Cohort, and Cross-Sectional studies ($N_{studies}$ = 35)

Lead author (year)	1: Research question or objective clear	2: Population clearly defined	3: Participation rate ≥ 50%	4: Groups recruited from the same population. Inclusion and exclusion applied uniformly	5: Sample size, power, variance, and effect estimate provided	6: QoL is measured	7: Study examined different QoL domains	8: QoL measures are defined	9: Tools or methods for measuring QoL were accurate and reliable	10: Potential confounding variables measured and adjusted for impact	Rating overall
Barry, 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Brenk, 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Contentti, 2017	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Fair
Fritz, 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Fruewald, 2001	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Giovagnoli, 2019	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Glavor, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Goverover, 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Gupta, 2014	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Fair
Hassan, 2014	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Hayter, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Hoogs, 2011	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Good
Isernia, 2017	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Jarcaz, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jones, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kerling, 2014	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Klevan, 2013	Yes	yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Labuz-Roszak, 2013	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
McCabe, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Meeuse, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Muhtarglou, 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Murphy, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Table E1. *Continued*

Lead author (year)	1: Research question or objective clear	2: Population clearly defined	3: Participation rate ≥ 50%	4: Groups recruited from the same population. Inclusion and exclusion applied uniformly	5: Sample size, power, variance, and effect estimate provided	6: QoL is measured	7: Study examined different QoL domains	8: QoL measures are defined	9: Tools or methods for measuring QoL were accurate and reliable	10: Potential confounding variables measured and adjusted for impact	Rating overall
Nicholas, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Nohara, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Nyland, 2019	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Odabas, 2017	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Newland, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Papuc, 2012	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Philips, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Postigo-Alonso, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Parakash, 2019	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Rostein, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Rosti, 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Solmaz, 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good
Uccelli, 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Good

Standardisation key derived from: ⩽ 50% = Poor, 50%-75% = Fair, > 75% = Good

Appendix F: Overlapping Samples

Included studies and studies using overlapping samples.

Included studies	Studies using overlapping samples
McCabe, 2009	McCabe & McKern, 2002
	McCabe & Battista, 2004
	McCabe, 2005
	McCabe, 2006
Phillips, 2014	Phillips, Henry, Summers & Whyte, 2011
Jones, Pohar, Warren, Turpin & Warren, 2008	Pohar, Jones, Warren, Turpin & Warren, 2007

Appendix G

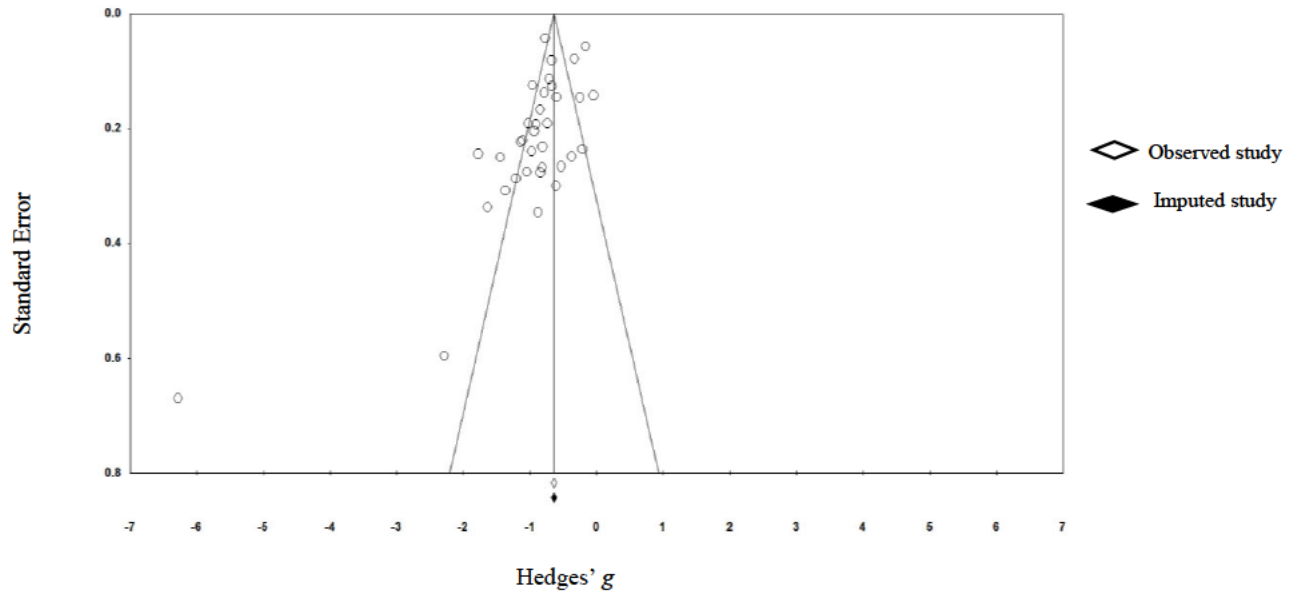

Figure 5: Funnel plot of QoL ratings across all studies ($N_{studies}$= 35)

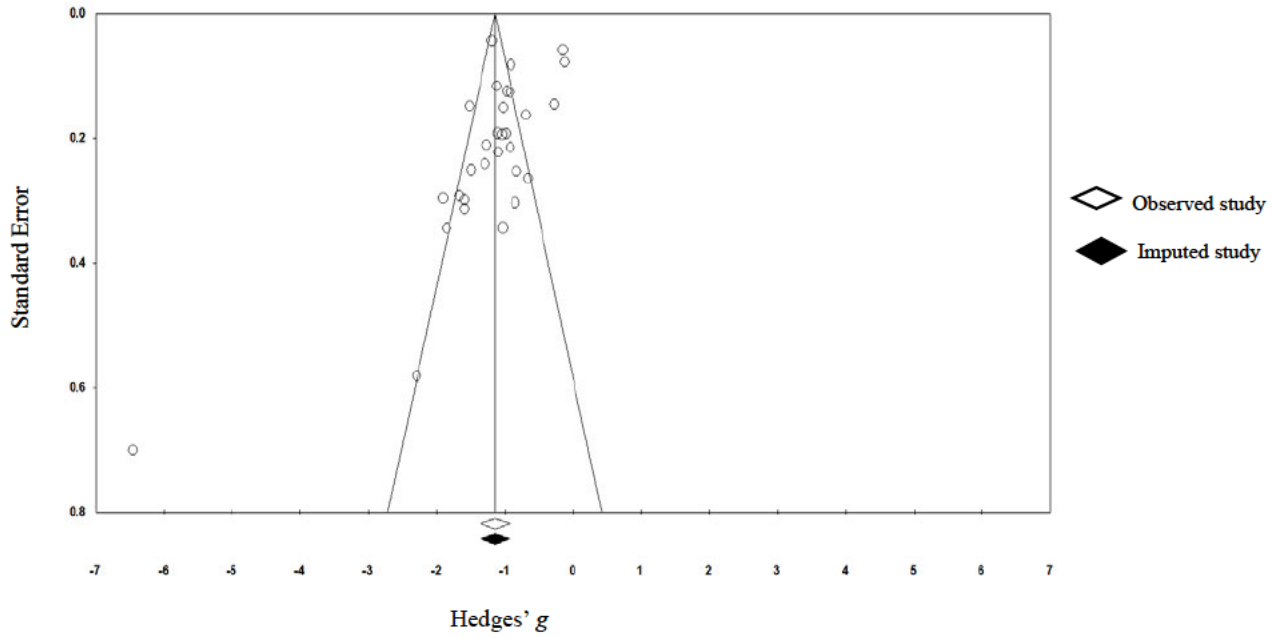

Figure 6. Funnel plot of physical QoL ratings ($N_{studies}$ = 30)

Appendix G

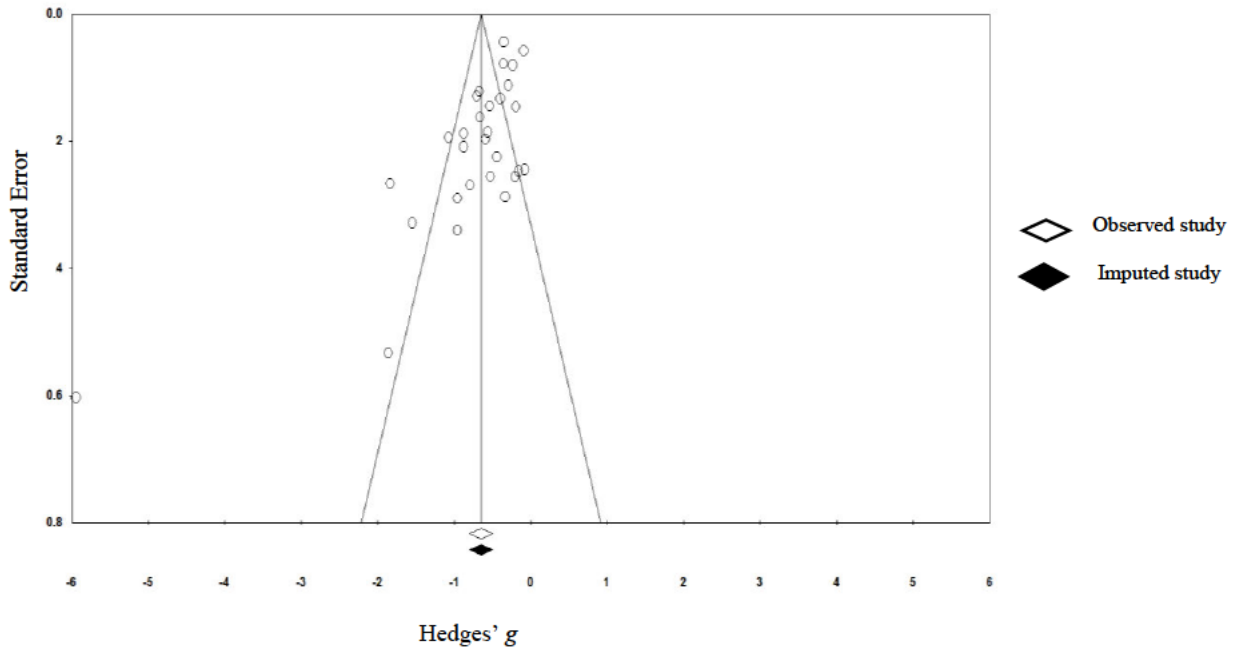

Figure 7. Funnel plot of psychological QoL ratings ($N_{studies}$ = 29)

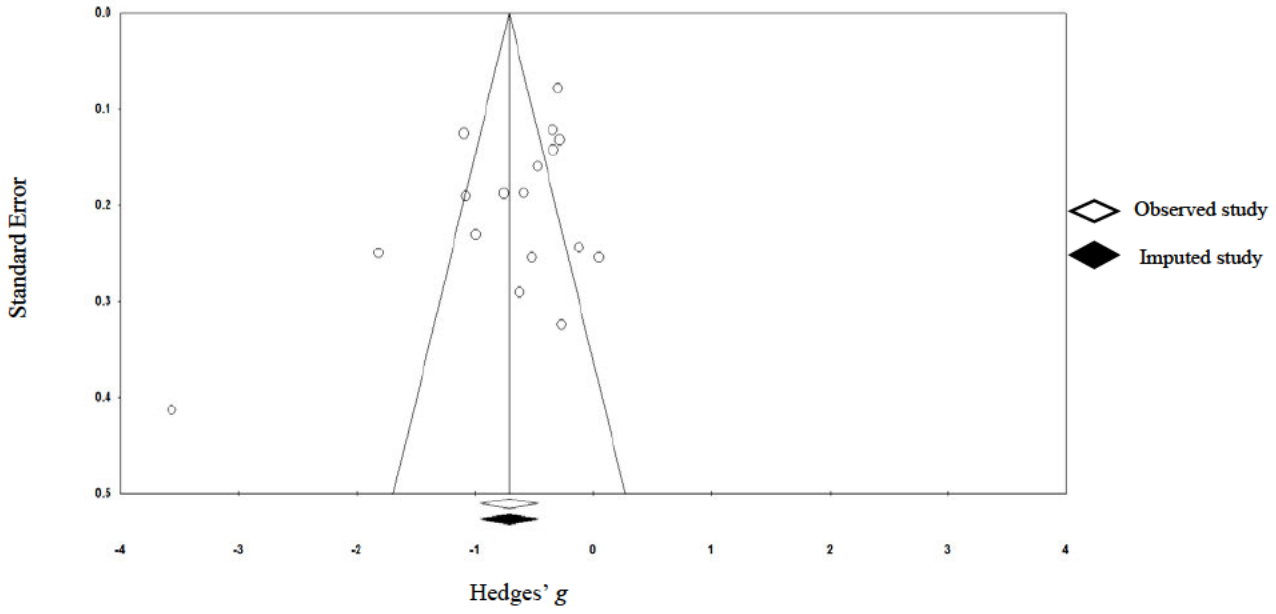

Figure 8. Funnel plot of social QoL ratings ($N_{studies}$ = 17)

Appendix H

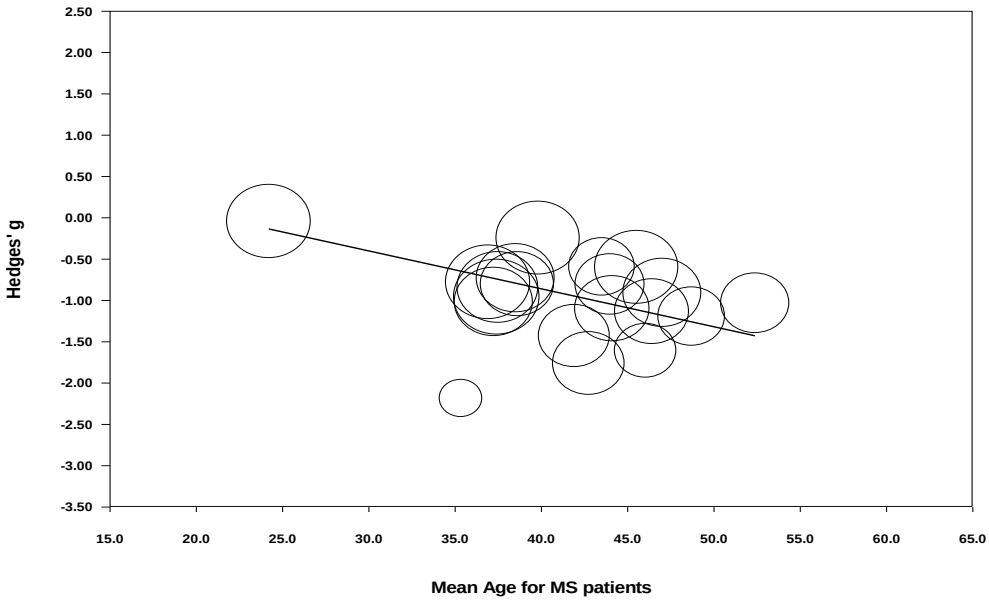

Figure 9: Regression scatterplot with mean age as covariate

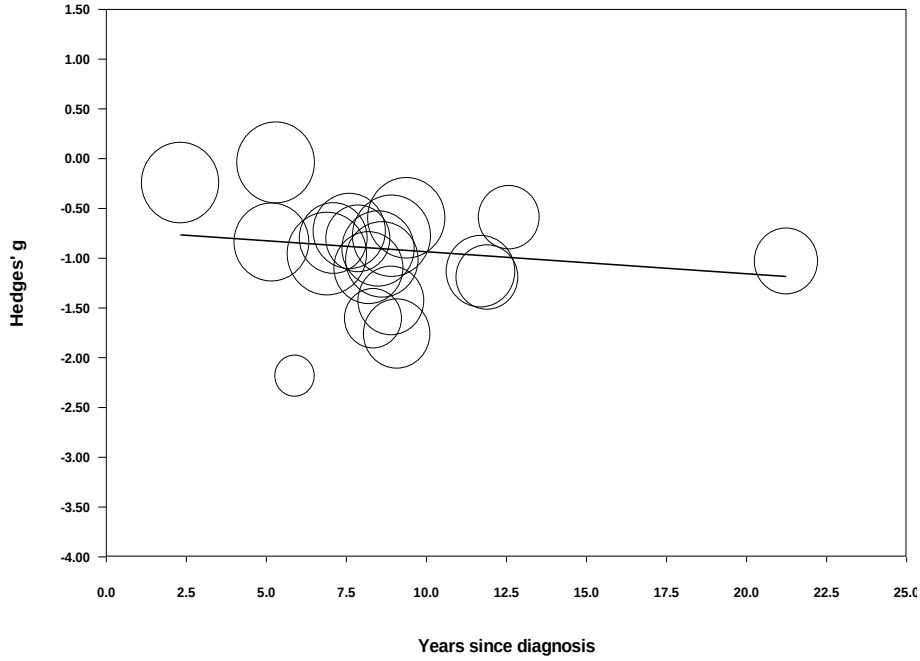

Figure 10: Regression scatterplot with years since diagnosis as covariate

Appendix H

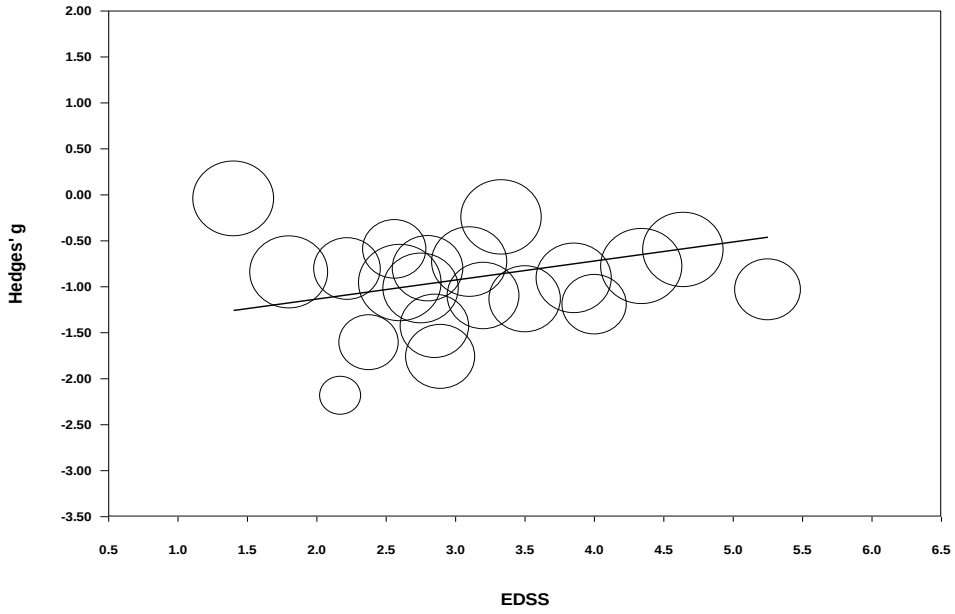

Figure 11: Regression scatterplot with disability severity (EDSS) as covariate