BMJ Open

Quality of life in adults with Multiple Sclerosis: a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041249
Article Type:	Original research
Date Submitted by the Author:	03-Jun-2020
Complete List of Authors:	Gil-González, Irene; Universidad de Sevilla, Personality, Assessment, and Psychological Treatment Martín-Rodríguez, Agustín; Universidad de Sevilla, Department of Personality, Assessment, and Psychological Treatment Conrad, Rupert; Department of Psychosomatic Medicine and Psychotherapy, University of Bonn, Bonn, Germany Pérez-San-Gregorio, María Ángeles; Universidad de Sevilla Facultad de Psicologia, Personality, Assessment, and Psychological Treatment
Keywords:	Multiple sclerosis < NEUROLOGY, MENTAL HEALTH, Adult neurology < NEUROLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Quality of life in adults with Multiple Sclerosis: a systematic review

Irene Gil-González[a*], MD, igil2@us.es

Agustín Martín-Rodríguez[a*], PhD, amartinr@us.es

Rupert Conrad[b*], MD, Rupert.Conrad@ukbonn.de

María Ángeles Pérez-San-Gregorio[a*], PhD, anperez@us.es

[*]All authors have contributed equally.

[a]Department of Personality, Assessment, and Psychological Treatment, University of Seville, Seville, Spain.
[b]Department of Psychosomatic Medicine and Psychotherapy, University of Bonn, Bonn, Germany.

Corresponding author: Irene Gil-González. Department of Personality, Assessment, and Psychological Treatment. Faculty of Psychology, Camilo José Cela s/n, 41018-Seville (Spain).
Phone: +34954556939. E-mail: igil2@us.es.

ABSTRACT

Objective

In recent years, quality of life (QoL) in multiple sclerosis (MS) is considerably gaining relevance in clinical research and practice. Against this backdrop the current systematic review aims to give a broad overview over clinical, sociodemographic and psychosocial risk or protective factors for QoL in adults with MS and analyzes psychological interventions to improve QoL.

Method

The literature research was conducted in Scopus, Web of Science and ProQuest electronic data bases. Document type was limited to articles written in English, published from 2014, January 1st to 2019, January 31st. Information of the selected articles were extracted using a coding sheet and qualitatively synthesized.

Results

4886 records were identified by the search strategy. After removing duplicates and screenings, 106 articles met the inclusion and exclusion criteria for qualitative synthesis and were assessed for study quality. Disability, fatigue, depression, cognitive impairments, and unemployment were consistently identified as risk factors for QoL, whereas higher self-esteem, self-efficacy, resilience and social support proved to be protective. Regarding psychological interventions for QoL the review analyzed a wide spectrum of different approaches such as mindfulness, cognitive-behavioral therapy, self-help groups as well as self-management. The vast majority of interventions was successful in improving different aspects of QoL.

Conclusion

Treating risk factors and promoting protective factors is vital in improving QoL in patients with MS in ordinary care practice highlighting the relevance of an adequate biopsychosocial assessment.

Key words

Multiple sclerosis, quality of life, protective and risk factors, mental and physical quality of life.

Abbreviation

QoL= Quality of life, MS= multiple sclerosis, EDSS= Expanded Disability Status Scale, PwMS= People with Multiple Sclerosis, WHO= World Health Organization, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SF-36= Short Form Health Survey 36, MSQoL-54= Multiple Sclerosis Quality of Life-54, MCS= mental composite score, PCS= physical composite score, ACT= acceptance and commitment therapy, MSIS-29= multiple sclerosis impact scale.

Strengths and limitations of this study

-First systematic review on risk factors and psychological interventions for quality of life in multiple sclerosis for more than a decade.

-Comprehensive and robust search strategy as well as strict inclusion criteria to cover all the relevant evidence.

-Careful and standardized assessment of risk of bias in all 106 included studies.

-Heterogeneity of studies only allows for qualitative synthesis of results.

-Huge amount of publications makes a limitation of included studies to the time-span between 2014, January 1st to 2019, January 31st necessary.

1. Introduction

Multiple Sclerosis (MS) is a chronic neurodegenerative condition, characterized by a wide range of symptoms and a highly unpredictable prognosis, which can severely affect patients quality of life (QoL).[1-4]

The constitution of the World Health Organization (WHO) declares health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[5] QoL is a multidimensional concept that encompasses the domains included in the cited definition of health.[1,6] Its introduction in the medical literature dates back to 1960[7] with a continuously growing relevance up to now.[8]

In recent years, the number of published research on MS QoL has highly increased.[1,9] Besides providing practitioners useful information on the impact of symptoms and therapy on patients life, QoL is a predictor of disease progression.[10,11]

Considering its relevance in health care research and practice, there is an urgent need to synthetize the available scientific evidence. This systematic review aims at analysing risk and protective factors related to QoL in MS as well as relevant psychological interventions.

2. Methodology

The current systematic review was completed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Ethical approval (or informed consent) was not necessary because the present study is a review of prior publications.

2.1 *Search strategy*

The systematic search focused on journal articles published between 2014, January 1st to 2019, January 31st. The data bases consulted were: Scopus, Web of Science and ProQuest, the search was performed in February and March 2019. The following key words were used: ("multiple sclerosis") AND ("quality of life" OR "health-related quality of life" OR "well-being" OR "wellbeing" OR "life satisfaction"). The search terms were markedly wide to guarantee the greatest coverage of literature. The search field was limited to "title/abstract" and language was limited to "English". There is no published systematic review on this topic in Cochrane Library.

2.2 *Study selection*

Firstly, title and abstract screening was carried out to identify suitable articles for full text screening. The screening process was performed independently by two investigators. Any disagreement about study selection was resolved by consensus with a third reviewer.

Inclusion criteria were set as following:

1. Studies primarily focusing on QoL determinants as well as psychological interventions to improve QoL.
2. Study participants aged above 18 years with a confirmed MS diagnosis.

The following exclusion criteria were applied:

1. Non-psychological intervention.
2. No primary research studies (systematic reviews, meta-analysis, protocols or clinical guidelines were excluded).
3. Studies focused on the development and validation of quality of life measurement instruments.
4. QoL risk or intervention studies aiming at health behavior, physical activity or pharmacological treatment were excluded.

5. Studies focusing on the comorbidity with another illness or mental health diagnosis.

6. Sample selection based on a special condition (for example: only employees or PwMS under certain pharmacological treatment).

7. Studies not using a validated QoL measurement tool.

2.3 *Quality assessment*

The methodological quality of the included studies was appraised based on a well-established standardized 12-items Checklist.[13] Every item represents a methodological feature: inclusion/exclusion criteria, methodology/design, attrition rate, attrition between groups, exclusions after, follow up, occasion of measurements, pre/post measures, dependent variables, control techniques, construct definition and imputing missing data. The codification criteria proposed by the checklist authors was followed. No article was excluded in the quality appraisal phase.

2.4 *Data abstraction*

Data extraction from selected articles was carried out based on a coding sheet. The coding sheet was previously elaborated and piloted by consensus. The extracted information includes: title, authors and publication year, country (city), design, sample characteristics, studied variables and measurement tools, main results and conclusions. After the extraction process was completed, the obtained information was independently reviewed by two authors to avoid mistakes and missing data.

Conducting a meta-analysis was not possible due to the heterogeneity of study designs and outcomes, so a narrative synthesis was undertaken.

3. Results

3.1 Literature screening

A total of 4886 articles were initially identified from SCOPUS, Web of Science and ProQuest. After removing duplicates and abstract analysis, 188 studies were eligible for full text screening. Finally, 106 were selected for the narrative analysis. The selection process is detailed in a PRISMA flow diagram (Figure 1).

Figure 1 around here

3.2 Methological quality

The methodological quality scoring of the included articles by the 12-Check-list is summarized in table 1.

Table 1

Methodological quality of articles (n = 106)

Inclusion criteria		Design			Attrition		Attrition between groups		Exclusion after		Follow up period		Occasion of measurement		Same pre-post measurement		Normalization of D.V. measurement	Control techniques		Construct definition	Imputing missing data	
Yes	No or N/A*	Pre-experimental	Quasi experimental	Experimental	Yes	No or N/A*	Yes	No or N/A*	Yes	No or N/A*	Yes	No or N/A*	One	Two or more	Yes	N/A		Yes	No or N/A*		Yes	No or N/A*
99	1	7.7	33.7	58.7	48.1	51.9	28.9	62.9	22.1	77.9	32.7	67.3	70.2	29.8	70.2	29.8	100	70.2	29.8	100	19.2	80.8

No or N/A* = the item is not proceeded or does not appear

3.3 Study characteristics

The included articles were analyzed according to their primary and secondary outcomes. Concerning the articles objectives, 70 studies aimed at analyzing risk and protective factors for QoL (Table 2), 11 focused on the development of QoL at different ages and time points in disease history (Table 3) and 25 studied the effect of a psychological intervention on QoL in MS (Table 4).

All the included articles employed standardized and validated QoL measurement; 64 studies evaluated QoL with a generic measure and 50 studies made use of a disease-specific measure. Short Form Health Survey 36 (SF-36) was mainly used (n = 29) as a generic measure and Multiple Sclerosis Quality of Life-54 (MSQoL-54) (n = 28) as a disease-specific measure. Finally, 11 studies used more than one measure to evaluate QoL. The study designs were mostly cross-sectional (n = 74), and sample sizes ranged from 7 to 74451 participants.

In the following section a summary of the main findings from the included articles is provided.

3.4 Risk and protective MS QoL factors

Factors influencing PwMS QoL are summarized in Table 2.

3.4.1 Clinical factors

Concerning MS characteristics, functional impairment as assessed by the EDSS level was one of the leading causes of QoL diminishment.[14-24] Disease duration, [19,20] MS progressive type,[15,25,26], progressive MS onset[27] and relapses in the last three months were pointed out as further relevant factors negatively affecting QoL. [15]

Several studies found a significant association between the severity and number of symptoms and the decline of QoL in MS.[22,26,28-30] The symptom fatigue was identified as a main risk factor.[17,18,28,29,31-41]

A number of articles stated the importance of sensory[42,43] and motor [38,41,43,44] dysfunctions on quality of life, including: paralysis, walking difficulties, balance, stiffness, and spasms as motor problems and low sensory sensitivity and sensation avoidance as sensory problems. Specifically, the role of pain[23,28,39,40,44,45] and spasticity[38,46,47] were emphasized.

Bladder dysfunction,[23,48,49] bowel dysfunction,[23] sexual,[49-51] and sleeping[23,28,37,52,53] problems contributed to the deterioration of QoL.

Diverse cognitive impairments, for instance, cognitive fatigue, memory loss and planning/organization dysfunction, were recognized as risk factors by a number of studies.[28,39,41,42,54-56] Sgaramella et al[57] showed that the preservation of executive functioning is a protective factor of QoL.

3.4.2 Psychosocial factors

3.4.2.1 Emotional symptoms

There were investigations pointing out the beneficial effect of emotional stability on QoL,[58] as well as the damaging effect of emotional problems.[41,59] The most studied outcome among emotional symptoms was depression [17,18,21,23,24,28,29,40,44,55,58,60-64] followed by anxiety.[28,29,40,58,60-63,65] Both symptoms were confirmed as risk factors for QoL in MS. Similarly, high levels of perceived stress,[26,29,30] anger expression-in[63] and apathy[18] were identified as factors

related to emotional regulation negatively affecting QoL in MS.

3.4.2.2 Personality domains

The role of personality domains has been explored in several studies. Cyclothymic and depressive temperament were associated with a lower QoL in MS, in contrast to hyperthymic temperament, which was associated with higher QoL.[66] Another investigation recognized extraversion as a personality trait related to higher QoL levels.[58] Additionally, Cioncoloni et al.[23] recognized introverted personality as a risk factor for QoL in MS. Finally, personality type D was another relevant factor related to lower QoL.[67]

3.4.2.3 Coping strategies

In reference to coping strategies, the eligible studies showed consistent results; active coping, problem resolution, the planning of problem solving, cognitive positive restructuring, emotional and instrumental social support, emotional expression, acceptance, and growth were related with higher QoL in MS.[40,60,68-71] In addition, Grech et al[69] found a similar connection with restrained coping, Strober[40] with the use of humor, and Mikula el at[71] with stopping unpleasant emotion coping. Conversely, problem avoidance,[60,70] behavioral disengagement,[40,69] distancing,[70] self-distraction,[68] denial,[40,68] emotion-focused and venting coping,[69] social withdrawal,[60] wishful thinking,[60] self-criticism,[60,70] suppression,[69] and self-controlling coping[70] were associated with lower QoL.

Coping strategies were also identified as relevant mediator variables for QoL. Problem focused, emotional focused, and stopping unpleasant emotion coping were partial mediators between fatigue[72] or type D personality[73] and QoL as measured by the mental composite score (MCS).

3.4.2.4 Other psychological factors

According to Van Damme et al[74], acceptance of the illness is a protective factor for QoL. Differently, the role of flexible adjustment and tenacious goal pursuit in achieving personal blocked goals was not so clear, findings showed a tendency towards a positive relationship.

Resilience was confirmed as a protective factor of QoL in MS.[16,75] Moreover, Koelmel et al[76] highlighted its role as a mediator variable in the relation between social support and MCS.

High levels of self-efficacy,[40,77] self-esteem,[77] illness identity[77] and sense of coherence[78] correlated with higher QoL. Self-esteem played a mediational role in the relationship of social support with MCS.[79] Ultimately, cognitive fusion, the extent to which people feel fused or attached to their thoughts, mediated the relation between stigma and QoL in MS.[80]

3.4.2.5 Social factors

Social support[81] and participation[82] were positively related with QoL, several mediator variables affecting this relationship were mentioned above.

3.4.3 Demographic factors

Employment was found to be the leading sociodemographic factor influencing QoL. Several studies displayed an association of unemployment with lower QoL.[19,23,43,56,83] Other studies showed a positive correlation between jobs adapted to disability,[83] job match and job satisfaction,[30] high employment status,[22,30] and QoL in MS. Low socioeconomic status[24] as well as financial straits[26] were also risk factors for lower QoL.

Brola et al[19,20] noted that not having access to an adequate pharmacological treatment put QoL in danger. Congruently with this finding, Boogar et al[24] recognized a positive treatment experience as a protective factor.

Regarding other socio-demographic variables male sex,[26] older age,[19,20] not being married or living with significant others[26] were related with poorer QoL in MS, whereas high educational level was a protective factor.[22]

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (mean) Sex (Female%)	Main results: Risk factors	Main results: Protective factors
Clinical variables					
Gupta et al (2014)[14]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 74451 47.9 years 51.3 %	EDSS (PCS)	
Gross et al (2017)[25]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 810 RRMS 48.9years SPMS 55.7 years RRMS 71.6 % SPMS 56.2 %	Progressive MS type (PCS)	
Zhang et al (2019)[27]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D)	N = 1958 55.3 years 78.1%	Progressive MS type, onset	
Rezapour et al (2017)[15]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 171 35.7 years 76.6%	Relapses in the last 3 months	Mild EDSS RRMS Type
Marck et al (2017)[45]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 2296 45.5 years 82.2%	Pain	
Milinis et al (2016)[46]	Cross- sectional	Leeds MS Quality of Life Scale (MSQoL)	N = 701 48.8 years 72%	Spasticity	
Zettl et al (2014)[47]	Cross- sectional	EuroQol 5-Dimensions (EQ-5D) Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 414 48.6 years 64.3 %	Spasticity	
Leonavicius et al (2016)[31]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 137 44.7 years 72.3%	Fatigue (MCS)	
Garg et al (2016)[32]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 89 54.26 years 66%	Fatigue	
Fernández-Muñoz et al (2015)[33]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 108 44 years 55%	Fatigue	
Weiland et al (2015)[34]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 2738 45.5 years 82.3%	Fatigue	
Aygünoğlu et al (2015)[35]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 120 34.24 years 70 %	Fatigue	
Wister et al (2015)[36]	Cross- sectional	World Health Organization Disability Assessment Schedule (WHODAS) 2.0	N = 210 50.8 years 72.4 %	Fatigue	

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Protective factors
Tabrizi et al (2015)[37]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 217 36.2 years 79 %	Fatigue Poor sleep quality Low MCS (PCS)	
White et al (2019)[53]	Cross- sectional	EuroQol 5-Dimensiones (EQ-5D)	N = 531 51.60 years 70.1 %	Sleep disorder	
Barin et al (2018)[38]	Cross- sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS)	N = 855 48 years 72.7 %	Fatigue Balance Spasticity Paralysis Walking difficulties	
Kratz et al (2016)[39]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 180 50.5 years 78 %	Fatigue (MCS) Pain (MCS) Memory loss (MCS)	
Colbeck et al (2018)[42]	Cross- sectional	RAND-36 Health Item Survey (RAND-36)	N = 30 - 73.33%	Cognitive fatigue Low sensory sensitivity Sensation avoiding	
Grech et al (2015)[54]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 107 48.8 years 77.6 %	Cognitive inflexibility	
Sgaramella et al (2014)[57]	Cross- sectional	Quality of life questionnaire (QoL)	N = 39 42.2 years 71.8 %		Executive function
Khalaf et al (2016)[48]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 1048 47.8 years 81%	Lower urinary tract symptoms	
Vitkova et al (2014)[49]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 223 38.4 years 67.3 %	Bladder dysfunction (PCS) Sexual dysfunction (MCS)	
Qaderi et al (2014)[50]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 132 36.9 years 100 %	Sexual problems (PCS and MCS)	
Schairer et al (2014)[51]	Cross- sectional	Short-Form Health Survey 12 (SF-12)	N = 6138 50.6 years 74.7 %	Sexual dysfunction	
Ma et al (2017)[52]	Cross- sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 231 40.2 years 58.4 %	Sleep disorders	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results: Risk factors	Main results: Protective factors
Psychosocial variables					
Ledesma et al (2018)[60]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 26 39.2 years 57.5%	Problem avoidance Social withdrawal Wishful thinking Self-criticism Anxiety Depression	Problem resolution Cognitive restructuring Emotional social and instrumental support Emotional expression
Grech et al (2018)[69]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 107 48.8 years 77.57%	Behavioral disengagement Suppression and self-control Emotional venting	Acceptance Growth Restrain
Zengin et al (2017)[68]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 214 36-46 years 53.2%	Self-distraction Denial Substance use	Planning Active coping Acceptance Positive reinterpretation Social support
Farran et al (2016)[70]	Cross- sectional	Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL)	N = 34 36 years 56%	Self-criticism Escape avoidance Distancing Self-controlling	Emotional social support Instrumental social support Planful problem solving Positive reappraisal
Mikula et al (2014)[71]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 113 40.8 years 77 %		Problem focused coping Stopping unpleasant emotion Getting support
Van Damme et al (2016)[74]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 117 41 years 70.2 %		Acceptance (PCS and MCS) Tenacious goal pursuit (PCS) Flexible goal adjustment (MCS)
Wilski et al (2016)[77]	Cross- sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 257 47.9 years 69.93%		Self-efficacy Self-esteem Illness identity
Tery-Hurwit et al (2018)[75]	Cross- sectional	Function Neutral Health-Related Quality of Life Short Form (FuNHRQOL-SF)	N = 259 48.6 years 84.23%		Resilience Self-compassion
Calandri et al (2018)[78]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 90 37 years 61.1 %		Sense of Coherence
Fernández-Muñoz et al (2018)[64]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 108 44 years 55 %	Depression	
Pham et al (2018)[65]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 310 49 years 73.6 %	Anxiety	
Prisnie et al (2018)[61]	Longitudinal (T1 = basal level/ T2 = 2 weeks later)	Short Form Health Survey 12 (SF-12)	N = 139 40 years 70.5%	Anxiety Depression	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Protective factors
Alsaadi et al (2018)[62]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 80 35.1 years 65 %	Anxiety Depression	Alsaadi et al (2018)[62]
Labiano-Fontcuberta et al (2015)[63]	Cross- sectional	Functional Assessment of Multiple Sclerosis (FAMS)	N = 157 41.7 years 66.9%	Depression Anxiety Anger expression	
Paziuc et al (2018)[58]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 60 46 years 85 %	Trait anxiety State anxiety Depression	Extraversion Emotional Stability
Phillips et al (2014)[59]	Cross-seccional	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N = 32 44.0 years 75 %	Emotional problems	
Salhofer-Polanyi et al (2018)[66]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 139 40.0 years 70.5%	Depressive temperament Cyclothymic temperament	Hyperthymic temperament
Demirci et al (2017)[67]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 74 35.3 years 65.51%	Type D personality	
Mikula et al (2015)[82]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 116 40.4 years 72.4%		Social participation (MCS y PCS)
Costa et al (2017)[81]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 150 41.7 years 70.7%		Social support
Clinical, psychosocial, and demographic variables					
Nakazawa et al (2018)[16]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 63 41.7 years 66.67 %	EDSS level	Resilience
Ciampi et al (2018)[17]	Cross-sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 43 57.2 years 65.1 %	EDSS level Fatigue Depression	
Fernández-Jiménez et al (2015)[21]	Cross-sectional	Functional Assessment of Multiple Sclerosis (FAMS)	N = 97 47.3 years 82.5 %	EDSS level Depression	
Klevan et al (2014)[18]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 93 41.8 years 69 %	EDSS (PCS) Fatigue Depression Apathy	
Williams et al (2014)[44]	Cross-sectional	Short-Form Health Survey 36 (SF-36) Short-Form Health Survey 12 (SF-12)	N = 447 49.3 years 70.02 %	Pain (PCS) Muscle spasms (PCS) Stiffness (PCS) Depression (MCS)	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Protective factors
Hyncicova et al (2018)[29]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 67 32.3 years 53.7%	Number and severity of symptoms Fatigue Stress Depression Anxiety	
Shahrbanian et al (2015)[28]	Cross- sectional	Person Generated Index (PGI)	N = 188 43 years 74%	Pain Fatigue Irritability Anxiety Depression Sleep disorder Cognitive deficit	
Strober et al (2018)[40]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 69 40.4 years 89.5%	Pain Fatigue Behavioral disengagement Denial Depression Anxiety High neuroticism Low extroversion Low self-efficacy	Acceptance Growth Emotional social and instrumental support Planning Active coping Positive reinterpretation Humor
Wymecka et al (2018)[41]	Cross-sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 137 46.5 years 53.3 %	Fatigue Upper-limb disability Lower-limb disability Cognitive disorders Emotional problems	
Tamartzis et al (2014)[55]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 100 40.5 years 64 %	Perceived planning/organization dysfunction Perceived retrospective memory dysfunction Depression	
Brola et al (2016)[20]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS) Multiple Sclerosis Impact Scale (MSIS-29)	N = 2385 37.8 years 69.7%	EDSS level MS duration Lack of DMD treatment Age	
Brola et al (2017)[19]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS) Multiple Sclerosis Impact Scale (MSIS-29)	N = 765 44.9 years 67.7 %	EDSS MS duration Be unemployed Age No immunomodulatory therapy	
Abdullah et al (2018)[43]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 200 35.1 years 68%	Motor symptoms Low resistance Sensory symptoms Low income Be unemployed	

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Risk factors	Main results Risk factors
Nickel et al (2018)[22]	Cross-sectional	Multiple Sclerosis International Quality of Life (MusiQoL)	N = 1220 47.8 years 76 %	EDSS Comorbidity	High educational level High employment status
Campbell et al (2017)[56]	Cross-sectional	Functional assessment of multiple sclerosis (FAMS) EuroQol 5-Dimensions (EQ-5D)	N = 62 49.4 years 69.35%	Cognitive deficit Be unemployed	
Chiu et al (2015)[83]	Cross-sectional	Short Form Health Survey 12 (SF-12)	N = 157 43.8 years 86%	Be unemployed	Disability adjusted employment
Boogar et al (2018)[24]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 193 38.1 years 64.8 %	High disability Depression Low socioeconomic status	Positive story treatment
Bishop et al (2015)[30]	Cross-sectional	Quality of Life Scale (QOLS)	N = 1839 54 years 78.1 %	Number and severity of symptoms Perceived stress	High educational level High employment status Job satisfaction Job match
Cioncoloni et al (2014)[23]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 57 41.7 years 68.42%	EDSS level Fatigue Pain Bladder dysfunction Bowel dysfunction Depressive manifestation Sleeping problem Introverted personality Be unemployed	
Cichy et al (2016)[26]	Cross-sectional	Quality of Life Scale (QOLS)	N = 703 63 years 76 %	Progressive MS Progressive diagnosis Number and severity of symptoms Perceived stress Be male Not married/not living with significant other Unable to meet living expenses	
Mediational variables				*Mediator variable*	*Mediated relation*
Mikula et al (2016)[73]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 156 40 years 75 %	Coping strategies Problem focused Emotional focused Stopping	Personality type D and MCS
Mikula et al (2015)[72]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 154 40.05 years 76%	Coping strategies	Fatigue and MCS and PCS
Mikula et al (2017)[79]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 74 35.3 years 65.51%	Self-esteem	Social participation and MCS

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results: Risk factors	Main results: Risk factors
Koelmel et al (2017)[76]	Longitudinal (T1 = basal level/ T2 = 10 weeks later/ T3 = 26 weeks later/ T4 = 52 weeks later)	Short Form Health Survey 8 (SF-8)	N = 163 52.2 years 87.1%	Resilience	Social support and MCS
Valvano et al (2016)[80]	Cross- sectional	Leeds MS Quality of Life Scale (MSQoL)	N = 128 45.5 years 85%	Cognitive fusion	Stigma and QoL

EDSS = expanded disability status scale; PCS = physical composite; RRMS = remittent remitting; SPMS = secondary progressive; MS= multiple sclerosis; MCS = mental composite score; DMD = disease modifying drug; QoL = quality of life

3.5 Disease history

Table 3 summarized the characteristics of studies focusing on QoL at different ages and time points in disease history. Some of the selected studies examined QoL in MS at the earliest years. According to Possa et al[84], in the first year of diagnosis QoL assessed by MCS and physical composite score (PCS) decreased. Stern et al[85] showed the worst QoL in the youngest group of MS patients.

During the first three years of diagnosis, Calandri et al[86] found that problem solving and avoidance coping have a positive effect on QoL. Nourbakhsh et al[87] also studied factors influencing the development of QoL in the first three years. The results showed that higher baseline levels of fatigue and depression predicted worse QoL assessed by the PCS, whereas lower cognitive functioning and higher fatigue predicted worse MCS.

Another study focused on QoL in MS at an advanced age. Buhse et al[88] identified neurological impairment, physical disability, depression, and the comorbidity with thyroid disease as risk factors for worse QoL assessed by PCS in an elderly MS sample. On the contrary, being widowed and employed was identified as a protective PCS factor.

Regarding MS progression, Kinkel et al[89] pointed out that a second clinical event consistent with clinically defined MS, higher EDSS at the time of diagnosis and an earlier MS onset predicted a decrease in PCS 10 years after the diagnosis. Besides, Bueno et al[90] indicated that a progression from benign MS to non-benign MS predicted a decrease in PCS 25-30 years after the diagnosis.

Among the longitudinal predictors of QoL, studies identified the following. Longer MS duration predicted worse QoL 2 years later,[91] and worse EDSS predicted worse QoL 2,[91] 6,[92] and 10[93] years later. Depression predicted worse QoL 6[92] and 10[93] years later, and higher pain[94] and cognitive impairment[93] predicted worse QoL 10 years later.

Table 3
Characteristics of included studies

Authors, Publication year	Study design (T1: /T2:…)	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Years of diagnosis				
Possa et al (2017)[84]	Cross-sectional	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 38 32.9 years 58%	Decrease in MCS (38%) and PCS (19%) in the first year after diagnosis.
Calandri et al (2017)[86]	Cross-sectional	Short Form Health Survey 12 (SF-12)	N = 102 35.8 years 61.8%	Problem solving ($\beta = 0.28$) and avoidance ($\beta = 0.25$) was related to a higher MCS in the first 3 years of diagnosis.
Nourbakhsh et al (2016)[87]	Longitudinal (T1 = basal level/ T2 = 3 months after diagnosis/ T3 = 6 months after diagnosis/ T4 = 12 months after diagnosis/ T5 = 18 months after diagnosis/ T6 = 24 months after diagnosis / T6 = 36 months after diagnosis)	Short Form Health Survey 36 (SF-36)	N = 43 36 years 72%	Baseline severity of fatigue and depression predicts PCS and cognitive function and fatigue MCS in the first 3 years of diagnosis.
MS progression				
Kinkel et al (2015)[89]	Longitudinal (T1 = CIS diagnosis/T2 = 5 years after diagnosis/ T3 = 10 years after diagnosis)	Short Form Health Survey 36 (SF-36) Multiple Sclerosis Quality of Life Inventory (MSQLI)	N = 127 34.1 years 74%	A second clinic event consistent with CDMS, higher EDSS at the diagnosis and an earlier onset CDMS predicts a decrease in
Bueno et al (2014)[90]	Cross-sectional (25-30 years after diagnosis)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 61 54.9 years 83.6%	Patient changing from benign (EDSS<3) to non-benign (EDSS>3) decreases PCS.
Years of MS duration				
Baumstarck et al (2015)[91]	Longitudinal (T1 = basal level/ T2 = 24 months later)	Multiple Sclerosis International Quality of Life questionnaire (MusiQol) Short-Form Health Survey 36 (SF-36)	N = 526 40.0 years 74.3%	Low levels of QoL, higher MS duration and higher EDSS level at T1 predicted worse QoL at T2.
Tepavcevic et al (2014)[92]	Longitudinal (T1 = basal level/ T2 = 3 years later/ T3 = 6 years later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 93 41.5 years 71%	Higher EDSS and depression at basal level predicted a decrease of QoL at T1 and T2.
Young et al (2017)[94]	Longitudinal (T1 = basal level/ T2 = 7 years later/ T3 = 10 years later)	Assessment of Quality of life (AQoL)	N = 70 59.8 years 71.6%	Higher pain predicts a decrease in QoL.
Chruzander et al (2014)[93]	Longitudinal (T1 = basal level/ T2 = 10 years later)	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analog Scale (EQ-VAS) Sickness Impact Profile (SIP)	N = 118 49 years 72%	Cognitive impairment, depressive symptoms and EDSS predicted a decrease in QoL at T2.
Group age				
Stern et al (2018)[85]	Cross-sectional	Multiple Sclerosis Quality of Life Instrument (MSQOL-54)	N = 57 50 years 73.7%	The youngest group (35-44) presents worst PCS vs the oldest (55-65).
Buhse et al (2014)[88]	Cross-sectional	Multiple Sclerosis Quality of Life–54 (MSQOL- 54)	N = 211 65.5 years 80%	Risk of neurologic impairment, physical disability, depression, and the comorbidity of thyroid disease was associated with decrease in PCS. Being widowed and employed was associated with increase in PCS.

MCS = mental composite score; PCS = physical composite score; CIS = clinical isolated syndrome; CDMS = clinical defined multiple sclerosis; EDSS = expanded disability status scale; QoL = quality of life.

3.6 Interventions

The details of the selected articles of psychological interventions are presented in Table 4.

3.6.1 Based on Mindfulness

All intervention programs showed improvements in QoL at some evaluation point and at least in some QoL domains. A body-affective mindfulness intervention increased the general QoL score up to 6 months after the treatment.[95]

Three studies investigated mindfulness-based stress reduction programs and two studies showed a significant increase in QoL after the treatment.[96-98] One study[98] resulted just in a small and insignificant increase after the treatment and at the follow up 3 months after the intervention.

Moreover, the community based mindfulness program treatment resulted in a significant increase in MCS.[99]

Finally, mindfulness-based cognitive therapy did not show significant differences in general QoL between the control and the experimental group, but it showed significant differences in the following aspects of QoL: health distress, mental well-being, role limitation due to emotional problems and cognitive performance.[100]

3.6.2 Cognitive-behavioral

A wide spectrum of cognitive behavioral interventions were analysed.

In a study by Case et al[101] the experimental group underwent 10 weekly sessions of 1 hour of healing light guided imagery. The results revealed a greater increase of QoL in the intervention group compared to the active control group exposed to 10 hours of positive journaling.

Blair et al[102] focused their intervention on emotion regulation. The design consisted on 16 bi-weekly sessions of 1.5 hours during 8 weeks. The intervention resulted in a significant increase in QoL 6 months after the treatment.

The interventions by Calandri et al[103] and Graziano et al[104] applied a comparable design. Participants were divided into two subgroups based on age. The intervention comprised 4-5 sessions of 2 hours over the course of 2 months, and 1 follow up session 6 months after the treatment. Calandri et al[103] also included 1 follow up session 12 months after the treatment. The intervention group experienced an increase in QoL at the follow up in both studies.

Three studies[105-107] focused their intervention on depressive symptoms. Kiropoulos et al[105] and Chruzander et al[106] found improvements in QoL at post-treatment and follow up assessment points. Kikuchi et al[107] also found a post-treatment improvement but did not reach significant levels.

Two of the retrieved studies based their intervention on Acceptance and Commitment Therapy (ACT). Pakenham et al[108] implemented an 8 weeks session program aimed to train resilience. The results showed an increase in QoL after the treatment and 3 months later. Besides, Proctor et al[109] implemented an 8 weeks intervention comprising telephone calls plus self-help ACT books. No significant increase of QoL was observed.

3.6.3 Based on social and group support

Among interventions founded on social and group support, the following made an impact on QoL in MS.

Abolghasemi et al[110] implemented a 12 sessions Supportive-expressive therapy program, which resulted in an improvement of QoL.

Jongen et al[111] investigated an intensive social-cognitive wellness program, which involved the inclusion of the partner or another significant informal caregiver. The results showed an increase in MCS 1, 3 and 6 months post-

treatment, and in PCS 6 months after the treatment. The results of the program were evaluated again 12 months after the treatment. The relapsing-remittent MS group displayed an increase in PCS and MCS. [112]

Eliášová et al[113] found in MS patients an improvement across several QoL domains after attending Self-help groups, in comparison to patients who did not visit Self-help groups. Liu et al[114] detected an increase in physical and psychological QoL in women with MS after participating in a 1 hour twice a week 8 weeks Hope based group therapy program.

3.6.4 Based on symptoms and self-management

Two studies analyzed a self-management fatigue group therapy. Mulligan et al[115] study reported positive but not significant changes in QoL after the treatment. Thomas et al[116] reported significant positive changes in physical health assessed by the Multiple Sclerosis Impact Scale (MSIS-29) and vitality as measured by the SF-36 in the intervention group 12 months after the treatment.

In addition to fatigue self-management, Ehde et al[117] focused in their intervention on pain and depression self-management. The results were compared to an educational program. There was a higher QoL post-treatment and 12 months follow-up score in the self-management group. Feicke et al[118] implemented a program focused on MS self-management. As in Ehde et al[117] improvements in QoL were maintained at 6 months follow up.

3.6.5 Other psychological intervention

LeClaire et al[119] investigated a 5 weeks program based on positive psychology. The results showed only a significant improvement in the SF-36 vitality subscale.

Table 4

Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Based on Mindfulness					
Carletto et al (2017) [95]	Body-affective mindfulness (BAM)	Longitudinal (T1 = basal level /T2 = post-treatment /T3 = 6 months later)	Functional Assessment of Multiple Sclerosis (FAMS)	N = 45 44.1 years 71.1%	Increase in general score FAMS from T1 to T2 (P< 0.001) and from T2 to T3 (P= 1).
Besharat et al (2017) [96]	Mindfulness-based stress reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Short Form Health Survey 36 (SF-36)	N intervention/ control= 35 years 100%	Increase in general QoL score in the intervention group (P< 0.05).
Blankespoor et al (2017) [97]	Mindfulness-based Stress Reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 25 52.6 years 84%	Increase PCS (P< 0.001).
Simpson et al (2017) [98]	Mindfulness-based Stress Reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 3 months later)	Multiple Sclerosis Quality of Life Inventory (MSQLI)	N = 25 43.6 years 92%	Small and insignificant increase QoL from T1 to T2 (P= 0.48) and insignificant increase from T2 to T3 (P= 0.71).
Spitzer et al (2018) [99]	Community-based group mindfulness	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 8 weeks later)	Short Form Health Survey 36 (SF-36)	N = 23 48.4 years 91.3%	Increase MCS from T1 to T2 (P= 0.008).
Ghodspour et al (2018) [100]	Mindfulness-based Cognitive Therapy (MBCT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 15/ 36 years 100%	Increase in health distress (P=0.032), mental well-being (P 0.001), role limitation due to emotional problems (P= 0.005) and cognitive performance (P= 0.04) subscales.
Cognitive behavioral					
Case et al (2018) [101]	Trial of healing light guided imagery (HLGI)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 9/ 8 49.1 years -	Increase in PCS (P= 0.01) and MCS (P< 0.01) in the intervention group.
Blair et al (2017) [102]	Dialectical Behavior Group Therapy (TCD)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 6 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 10/ 40.4 years 90%	Increase in MSQoL-54 from T1 to T3 (P= 0.01).
Calandri et al (2017) [103]	Group-based cognitive behavioral therapy (CBT)	Longitudinal (T1 = pre-treatment/ T2 = 6 month post-treatment/ T3 = 1 year post-treatment)	Short Form Health Survey 12 (SF-12)	N intervention/ control= 54/ 38 years 61%	Increase in MCS T2 in the CBT group vs control (P= 0.036). Increase in MCS T3 in the CBT group vs control (P= 0.049).
Graziano et al (2014) [104]	Group-based cognitive behavioral therapy (CBT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 6 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 41/ 42.3 years	Increase in MSQoL-54 at T3 in the CBT group vs control group (P< 0.05).

Table 4
Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
				66%	
Kiropoulos et al (2016) [105]	Cognitive behavioral therapy (CBT) for depressive symptoms	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 20 weeks later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 15/ 34.6 years 86.7%	Differences between control and CBT group MCS and PCS in T2 and T3 (P< 0.001).
Chruzander et al (2016) [106]	Cognitive behavioral therapy (CBT) focused on depressive symptoms	Longitudinal (T1 = basal level/ T2 = 3 weeks post-treatment/ T3 = 3 months post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29) EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analog Scale (EQ-VAS)	N = 15 38 years 80%	Improvement in QoL from MSIS-29 and EQ-5D in T2 and T3 (P< 0.05).
Kikuchi et al (2019) [107]	Cognitive behavioral therapy (CBT) on depression	Longitudinal (T1 = pre-treatment/ T2 = mind-treatment/ T3 = post-treatment)	Functional Assessment of Multiple Sclerosis (FAMS)	N = 7 46.1 years 71.4%	Positive but not significant increase in FAMS (P> 0.05).
Pakenham et al (2018) [108]	Resilience Training Program (ACT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 3 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 37 39.4 years 73%	Increase in PCS (P< 0.001) and MCS (P< 0.006) from T1 to T2, maintained at T3, without significant changes.
Proctor et al (2018) [109]	Telephone-supported acceptance and commitment bibliotherapy (ACT)	Longitudinal (T1 = pre-randomization / T2 = 12 weeks after randomization)	EuroQol 5-Dimensions (EQ-5D)	N intervention/ control= 14/ 45.8 years 78%	No significant increase in QoL (P= 0.62).
Based on social and group support					
Liu (2017) [114]	Hope-Based Group Therapy (HBGT)	Longitudinal (T1 = pre-treatment / T2 = post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29)	N intervention/ control= 18/ 35.1 years 100%	Physical and psychological QoL increase in HBT group (P< 0.05).
Abolghasemi et al (2016) [110]	Supportive-Expressive Therapy (SE)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N intervention/ control= 16/ 31.8 years 41.7%	Increase QoL from T1 to T2 (P<0.001).
Jongen et al (2016) [112]	Intensive social cognitive treatment (can do treatment) with participation of support partners	Longitudinal (T1 = basal level/ T2 = 12 months post-treatment)	Multiple Sclerosis Quality of Life Instrument (MSQoL-54)	N = 38 - 65.8%	PCS increase (P= 0.032) and MCS (P= 0.087) in the RR group.
Jongen et al (2014) [111]	Intensive social cognitive wellness program with participation of support partners	Longitudinal (T1 = basal level/ T2 = 1 months post-treatment/T3 = 3 months post-treatment T4 = 6 months post-treatment	Multiple Sclerosis Quality of Life Instrument (MSQoL-54)	N = 44 45.7 years 79.5%	MCS increase at T2, T3 and T4 and PCS at T4 (P< 0.05).

Table 4

Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Eliášová et al (2015) [113]	Self-Help group (SH)	Cross-sectional (T1 = after the treatment)	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N intervention/ control= 46/ 42.2 years 59%	Increase in physical (P< 0.001), psychological (P< 0.001) and social relationships (P< 0.001) in the SH group.
Based on symptoms and self-management					
Mulligan et al (2016) [115]	Fatigue self-management program "Minimize Fatigue, Maximize Life: Creating Balance with Multiple Sclerosis (MFML)"	Longitudinal (T1 = 1 month pre-treatment/ T2 = pre-treatment/ T3 = post-treatment).	Short Form Health Survey 12 (SF-12)	N = 24 49.3 years 100%	Positive but not significant changes in SF-12 (P> 0.05).
Thomas et al (2014) [116]	Group-based fatigue management (FACETS)	Longitudinal (T1 = 1 week before treatment/ T2 = 1 month post-treatment/ T3 = 4 month post-treatment/ T4 = 12 month post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29) Short Form Health Survey 36 (SF-36)	N intervention/ control= 83/ 88 48 years 73%	Changes in physical health MSIS-29 (P= 0.046) and vitality SF-36 (P= 0.03) at T4.
Ehde et al (2015) [117]	Telephone-Delivered Self-Management (SM)	Longitudinal (T1 = before group randomization/ T2 = post-treatment/ T3 = 6 month post-treatment/ T4 = 12 month post-treatment)	Short Form Health Survey 8 (SF-8)	N intervention/ control= 77/ 51 years 89.3%	MCS and PCS increase at T2, T3 and T4 (P< 0.05).
Feicke et al (2014) [118]	Education program for self-management competencies (S.MS)	Longitudinal (T1 = 1 basal level/T2 = post-treatment /T3 = 6 month post-treatment)	Hamburg quality of life questionnaire in multiple sclerosis (HAQUAMS)	N intervention/ control= 31/ 41.9 years 87.1%	Stable positive changes in QoL (P= 0.007).
Other psychological intervention					
Leclaire et al (2018) [119]	Group Positive Psychology	Longitudinal (T1 = basal level /T2 = post-treatment)	Short Form Health Survey 36 (SF-36)	N = 11 53.5 years 100%	Increase in SF-36 vitality subscale score (P= 0.016). Increase in mental health SF-36 subscale (P= 0.098) that did not reach statistical significance.

FAMS = functional assessment of multiple sclerosis; QoL = quality of life; PCS = physical component score; MCS = mental component score; MSQoL-54 = multiple sclerosis quality of life instrument; CBT = cognitive behavioral therapy; SF-36 = short form health survey 36; MSIS-29 = multiple sclerosis impact scale; EQ-5D = euroqol 5-dimensions; HBT = hope-based group therapy; RR= relapsing-remitting; SH = self-help group; SF-12 = short-form health survey

4. Discussion

Firstly, the present systematic review was intended to identify risk and protective factors of QoL in MS. The results showed that investigations tend to focus on the assessment of functional impairment by the EDSS [14-24]. As expected the number and severity of symptoms and the associated impairment appeared to play a crucial role for QoL. Particularly, the MS symptoms fatigue[17,18,28,29,31-41], cognitive impairment[28,39,41,42,52,55,56], and pain[24,28,39,40,44,45] were focused in a vast amount of studies and confirmed as important risk factors. Longitudinal studies suggest that higher fatigue,[87] pain,[94] and cognitive impairment symptoms,[87,93] also predict worse QoL up to 10 years later. This has important clinical implications, as in treatment above mentioned symptoms should be prioritized. In general, functional impairment[91-93] as well as longer duration of illness[91] were predictors of QoL 2 to 10 years later, whereas progression of disease[90] from benign to non benign MS predicted QoL as measured by the PCS up to 30 years later.

With regard to emotional symptoms there was convincing evidence that depression[17,18,21,23,24,28,29,40,44,55,58,60-64] alongside depressive temperament[66] and anxiety[27,29,40,58,60-63,65] were associated with lower QoL and that depression also predicted QoL up to 10 years later[93].

The applied coping strategies obviously influence QoL in MS, however the effect depends on the specific circumstances of disease history. For example, problem solving and avoidance coping, normally classified as opposed strategies, both seemed to have a positive effect on MCS in the first three years of diagnosis.[86] However, in general strategies associated with denial[40,68] and avoidance of disease challenges such as problem avoidance,[60,70] behavioral disengagement,[40,69] distancing,[70] self-distraction,[68] social withdrawal,[60] wishful thinking,[60] were associated with a lower QoL. On the other hand strategies based on acceptance and active commitment such as active coping, humor, problem resolution, cognitive positive restructuring, and emotional expression led to higher QoL in MS.[40,60,68-71] Obviously, there is a close connection between the active confrontation of illness challenges and specific personality-based convictions, such as a high self-efficacy. In accordance a higher self-efficacy[40,77], self-esteem[77], and sense of coherence[78] improved QoL in MS.

Regarding sociodemographic influences on QoL, not surprisingly unemployment proved to be a major risk factor[19,23,43,56,83] as well as a low socioeconomic status[24] and financial difficulties[26]. In keeping with the negative influence of the scarcity of resources, lack of access to therapy was also identified as a risk factor.[19,20]

This systematic review second aim was to study QoL in MS patients at different times of disease history. Two studies showed the diminishment of QoL in MS patients in its earliest stage.[84,85] This might have to do with the fact that patients being diagnosed with a severe and chronic disease need a certain time to come to terms with this emotional shock. The oscillation between avoidance and problem solving, which both have a positive influence in the first three years after diagnosis,[86] may stand for this inner struggle. In older patients neurologic impairment and physical disability,[86] which represent the age-associated increase in physical impairment, were identified as risk factors for QoL in MS.

Finally, the third aim of this review was to analyze psychological interventions for the improvement of QoL in MS.

Eight of the included intervention studies specifically aimed at the treatment of depressive symptomatology[95,99-101,104,106-107] by either mindfulness-based or cognitive-behavioral approaches both of which proved to be successful.

Three studies were specifically directed towards the treatment of fatigue[101,115,116] by light guided imagery or self-management programs. The imagery approach as well as the self-management group intervention were successful, whereas the individual self-management program did not show a significant improvement.

A variety of mindfulness-based approaches[96-98] aimed at stress. reduction as well as a Community based intervention[99]. Three of the four studies showed some kind of improvement of QoL, among these the only study with a control group.

Several of the investigated interventions had the objective to reinforce protective factors in MS patients. Graziano et al[104] focused on identity redefinition, sense of coherence and self-efficacy. Pakenham et al[108] implemented a program based on resilience training, and the program by Blair et al[102] focused on the improvement of emotion regulation. All studies were successful in improving QoL confirming the alternative focus on protective factors instead of risk factors.

Interventions based on social support concentrate on the reinforcement of the social network. A wide spectrum of these approaches was investigated in MS, as for example, self-help groups[113], hope based group therapy[114], supportive-expressive therapy[110], and social cognitive training with support partners[111,112]. All interventions aimed to help people overcome MS barriers in daily living by strengthening the social support and resulted in the improvement of some aspects of QoL. This is consistent with above mentioned studies[81,82] pointing out the relevance of social support and participation as a protective factor for QoL.

5. Limitations

The main limitation of this study was the unfeasibility to carry out a quantitative synthesis of the results, due to the heterogeneity of studies methodologies and designs. Due to the vast amount of topics and limited resources we had to restrict our search on a five year period up to January 2019.

6. Conclusions

This review was conducted to give a broad overview over QoL in MS. The findings show the importance of clinical, psychosocial and demographic variables as risk and protective factor for QoL. A variety of psychological interventions ranging from mindfulness-based and cognitive-behavioral approaches to self-help groups were identified as promising options to improve QoL addressing these factors. These findings have important clinical implications. A sound biopsychosocial assessment of MS patients in daily clinical practice is necessary to ensure the possibility of identifying risk factors for QoL early on and to recommend evidence-based psychological interventions to improve or stabilize QoL.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

This study was financially supported by the program of Formation of University Professor of Ministry of Education, Culture and Sport of Spain grant number: FPU 17/04240.

Patient and public involvement

No patient involved.

Authors Contribution

Irene Gil-González: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

Agustín Martín-Rodríguez: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

Rupert Conrad: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

María Ángeles Pérez-San-Gregorio: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

References

[1] Patti F, Pappalardo A. Quality of life in patients affected by multiple sclerosis: a systematic review. In: Preedy V.R., Watson R.R., eds. Handbook of Disease Burdens and Quality of Life Measures. New York: Springer, New York (NY) 2010:3769-3783. doi:10.1007/978-0-387-78665-0_218

[2] Benito-León J, Morales JM, Rivera-Navarro J, Mitchell AJ. A review about the impact of multiple sclerosis on health-related quality of life. *Disabil Rehabil* 2003;25:1291-1303.doi:10.1080/0963828031000160859 1

[3] Hyarat SY, Subih M, Rayan A, Salami I, Harb A. Health related quality of life among patients with multiple sclerosis: the role of psychosocial adjustment to illness. *Arch Psychiatr Nurs* 2019;33:11-16.doi:10.1016/j.apnu.2018.08.006

[4] Yalachkov Y, Soydaş D, Bergmann J, et al. Determinants of quality of life in relapsing-remitting and progressive multiple sclerosis. *Mult Scler Relat Disord* 2019;30:33-37.doi:10.1016/j.msard.2019.01.049

[5] World Health Organisation. Governance. Basic documents. World Health Organisation. https://www.who.int/about/who-we-are/constitution. Published 2019.Accesed December 15, 2019.

[6] Bernstein U. The World Health Organization Quality of Life Assessment (WHOQOL): Position Paper from the World Helath Organization. *SocSciMed* 1995;41(10):1403-1409.

[7] Marcel W.M. Definitions of quality of life: What has happened and how to move on.*Top Spinal Cord Inj Rehabil* 2014;20:167-180.doi:10.1310/sci2003-167

[8] Gellert GA. The importance of quality of life research for health care reform in the USA and the future of public health. *Qual Life Res* 1993;2:357-361.doi:10.1007/BF00449431

[9] Baumstarck K, Boyer L, Boucekine M, Michel P, Pelletier J, Auquier P. Measuring the quality of life in patients with multiple sclerosis in clinical practice: a necessary challenge. *Mult Scler Int* 2013;2013:1-8.doi:10.1155/2013/524894

[10] Ysrraelit MC, Fiol MP, Gaitán MI, Correale J. Quality of life assessment in multiple sclerosis: Different perception between patients and neurologists. *Front Neurol* 2018;8:1-6.doi:10.3389/fneur.2017.00729

[11] Revicki DA, Osoba D, Fairclough D, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. *Qual Life Res* 2000;9:887-900.doi:10.1023/A:1008996223999

[12] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

[13] Chacón-Moscos S, Sanduvete-Chaves S, Sánchez-Martín M. The development of a checklist to enhance methodological quality in intervention programs. *Front Psychol* 2016;*7*:1811.doi:10.3389/fpsyg.2016.01811

[14] Gupta S, Goren A, Phillips AL, Dangond F, Stewart M. Self-reported severity among patients with multiple sclerosis in the U . S . and its association with health outcomes. *Mult Scler Relat Disord* 2014;3:78-88.doi:10.1016/j.msard.2013.06.002

[15] Rezapour A, Kia AA, Goodarzi S, Hasoumi M, Motlagh SN, Vahedi S. The impact of disease characteristics on multiple sclerosis patients ' quality of life. *Epidemiol Health* 2017;39:1-7.doi:10.4178/epih.e2017008

[16] Nakazawa K, Noda T, Ichikura K, Okamoto T. Resilience and depression / anxiety symptoms in multiple sclerosis and neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord* 2018;25:309-315.doi:10.1016/j.msard.2018.08.023

[17] Ciampi E, Uribe-San-Martin R, Vásquez M, et al. Relationship between Social Cognition and traditional cognitive impairment in Progressive Multiple Sclerosis and possible implicated neuroanatomical regions. *Mult Scler Relat Disord* 2018;20:122-128.doi:10.1016/j.msard.2018.01.013

[18] Klevan G, Jacobsen CO, Aarseth JH, et al. Health related quality of life in patients recently diagnosed with multiple sclerosis. *Acta Neurol Scand* 2014;129:21-26.doi:10.1111/ane.12142

[19] Brola W, Sobolewski P, Jantarski K. Multiple sclerosis: patient-reported quality of life in the Świętokrzyskie Region. *Med Stud Med* 2017;33:191-198.

[20] Brola W, Sobolewski P, Fudala M et al. Self-reported quality of life in multiple sclerosis patients : preliminary results based on the Polish MS Registry. *Patient Prefer Adherence* 2016;10:1647-1656.

[21] Fernández-Jiménez E, Arnett PA. Impact of neurological impairment, depression, cognitive function and coping on quality of life of people with multiple sclerosis: a relative importance analysis. *Mult Scler J* 2015;21(11):1468-1472.doi:10.1177/1352458514562439

[22] Nickel S, Kofahl OVKC, Kofahl C. Assessments and determinants of HRQoL in a German MS population. *Acta Neurol Scand* 2018; 137(2): 174-180.doi:10.1111/ane.12854
[23] Cioncoloni D, Innocenti I, Bartalini S, et al. Individual factors enhance poor health-related quality of life outcome in multiple sclerosis patients. Significance of predictive determinants. *J Neurol Sci* 2014;345:213-219.doi:10.1016/j.jns.2014.07.050
[24] Boogar IR, Talepasand S, Jabari M. Psychosocial and Medical Determinants of Health-related Quality of Life in Patients with Relapsing-Remitting Multiple Sclerosis. *Noro Psikiyatr Ars* 2018;13:29-35.doi:10.29399/npa.16983
[25] Gross HJ, Watson C. Characteristics, burden of illness, and physical functioning of patients with relapsing-remitting and secondary progressive multiple sclerosis: a cross-sectional US survey. *Neuropsychiatr Dis Treat* 2017;13:1349-1357.doi:10.2147/NDT.S132079
[26] Cichy KE, Li J, Rumrill PD, Bishop M, Roessler RT. Non-vocational health-related correlates of quality of life for older adults living with multiple sclerosis. *J Rehabil* 2016;82:36-44.
[27] Zhang Y, Taylor BV, Simpson SJ, Blizzard L, van der Mei I. Patient-reported outcomes are worse for progressive-onset multiple sclerosis than relapse-onset multiple sclerosis, particularly early in the disease process. *Eur J Neurol* 2019;26: 155-161. doi:10.1111/ene.13786
[28] Shahrbanian S, Duquette P, Kuspinar A, Mayo NE. Contribution of symptom clusters to multiple sclerosis consequences. *Qual Life Res* 2015;24: 617-629.doi:10.1007/s11136-014-0804-7
[29] Hyncicova E, Kalina A, Vyhnalek M, et al. Health-related quality of life , neuropsychiatric symptoms and structural brain changes in clinically isolated syndrome. *PLoS ONE* 2018;13:1-13.doi:10.1371/journal.pone.0200254.
[30] Bishop M, Rumrill PD, Roessler RT. Quality of life among people with multiple sclerosis: replication of a three-factor prediction model. *Work* 2015;52:757-765.doi:10.3233/WOR-152203
[31] Leonavicius R, Ph DMD. Among multiple sclerosis and fatigue. *Neurol Psychiatry Brain Res* 2016;22:141-145.doi:10.1016/j.npbr.2016.08.002
[32] Garg H, Bush S, Gappmaier E. Associations between fatigue and disability, functional mobility, depression, and quality of life in people with multiple sclerosis. *Int J MS Care* 2016:18:71-77.doi:10.7224/1537-2073.2015-013
[33] Fernández-Muñoz, JJ, Morón-Verdasco A, Cigarán-Méndez M, Muñoz-Hellín E, Pérez-de-Heredia-Torres M, Fernández-de-las-Peñas C. Disability, quality of life, personality, cognitive and psychological variables associated with fatigue in patients with multiple sclerosis. *Acta Neurol Scand* 2015;132:118-124.doi:10.1111/ane.12370
[34] Weiland TJ, Jelinek GA, Marck CH, Hadgkiss EJ. Clinically significant fatigue: prevalence and associated factors in an international sample of adults with multiple sclerosis recruited via the internet. *PLoS ONE* 2015;10:1-18.doi:10.1371/journal.pone.0115541
[35] Aygünoğlu SK, Çelebİ A, Vardar N, Gürsoy E. Correlation of fatigue with depression, disability level and quality of life in patients with multiple sclerosis. *Noro Psikiyatr Ars* 2015;52:247-251.doi:10.5152/npa.2015.8714
[36] Vister E, Tijsma ME, Hoang PD, Lord SR. Fatigue, physical activity, quality of life, and fall risk in people with multiple sclerosis. *Int J MS Care* 2017;19(2):91-98.doi:10.7224/1537-2073.2015-077
[37] Tabrizi FM, Radfar M. Fatigue, sleep quality, and disability in relation to quality of life in multiple sclerosis. *Int J MS Care* 2015;17:268-274.doi:10.7224/1537-2073.2014-046
[38] Barin L, Salmen A, Disanto G, et al. The disease burden of multiple sclerosis from the individual and population perspective: which symptoms matter most? *Mult Scler Relat Disord* 2018;25:112–121.doi:10.1016/j.msard.2018.07.013.
[39] Kratz AL, Ehde DM, Hanley MA, Jensen MP, Osborne TL, Kraft GH. Cross sectional examination of the associations between symptoms, community integration, and mental health in Multiple Sclerosis. *Arch Phys Med Rehabil*. 2016;97:11-13.doi:10.1016/j.apmr.2015.10.093
[40] Strober LB. Quality of life and psychological well-being in the early stages of multiple sclerosis (MS): Importance of adopting a biopsychosocial model. *Disabil Health J* 2018;11:555-561.doi:10.1016/j.dhjo.2018.05.003
[41] Dymecka J. Biomedical variables and adaptation to disease and health-related quality of life in polish patients with MS. *Int J Environ Res Public Health* 2018; 15: 2678.doi:10.3390/ijerph15122678.
[42] Colbeck M. Sensory processing, cognitive fatigue, and quality of life in multiple sclerosis. *Can J Occup Ther* 2018;85:169-175.doi:10.1177/0008417417727298
[43] Abdullah EJ, Badr HE. Assessing the quality of life in patients with multiple sclerosis in Kuwait: a cross sectional study. *Psychol Heal Med*. 2018;23:391-399.doi:10.1080/13548506.2017.1366660
[44] Williams AE, Vietri JT, Isherwood G, Flor A. Symptoms and Association with Health Outcomes in Relapsing-Remitting Multiple Sclerosis : Results of a US Patient Survey. *Mult Scler Int*. 2014;2014:203183.doi: 10.1155/2014/203183
[45] Marck CH, Livera AM De, Weiland TJ, Jelinek PL. Pain in people with multiple sclerosis : associations with modifiable lifestyle factors, fatigue, depression, anxiety, and mental health quality of life. *Front Neurol* 2017;8:1-7.doi:10.3389/fneur.2017.00461
[46] Milinis K, Tennant A, Young CA. Spasticity in multiple sclerosis: associations with impairments and overall quality of life. *Mult Scler Relat Disord* 2016;5:34-39.doi:10.1016/j.msard.2015.10.007
[47] Zettl UK, Henze T, Essner U, Flachenecker P. Burden of disease in multiple sclerosis patients with spasticity in Germany: Mobility improvement study (Move I). *Eur J Heal Econ* 2014;15:953-966.doi:10.1007/s10198-013-0537-5
[48] Khalaf KM, Coyne KS, Globe DR, et al. The impact of lower urinary tract symptoms on health-related quality of life among patients with multiple sclerosis. *Neurourol Urodyn* 2016;54:48-54.doi:10.1002/nau
[49] Vitkova M, Rosenberger J, Krokavcova M, et al. Health-related quality of life in multiple sclerosis patients with

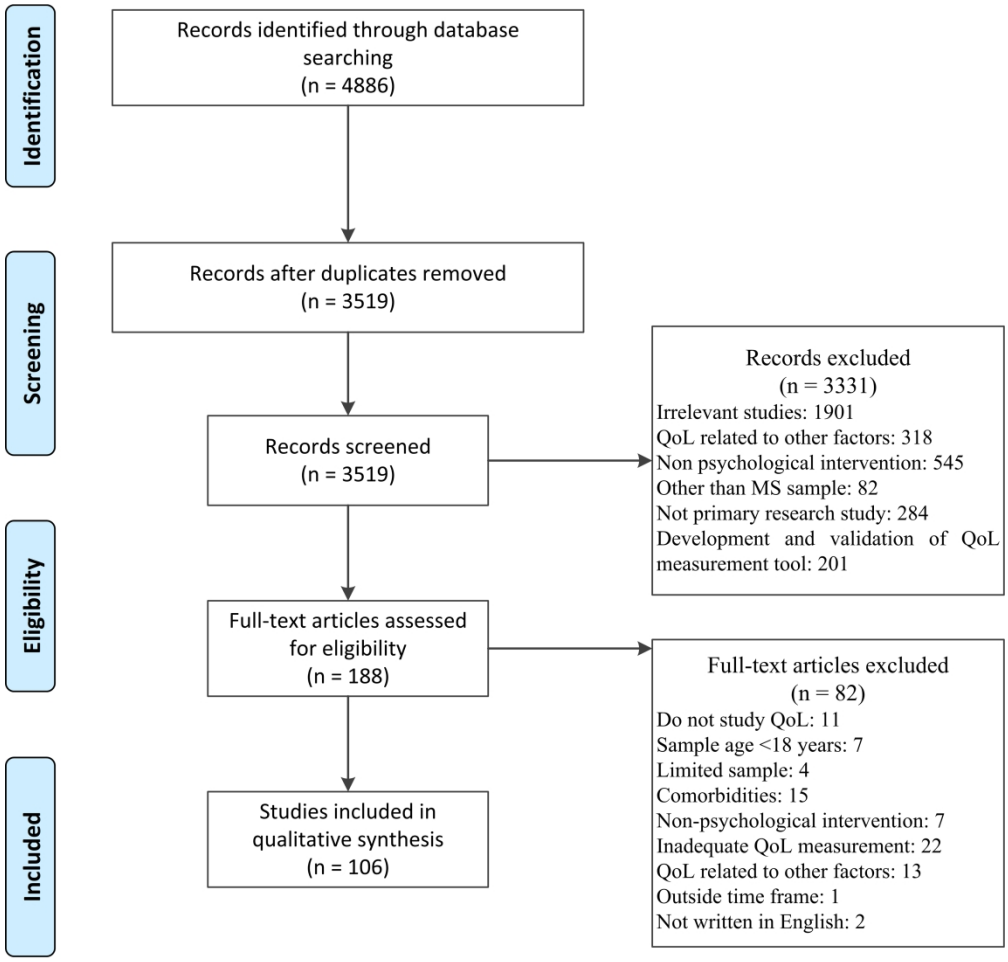
bladder, bowel and sexual dysfunction. *Disabil Rehabil* 2014;36:987-992.doi:10.3109/09638288.2013.825332
[50] Qaderi K, Merghati Khoei E. Sexual problems and quality of life in women with multiple sclerosis. *Sex Disabil* 2014;32:35-43.doi:10.1007/s11195-013-9318-4
[51] Schairer LC, Foley FW, Zemon V, et al. The impact of sexual dysfunction on health-related quality of life in people with multiple sclerosis. *Mult Scler J* 2014;20:610-616.doi:10.1177/1352458513503598
[52] Ma S, Rui X, Qi P, Liu G, Yang J. Sleep disorders in patients with multiple sclerosis in China. *Sleep Breath* 2017;21:149-154.doi:10.1007/s11325-016-1416-y
[53] White EK, Sullivan AB, Drerup M. Impact of sleep disorders on depression and patient-perceived health-related quality of life in multiple sclerosis. *Int J MS Care* 2019;21: 10-14.doi:10.7224/1537-2073.2017-068
[54] Grech LB, Kiropoulos LA, Kirby KM, Butler E, Paine M, Hester R. The effect of executive function on stress, depression, anxiety, and quality of life in multiple sclerosis. *J Clin Exp Neuropsychol* 2015;37:549-562.doi:10.1080/13803395.2015.1037723
[55] Samartzis L, Gavala E, Zoukos Y, Aspiotis A, Thomaides T. Perceived cognitive decline in multiple sclerosis impacts quality of life independently of depression. *Rehabil Res Pract* 2014;2014:128751.doi: 10.1155/2014/128751.
[56] Campbell J, Rashid W, Cercignani M, Langdon D. Cognitive impairment among patients with multiple sclerosis : associations with employment and quality of life. *Postgrad Med J* 2017;93:143-147. doi: 10.1136/postgradmedj-2016-134071.
[57] Sgaramella TM, Carrieri L, Stenta G, Bortolon F, Perini F, Soresi S. Self-reported executive functioning and satisfaction for quality of life dimensions in adults with multiple sclerosis. *Int J Child Heal Hum Dev* 2014;7:167.
[58] Paziuc LC, Radu MR. The influence of mixed anxiety-depressive disorder on the perceived quality of life in multiple sclerosis patients. *Bulletin of the Transilvania University of Brasov, Seriels VI: Medical Sciences* 2018;11:41–50.
[59] Phillips LH, Henry JD, Nouzova E, et al. Difficulties with emotion regulation in multiple sclerosis: links to executive function, mood, and quality of life. *J Clin Exp Neuropsychol* 2014;36:831-842.doi:10.1080/13803395.2014.946891
[60] Ledesma ALH., Méndez AJR, Vidal LSG, Cruz GT, García-Solís P, Esquivel FDJD. Coping strategies and quality of life in mexican multiple sclerosis patients: physical, psychological and social factors relationship. *Mult Scler Relat Disord* 2018;25:122-127.doi:10.1016/j.msard.2018.06.001
[61] Prisnie JC, Sajobi TT, Wang M, et al. CR. Effects of depression and anxiety on quality of life in five common neurological disorders. *Gen Hosp Psychiatry* 2018;52:58-63.doi:10.1016/j.genhosppsych.2018.03.009
[62] Alsaadi T, Hammasi K El, Shahrour TM, et al. Depression and anxiety as determinants of health-related quality of life in patients with multiple sclerosis - United Arab Emirates. *Neurol Int* 2017;9:75-78.doi:10.4081/ni.2017
[63] Labiano-fontcuberta A, Mitchell AJ, Moreno-garcía S, Puertas-martín V. Impact of anger on the health-related quality of life of multiple sclerosis patients. *Mult Scler J* 2015;21:630-641.doi:10.1177/1352458514549399.
[64] Fernández-muñoz JJ, Cigarán-méndez M, Navarro-pardo E, Pérez-de-heredia-torres M, Parás-bravo P. Is the association between health- related quality of life and fatigue mediated by depression in patients with multiple sclerosis ? A Spanish cross- sectional study. *BMJ Open* 2018; 8:1-6.doi:10.1136/bmjopen-2017-016297
[65] Pham T, Jetté N, Bulloch AGM, Burton JM, Wiebe S, Patten SB. The prevalence of anxiety and associated factors in persons with multiple sclerosis. *Mult Scler Relat Disord* 2018;19:35-39.doi:10.1016/j.msard.2017.11.003
[66] Salhofer-Polanyi S, Friedrich F, Löffler S, et al. Health-related quality of life in multiple sclerosis: temperament outweighs EDSS. *BMC Psychiatry* 2018;18:1-6. doi:10.1186/s12888-018-1719-6
[67] Demirci S, Demirci K, Demirci S. The Effect of type D personality on quality of life in patients with multiple sclerosis. *Noropsikiyatri Arsivi.* 2017;54:272-276.doi:10.5152/npa.2016.12764
[68] Zengin O, Erbay E, Yıldırım B, Altındağ Ö. Quality of life, coping, and social support in patients with multiple sclerosis: a pilot study. *Turk J Neurol* 2017;23: 211–218. https://doi.org/10.4274/tnd.37074
[69] Grech LB, Kiropoulos LA, Kirby KM, Butler E, Paine M, Hester R. Target coping strategies for interventions aimed at maximizing psychosocial adjustment in people with multiple sclerosis. *Int J MS Care* 2018;20:109-119.doi:10.7224/1537-2073.2017-008
[70] Farran N, Ammar D, Darwish H. Quality of life and coping strategies in lebanese multiple sclerosis patients: a pilot study. *Mult Scler Relat Disord* 2016;6:21-27.doi:10.1016/j.msard.2015.12.003
[71] Mikula P, Nagyova I, Krokavcova M, et al. Coping and its importance for quality of life in patients with multiple sclerosis. *Disabil Rehabil* 2014;36:732-736.doi:10.3109/09638288.2013.808274
[72] Mikula P, Nagyova I, Krokavcova M, et al. The mediating effect of coping on the association between fatigue and quality of life in patients with multiple sclerosis. *Psychol Health Med* 2015;20:653-661.doi:10.1080/13548506.2015.1032310
[73] Mikula P, Nagyova I, Krokavcova M, et al. Do coping strategies mediate the association between Type D personality and quality of life among people with multiple sclerosis ? *J Health Psychol* 2016;23:1557-1565.doi:10.1177/1359105316660180
[74] Van Damme S, De Waegeneer A, Debruyne J. Do flexible goal adjustment and acceptance help preserve quality of life in patients with Multiple Sclerosis? *Int J Behav Med* 2016;23, 333-339.
[75] Nery-hurwit M, Yun J, Ebbeck V. Examining the roles of self-compassion and resilience on health-related quality of life for individuals with Multiple Sclerosis. *Disabil Health J* 2018;11:256-261.doi:10.1016/j.dhjo.2017.10.010
[76] Koelmel E, Hughes AJ, Alschuler KN, Ehde DM. Resilience mediates the longitudinal relationships between social support and mental health outcomes in multiple sclerosis. *Arch Phys Med Rehabil* 2017;98:1139-1148. doi:10.1016/j.apmr.2016.09.127
[77] Wilski M, Tasiemski T. Health-related quality of life in multiple sclerosis: role of cognitive appraisals of self , illness

and treatment. *Qual Life Res* 2016;25:1761-1770.doi:10.1007/s11136-015-1204-3
[78] Calandri E, Graziano F, Borghi M, Bonino, S. Depression, positive and negative affect, optimism and health-related quality of life in recently diagnosed multiple sclerosis patients: the role of identity, sense of coherence, and self-efficacy. *J Happiness Stud* 2018;19:277-295.doi:10.1007/s10902-016-9818-x
[79] Mikula P, Nagyova I, Krokavcova M, et al. Self-esteem, social participation, and quality of life in patients with multiple sclerosis. *J Health Psychol* 2017;22:984-992.doi:10.1177/1359105315621778
[80] Valvano A, Floyd RM, Penwell-waines L, Stepleman L, Lewis K, House A. The relationship between cognitive fusion, stigma, and well-being in people with multiple sclerosis. *J Context Behav Sci* 2016;5:266-270.doi:10.1016/j.jcbs.2016.07.003
[81] Costa DC, Sá, MJ , Calheiros JM. Social support network and quality of life in multiple sclerosis patients. *Arq Neuropsiquiatr* 2017;75:267-271.https://doi.org/10.1590/0004-282x20170036
[82] Mikula P, Nagyova I, Krokavcova M, et al. Social participation and health-related quality of life in people with multiple sclerosis. *Disabil Health J* 2015;8:29-34.doi:10.1016/j.dhjo.2014.07.002
[83] Chiu C, Chan F, Edward S, Dutta A, Hartman E, Bezyak J. Employment as a health promotion intervention for persons with multiple sclerosis. *Work* 2015;52:749-756.doi:10.3233/WOR-152202
[84] Possa MF, Minacapelli E, Canale S, et al. The first year after diagnosis : psychological impact on people with multiple sclerosis. *Psychol Health Med* 2017;22:1063-1701.doi:10.1080/13548506.2016.1274043
[85] Stern BZ, Strober L, DeLuca J, Goverover Y. Subjective well-being differs with age in multiple sclerosis: A brief report. *Rehabil Psychol* 2018;63:474-478.doi:10.1037/rep0000220
[86] Calandri E, Graziano F, Borghi M, Bonino S. Coping strategies and adjustment to multiple sclerosis among recently diagnosed patients: The mediating role of sense of coherence. *Clin Rehabil* 2017;31:1386-1395.doi:10.1177/0269215517695374
[87] Nourbakhsh B, Julian L, Waubant E. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. *Eur J Neurol* 2016;23:1482-1486.doi:10.1111/ene.13102
[88] Buhse M, Banker WM, Clement LM. Factors associated with health-related quality of life among older people with multiple sclerosis. *Int J MS Care* 2014;16:10-19. doi:10.7224/1537-2073.2012-046
[89] Kinkel RP, Laforet G, You X. Disease-Related Determinants of quality of life 10 years after clinically isolated syndrome. *Int J MS Care* 2015;17:26-34.doi:10.7224/1537-2073.2013-041
[90] Bueno AM, Sayao AL, Yousefi M, Devonshire V, Traboulsee A, Tremlett H. Health-related quality of life in patients with longstanding "benign multiple sclerosis." *Mult Scler Relat Disord* 2015;4:31-38.doi:10.1016/j.msard.2014.09.211
[91] Baumstarck K, Pelletier J, Boucekine M, Auquier P. Predictors of quality of life in patients with relapsing-remitting multiple sclerosis: a 2-year longitudinal study. *Rev Neurol* 2015;171:173-180.doi:10.1016/j.neurol.2014.09.005
[92] Tepavcevic DK, Pekmezovic T, Stojsavljevic N, et al. Change in quality of life and predictors of change among patients with multiple sclerosis: a prospective cohort study. *Qual Life Res* 2014;23:1027-1037.doi:10.1007/s11136-013-0535-1
[93] Chruzander C, Ytterberg C, Gottberg K, Einarsson U, Widén L, Johansson S. A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm , Sweden: changes in health-related quality of life and the value of different factors in predicting health-related qualit. *J Neurol Sci* 2014;339:57-63.doi:10.1016/j.jns.2014.01.020
[94] Young J, Amatya B, Galea MP, Khan F. Chronic pain in multiple sclerosis: a 10-year longitudinal study. *Scand J Pain* 2017;16:198-203.doi:10.1016/j.sjpain.2017.04.070
[95] Carletto S, Tesio V, Borghi M, et al. The effectiveness of a body-affective mindfulness intervention for multiple sclerosis patients with depressive symptoms : a randomized controlled clinical trial. *Front Psychol* 2017;8:1-13.doi:10.3389/fpsyg.2017.02083
[96] Besharat M, massood Nabavi S, Geranmayepour S, Morsali D, Haghani S. Mindfulness-based Stress Reduction (MBSR) program: the effect of a novel psycho-interventional method on quality of life, mental health, and self-efficacy in female patients with multiple sclerosis: a randomized clinical trial. *J Biol Today's World* 2017;06:211-215. doi:10.15412/j.jbtw.01061101
[97] Blankespoor RJ, Schellekens MPJ, Vos SH, Speckens AEM, Jong BA De. The effectiveness of mindfulness-based stress reduction on psychological distress and cognitive functioning in patients with multiple sclerosis : a pilot study. *Mindfulness (N Y)* 2017;8:1251-1258.doi:10.1007/s12671-017-0701-6
[98] Simpson R, Mair FS, Mercer SW. Mindfulness-based stress reduction for people with multiple sclerosis – a feasibility randomised controlled trial. *BMC Neurol* 2017;17:1-12.doi:10.1186/s12883-017-0880-8
[99] Spitzer E, Pakenham KI. Evaluation of a brief community-based mindfulness intervention for people with multiple sclerosis: a pilot study. *Clin Psychol* 2018;22:182-191.doi:10.1111/cp.12108
[100] Ghodspour Z, Najafi M, Boogar IR, Boogar R. Research paper: effectiveness of mindfulness-based cognitive therapy on psychological aspects of quality of life, depression, anxiety, and stress among patients with multiple sclerosis. *J Pract Clin Psychol* 2018;6:215-222.
[101] Case LK, Jackson P, Kinkel R, Mills PJ. Guided imagery improves mood, fatigue, and quality of life in individuals with multiple sclerosis : an exploratory efficacy trial of healing light guided imagery. *Evid Base Integr Med* 2018;23:1-8.doi:10.1177/2515690X17748744
[102] Blair M, Ferreria G, Gill S, et al. Dialectical behavior group therapy is feasible and reduces emotional dysfunction in multiple sclerosis. *Int J Group Psychother* 2017;67:500-518.doi:10.1080/00207284.2016.1260457
[103] Calandri E, Graziano F, Borghi M, Bonino S. Improving the quality of life and psychological well-being of recently diagnosed multiple sclerosis patients: preliminary evaluation of a group-based cognitive behavioral intervention.

Disabil Rehabil 2017;39:1474-1481.doi:10.1080/09638288.2016.1198430
[104] Graziano F, Calandri E, Borghi M, Bonino S. The effects of a group-based cognitive behavioral therapy on people with multiple sclerosis: a randomized controlled trial. *Clin Rehabil* 2014;28:264-274.doi:10.1177/0269215513501525
[105] Kiropoulos LA, Kilpatrick T, Holmes A, Threader J. A pilot randomized controlled trial of a tailored cognitive behavioural therapy based intervention for depressive symptoms in those newly diagnosed with multiple sclerosis. *BMC Psychiatry* 2016;16:1-10.doi:10.1186/s12888-016-1152-7
[106] Chruzander C, Gottberg K, Ytterberg C, et al. A single-group pilot feasibility study of cognitive behavioural therapy in people with multiple sclerosis with depressive symptoms. *Disabil Rehabil* 2016;38:2383-2391. doi:10.3109/09638288.2015.1130179
[107] Kikuchi, H., Niino, M., Hirotani, M., Miyazaki, Y, Kikuchi, S. Pilot study on the effects of cognitive behavioral therapy on depression among japanese patients with multiple sclerosis. *Clin Exp Neuroimmunol* 2019;10: 180-185.doi:10.1111/cen3.12529
[108] Pakenham KI, Mawdsley M, Brown FL, Burton NW. (2018). Pilot evaluation of a resilience training program for people with multiple sclerosis. *Rehabil Psychol 2018;63*:29-42.doi:10.1037/rep0000167
[109] Proctor BJ, Moghaddam NG, Evangelou N. Telephone-supported acceptance and commitment bibliotherapy for people with multiple sclerosis and psychological distress: a pilot randomised controlled trial. *J Context Behav Sci* 2018;9:103-109.doi:10.1016/j.jcbs.2018.07.006
[110] Abolghasemi A, Farhang S, Taherifard M, Kiamarsi A. The effect of supportive-expressive therapy on hope and quality of life in patients with multiple sclerosis (MS). *Archives of Psychiatry and Psychotherapy* 2016;18:20-27. doi:10.12740/APP/64975
[111] Jongen PJ, Ruimschotel R, Heerings M, et al. Improved self-efficacy in persons with relapsing remitting multiple sclerosis after an intensive social cognitive wellness program with participation of support partners: a 6-months observational study. *Health Qual Life Outcomes.* 2014;12:1-9.doi:10.1186/1477-7525-12-40
[112] Jongen PJ, Heerings M, Ruimschotel R, et al. Intensive social cognitive treatment (can do treatment) with participation of support partners in persons with relapsing remitting multiple sclerosis: observation of improved self-efficacy, quality of life, anxiety and depression 1 year later. *BMC Res Notes* 2016;9:1-8.doi:10.1186/s13104-016-2173-5
[113] Eliášová A, Majerníková L, Hudáková A, Kaščáková M. Self-help group and the quality of life of patients with multiple sclerosis - pilot study. *Cent Eur J Nurs Midwifery* 2015;6:336-342.doi:10.15452/CEJNM.2015.06.0025
[114] Liu Y. A hope-based group therapy program to women with multiple sclerosis: quality of life. *Neuroquantology* 2017;15:127-132. doi:10.14704/nq.2017.15.4.1135
[115] Mulligan H, Wilkinson A, Barclay A, Whiting H, Heynike C, Snowdon J. Evaluation of a fatigue self-management program for people with multiple sclerosis. *Int J MS Care* 2016;18:116-121.doi:10.7224/1537-2073.2015-019
[116] Thomas PW, Thomas S, Kersten P, et al. One year follow-up of a pragmatic multi-centre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *BMC Neurol* 2014;14:1-6.doi:10.1186/1471-2377-14-109
[117] Ehde DM, Elzea JL, Verrall AM, Gibbons LE, Smith AE, Amtmann D. Efficacy of a telephone-delivered self-management intervention for persons with multiple sclerosis : a randomized controlled trial with a one-year follow-up. *Arch Phys Med Rehabil* 2015;96:1945-1958.e2.doi:10.1016/j.apmr.2015.07.015
[118] Feicke J, Spörhase U, Köhler J, Busch C, Wirtz M. A multicenter, prospective, quasi-experimental evaluation study of a patient education program to foster multiple sclerosis self-management competencies. *Patient Educ Couns* 2014;97:361-369. doi:10.1016/j.pec.2014.09.005
[119] Leclaire K, Cecil A, Larussa A, et al. A pilot study of a group positive psychology intervention for patients with multiple sclerosis. *Int J MS Care* 2018;20:136-141.doi:10.7224/1537-2073.2017-002

Figure Legend 1

PRISMA flow diagram of selection process.



PRISMA flow diagram of selection process

167x160mm (600 x 600 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			x
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	x
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	x
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	x
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	x
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4,5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	x
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's)	x
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	x
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	3
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	x
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	x

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Quality of life in adults with Multiple Sclerosis: a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041249.R1
Article Type:	Original research
Date Submitted by the Author:	12-Oct-2020
Complete List of Authors:	Gil-González, Irene; Universidad de Sevilla, Personality, Assessment, and Psychological Treatment Martín-Rodríguez, Agustín; Universidad de Sevilla, Department of Personality, Assessment, and Psychological Treatment Conrad, Rupert; Department of Psychosomatic Medicine and Psychotherapy, University of Bonn, Bonn, Germany Pérez-San-Gregorio, María Ángeles; Universidad de Sevilla Facultad de Psicologia, Personality, Assessment, and Psychological Treatment
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Global health
Keywords:	Multiple sclerosis < NEUROLOGY, MENTAL HEALTH, Adult neurology < NEUROLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Quality of life in adults with Multiple Sclerosis: a systematic review

Irene Gil-González[a*], MD, igil2@us.es

Agustín Martín-Rodríguez[a*], PhD, amartinr@us.es

Rupert Conrad[b*], MD, Rupert.Conrad@ukbonn.de

María Ángeles Pérez-San-Gregorio[a*], PhD, anperez@us.es

[*]All authors have contributed equally.

[a]Department of Personality, Assessment, and Psychological Treatment, University of Seville, Seville, Spain.

[b]Department of Psychosomatic Medicine and Psychotherapy, University of Bonn, Bonn, Germany.

Corresponding author: Irene Gil-González. Department of Personality, Assessment, and Psychological Treatment. Faculty of Psychology, Camilo José Cela s/n, 41018-Seville (Spain).

Phone: +34954556939. E-mail: igil2@us.es.

ABSTRACT

Objective

In recent years, quality of life (QoL) in multiple sclerosis (MS) has been gaining considerable importance in clinical research and practice. Against this backdrop, this systematic review aimed to provide a broad overview of clinical, sociodemographic and psychosocial risk and protective factors for QoL in adults with MS and analyze psychological interventions for improving QoL.

Method

The literature search was conducted in the Scopus, Web of Science and ProQuest electronic databases. Document type was limited to articles written in English, published from January 1, 2014 to January 31, 2019. Information from the selected articles was extracted using a coding sheet and then qualitatively synthesized.

Results

The search identified 4886 records. After duplicate removal and screening, 106 articles met the inclusion and exclusion criteria for qualitative synthesis and were assessed for study quality. Disability, fatigue, depression, cognitive impairment, and unemployment were consistently identified as QoL risk factors, whereas higher self-esteem, self-efficacy, resilience and social support proved to be protective. The review analyzed a wide spectrum of approaches for QoL psychological intervention, such as mindfulness, cognitive-behavioral therapy, self-help groups and self-management. The majority of interventions were successful in improving various aspects of QoL.

Conclusion

Adequate biopsychosocial assessment is of vital importance to treat risk and promote protective factors to improve QoL in patients with MS in general care practice.

Key words

Multiple sclerosis, quality of life, protective and risk factors, mental and physical quality of life.

Abbreviation

QoL= Quality of life, MS= multiple sclerosis, EDSS= Expanded Disability Status Scale, WHO= World Health Organization, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SF-36= Short Form Health Survey 36, MSQoL-54= Multiple Sclerosis Quality of Life-54, MCS= mental composite score, PCS= physical composite score, ACT= acceptance and commitment therapy, MSIS-29= multiple sclerosis impact scale.

Strengths and limitations of this study

-This is the first systematic review of risk factors and psychological intervention for quality of life in multiple sclerosis in over a decade.

-A comprehensive and robust search strategy and strict inclusion criteria were employed to cover all the relevant evidence.

-Careful standardized risk of bias was assessed in all 106 studies included.

-Due to heterogeneity of the studies only qualitative synthesis of results was possible.

-The huge number of publications made it necessary to limit the time span to the five-year period from January 1, 2014 to January 31, 2019.

1. Introduction

The Constitution of the World Health Organization (WHO) declares health to be "…a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[1] Quality of life (QoL) is a multidimensional concept that encompasses the domains included in this definition of health.[2,3] Its introduction in medical literature dates back to 1960[4], with its importance continuously growing to date.[5]

Multiple Sclerosis (MS) is a chronic neurodegenerative condition, characterized by a wide range of symptoms and a highly unpredictable prognosis, which can severely affect patient QoL.[6-8] MS patients tend to report lower QoL than the general population.[9-12] This diminished QoL may be due to their impaired functioning in daily living, more so if the help of caregivers is required, impeding family relations, work and social dynamics. [13,14] The impact of MS on QoL can be affected by numerous disease-related factors, such as disability level or MS type, and individual factors such as social support, education, age or employment.[15-18]

Identification of risk and protective factors is a key point in implementing strategies to improve patient QoL.[7] In this context, all influences must be considered to contribute to QoL in MS.[7,19] In addition to providing practitioners with useful information on the impact of symptoms and therapy on the patient's life, QoL is also an indicator of treatment success and a predictor of disease progression.[20-22]

In view of its relevance in healthcare research, the need to compile and condense available scientific evidence on the subject is urgent. Against this backdrop, this systematic review gives a comprehensive overview of risk and protective factors related to QoL in MS as well as relevant psychological interventions. The growing number of studies on this subject[2,22] provides a vast amount of data, which due to the inconsistency of findings, needs careful assessment to come to evidence-based conclusions.

2. Methodology

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] As a review of prior publications, ethical approval (or informed consent) was unnecessary. A review protocol is available from the corresponding author upon request.

2.1 *Search strategy*

The systematic search focused on journal articles published between January 1, 2014 to January 31, 2019. The Scopus, Web of Science and ProQuest databases were searched in February and March 2019. The key words used were ("multiple sclerosis") AND ("quality of life" OR "health-related quality of life" OR "well-being" OR "wellbeing" OR "life satisfaction"). The search terms were intentionally broad to ensure wide coverage of the literature. The search field was limited to "title/abstract" and language was limited to "English".

There is no published systematic review on this topic in the Cochrane Library.

2.2 *Study selection*

First, title and abstract were screened to identify suitable articles for full text review. The screening process was performed independently by two researchers. Any disagreement about study selection was resolved by consensus with a third reviewer.

Inclusion criteria were the following:

1. Studies primarily focusing on QoL determinants and psychological intervention to improve it.
2. Study participants aged over 18 with a confirmed MS diagnosis.

The following exclusion criteria were applied:

1. Nonpsychological intervention.
2. Not primary research studies (systematic reviews, meta-analyses, protocols and clinical guidelines were excluded).
3. Studies on the development and validation of QoL measurement instruments.
4. QoL risk or intervention studies for healthy behavior, cognitive rehabilitation, physical activity or pharmacological treatment.
5. Studies on comorbidity with another illness or mental health diagnosis.
6. Sample selection based on a special condition (for example: only employees or MS patients under certain pharmacological treatment).
7. Studies not using a validated QoL measurement tool.

2.3 *Quality assessment*

The methodological quality of the studies was appraised with a well-established standardized 12-item checklist,[24] in which every item represents a methodological feature: inclusion/exclusion criteria, methodology/design, attrition rate, attrition between-groups, exclusions after, follow-up, occasion of measurements, pre/post measures, dependent variables, control techniques, construct definition and imputing missing data. The codification criteria proposed by the checklist authors was used. No article was excluded from quality appraisal.

2.4 *Data abstraction*

Data were extracted from selected articles based on a previously designed coding sheet. The pilot study was approved by consensus. The information extracted included: title, authors and publication year, country (city), design, sample characteristics, study variables and measurement tools, main results and conclusions. After extraction, the information was independently reviewed by two authors to avoid errors or omitting data.

A meta-analysis was not possible due to the heterogeneity of study designs and outcomes, so a narrative synthesis was undertaken.

3. Results

3.1 Literature screening

A total of 4886 articles were initially identified from SCOPUS, Web of Science and ProQuest. After removal of duplicates and abstract analysis, 188 studies were eligible for full text review. Finally, 106 were selected for the narrative analysis. The selection process is detailed below in a PRISMA flow diagram (Figure 1).

Figure 1 around here

3.2 Methodological quality

Methodological quality scores using the 12-item checklist are summarized in Table 1.

Table 1

Methodological quality of articles (n = 106)

Inclusion criteria		Design			Attrition		Attrition between groups		Exclusion after		Follow up period		Occasion of measurement		Same pre-post measurement	Normalization of D.V. measurement	Control techniques		Construct definition	Imputing missing data	
Yes	No or N/A*	Pre-experimental	Quasi experimental	Experimental	Yes	No or N/A*	Yes	No or N/A*	Yes	No or N/A*	Yes	No or N/A*	One	Two or more	Yes		Yes	No or N/A*		Yes	No or N/A*
99	1	7.7	33.7	58.7	48.1	51.9	28.9	62.9	22.1	77.9	32.7	67.3	70.2	29.8	70.2	100	70.2	29.8	100	19.2	80.8

No or N/A* = the item is not proceeded or does not appear

3.3 Study characteristics

The articles included were analyzed by their primary and secondary outcomes. Seventy studies analyzed QoL risk and protective factors (Table 2), 11 focused on the development of QoL at different ages and times in the disease (Table 3), and 25 studied the effect of psychological intervention on QoL in MS (Table 4).

All the articles included employed standardized and validated QoL measurement instruments; 64 studies evaluated QoL with a generic measure and 50 studies made use of a disease-specific measure. The Short Form Health Survey 36 (SF-36) was mainly used (n = 29) as a generic measure and Multiple Sclerosis Quality of Life-54 (MSQoL-54) (n = 28) as a disease-specific measure. Finally, 11 studies used more than one measure to evaluate QoL. The study designs were mostly cross-sectional (n = 74), and sample sizes ranged from 7 to 74451 participants.

The main findings of the articles are summarized below.

3.4 Risk and protective MS QoL factors

Factors influencing MS patients QoL are summarized in Table 2.

3.4.1 Clinical factors

Functional impairment, as assessed by the EDSS level was one of the leading causes of diminished QoL.[25-35] Disease duration, [30,31] progressive type,[26,36,37] progressive MS onset[38] and relapses in the last three months were further relevant factors negatively affecting QoL.[26]

Several studies found a significant association between the severity and number of symptoms and the decline of QoL in MS.[33,37,38-41] Fatigue was identified as a main risk factor.[28,29,39,40,42-52]

A number of articles stated the importance of sensory[53,54] and motor[49,52,54,55] dysfunction on quality of life, including paralysis, walking difficulties, balance, stiffness, and spasms as motor problems, specifically emphasizing pain[34,39,50,51,55,56] and spasticity[49,57,58], and low sensory sensitivity and sensation avoidance as sensory problems.

Bladder dysfunction,[34,59,60] bowel dysfunction,[34] sexual,[60-62] and sleeping[34,39,48,63,64] problems contributed to deterioration of QoL.

A diversity of cognitive impairments, for instance, cognitive fatigue, memory loss and planning/organizational dysfunction, were recognized as risk factors by a number of studies.[39,50,52,53,65-67] Sgaramella et al.[68] showed that maintaining executive functioning was a protective factor of QoL. This was also the only study on the important subject of cognitive reserve and QoL.

3.4.2 Psychosocial factors

3.4.2.1 Emotional symptoms

Some studies reported the beneficial effect of emotional stability on QoL,[69] and the harmful effect of emotional problems.[52,70] The emotional symptom studied most was depression[28,29,32,34,35,39,40,51,55,65,69,71-75] followed by anxiety.[39,40,51,69,71-74,76] Both symptoms were confirmed as risk factors for QoL in MS. Similarly, high levels of perceived stress,[37,40,41] anger expression-in[74] and apathy[29] were identified as factors related to emotional regulation negatively affecting QoL in MS.

3.4.2.2 Personality domains

The role of personality domains was explored in several studies. Cyclothymic and depressive temperament were associated with a lower QoL in MS, in contrast to hyperthymic temperament, which was associated with higher QoL.[77] Another study recognized extraversion as a personality trait related to higher QoL levels.[69] Cioncoloni et al.[34] recognized introverted personality as a risk factor for QoL in MS, and finally, type D personality was another relevant factor.[78]

3.4.2.3 Coping strategies

Results with regard to coping strategies were consistent. Active coping, problem resolution, planning problem-solving, cognitive positive restructuring, emotional and instrumental social support, emotional expression, acceptance, and growth were related to a higher QoL in MS.[51,71,79-82] In addition, Grech et al.[80] found a similar connection with restrained coping, Strober[51] with humor, and Mikula et al.[82] with stopping unpleasant emotion coping strategies. On the contrary, problem avoidance,[71,81] behavioral disengagement,[51,80] distancing,[81] self-distraction,[79] denial,[51,79] emotion-focused and venting coping strategies,[80] social withdrawal,[71] wishful thinking,[71] self-criticism,[71,81] suppression,[80] and self-controlling coping[70] were associated with lower QoL.

Coping strategies were also identified as relevant mediator variables. Problem-focused, emotion-focused, and stopping unpleasant emotion coping strategies were partial mediators between fatigue[83] or type D personality[84] and QoL as measured by the mental composite score (MCS).

3.4.2.4 Other psychological factors

According to Van Damme et al.,[85] acceptance of the illness is a protective factor for QoL. The role of flexible adjustment and tenacious goal pursuit in achieving personally blocked goals was not as clear, although their findings showed a trend towards a positive relationship.

Resilience was confirmed as a protective factor of QoL in MS.[27,86] Moreover, Koelmel et al.[87] highlighted its role as a mediator variable in the relationship between social support and MCS.

High levels of self-efficacy,[51,88] self-esteem,[88] illness identity[88] and sense of coherence[89] correlated with higher QoL, and self-esteem mediated in the relationship of social support with MCS.[90] Ultimately, cognitive fusion, the extent to which people feel fused with or attached to their thoughts, mediated the relationship between stigma and QoL in MS.[91]

3.4.2.5 Social factors

Social support[92] and participation[93] were positively related with QoL. Several mediators in this relationship were mentioned above.

3.4.3 Demographic factors

Employment was found to be the leading sociodemographic factor influencing QoL. Several studies displayed an association between unemployment and lower QoL.[30,34,54,67,94] Others showed a positive correlation between jobs adapted to disability,[94] job match and job satisfaction,[41] high employment status,[33,41] and QoL in MS. Low socioeconomic status[35] and financial straits[37] were also risk factors for lower QoL.

Brola et al.[30,31] noted that not having access to an adequate pharmacological treatment put QoL in danger. Congruent with this finding, Boogar et al.[35] found a positive treatment experience to be a protective factor.

Other sociodemographic variables related to poorer QoL in MS were male sex,[37] old age,[30,31] unmarried or living with significant others,[37] whereas a higher education was a protective factor.[33]

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (mean) Sex (Female%)	Main results: Risk factors	Main results: Protective factors
Clinical variables					
Gupta et al (2014)[25]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 74451 47.9 years 51.3 %	EDSS (PCS)	
Gross et al (2017)[36]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 810 RRMS 48.9years SPMS 55.7 years RRMS 71.6 % SPMS 56.2 %	Progressive MS type (PCS)	
Zhang et al (2019)[38]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D)	N = 1958 55.3 years 78.1%	Progressive MS at onset	
Rezapour et al (2017)[26]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 171 35.7 years 76.6%	Relapses in the last 3 months	Mild EDSS RRMS Type
Marck et al (2017)[56]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 2296 45.5 years 82.2%	Pain	
Milinis et al (2016)[57]	Cross- sectional	Leeds MS Quality of Life Scale (MSQoL)	N = 701 48.8 years 72%	Spasticity	
Zettl et al (2014)[58]	Cross- sectional	EuroQol 5-Dimensions (EQ-5D) Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 414 48.6 years 64.3 %	Spasticity	
Leonavicius et al (2016)[42]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 137 44.7 years 72.3%	Fatigue (MCS)	
Garg et al (2016)[43]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 89 54.26 years 66%	Fatigue	
Fernández-Muñoz et al (2015)[44]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 108 44 years 55%	Fatigue	
Weiland et al (2015)[45]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 2738 45.5 years 82.3%	Fatigue	
Aygünoğlu et al (2015)[46]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 120 34.24 years 70 %	Fatigue	
Vister et al (2015)[47]	Cross- sectional	World Health Organization Disability Assessment Schedule (WHODAS) 2.0	N = 210 50.8 years 72.4 %	Fatigue	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results: Risk factors	Main results: Protective factors
Tabrizi et al (2015)[48]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 217 36.2 years 79 %	Fatigue Poor sleep quality Low MCS (PCS)	
White et al (2019)[64]	Cross- sectional	EuroQol 5-Dimensiones (EQ-5D)	N = 531 51.60 years 70.1 %	Sleep disorder	
Barin et al (2018)[49]	Cross- sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS)	N = 855 48 years 72.7 %	Fatigue Balance Spasticity Paralysis Walking difficulty	
Kratz et al (2016)[50]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 180 50.5 years 78 %	Fatigue (MCS) Pain (MCS) Memory loss (MCS)	
Colbeck et al (2018)[53]	Cross- sectional	RAND-36 Health Item Survey (RAND-36)	N = 30 - 73.33%	Cognitive fatigue Low sensory sensitivity Sensation avoiding	
Grech et al (2015)[65]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 107 48.8 years 77.6 %	Cognitive inflexibility	
Sgaramella et al (2014)[68]	Cross- sectional	Quality of life questionnaire (QoL)	N = 39 42.2 years 71.8 %		Executive function
Khalaf et al (2016)[59]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 1048 47.8 years 81%	Lower urinary tract symptoms	
Vitkova et al (2014)[60]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 223 38.4 years 67.3 %	Bladder dysfunction (MCS) Sexual dysfunction (MCS)	
Qaderi et al (2014)[61]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 132 36.9 years 100 %	Sexual problems (PCS and MCS)	
Schairer et al (2014)[62]	Cross- sectional	Short-Form Health Survey 12 (SF-12)	N = 6138 50.6 years 74.7 %	Sexual dysfunction	
Ma et al (2017)[63]	Cross- sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 231 40.2 years 58.4 %	Sleep disorders	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results: Risk factors	Main results: Protective factors
Psychosocial variables					
Ledesma et al (2018)[71]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 26 39.2 years 57.5%	Problem avoidance Social withdrawal Wishful thinking Self-criticism Anxiety Depression	Problem resolution Cognitive restructuring Emotional social and instrumental support Emotional expression
Grech et al (2018)[80]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 107 48.8 years 77.57%	Behavioral disengagement Suppression and lack control Emotional venting	Acceptance Growth Restrain
Zengin et al (2017)[79]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 214 36-46 years 53.2%	Self-distraction Denial Substance use	Planning Active coping Acceptance Positive reinterpretation Social support
Farran et al (2016)[81]	Cross- sectional	Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL)	N = 34 36 years 56%	Self-criticism Escape avoidance Distancing Self-controlling	Emotional social support Instrumental social support Planful problem solving Positive reappraisal
Mikula et al (2014)[82]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 113 40.8 years 77 %		Problem focused coping Stopping unpleasant emotion Getting support
Van Damme et al (2016)[85]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 117 41 years 70.2 %		Acceptance (PCS and MCS) Tenacious goal pursuit (PCS) Flexible goal adjustment (MCS)
Wilski et al (2016)[88]	Cross- sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 257 47.9 years 69.93%		Self-efficacy Self-esteem Illness identity
Nery-Hurwit et al (2018)[86]	Cross- sectional	Function Neutral Health-Related Quality of Life Short Form (FuNHRQOL-SF)	N = 259 48.6 years 84.23%		Resilience Self-compassion
Calandri et al (2018)[89]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 90 37 years 61.1 %		Sense of Coherence
Fernández-Muñoz et al (2018)[75]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 108 44 years 55 %	Depression	
Pham et al (2018)[76]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 310 49 years 73.6 %	Anxiety	
Prisnie et al (2018)[72]	Longitudinal (T1 = basal level/ T2 = 2 weeks later)	Short Form Health Survey 12 (SF-12)	N = 139 40 years 70.5%	Anxiety Depression	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Protective factors
Alsaadi et al (2018)[73]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 80 35.1 years 65 %	Anxiety Depression	Alsaadi et al (2018)[62]
Labiano-Fontcuberta et al (2015)[74]	Cross- sectional	Functional Assessment of Multiple Sclerosis (FAMS)	N = 157 41.7 years 66.9%	Depression Anxiety Anger expression-in	
Paziuc et al (2018)[69]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 60 46 years 85 %	Trait anxiety State anxiety Depression	Extraversion Emotional Stability
Phillips et al (2014)[70]	Cross-seccional	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N = 32 44.0 years 75 %	Emotional problems	
Salhofer-Polanyi et al (2018)[77]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 139 40.0 years 70.5%	Depressive temperament Cyclothymic temperament	Hyperthymic temperament
Demirci et al (2017)[78]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 74 35.3 years 65.51%	Type D personality	
Mikula et al (2015)[93]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 116 40.4 years 72.4%		Social participation (MCS y PCS)
Costa et al (2017)[92]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 150 41.7 years 70.7%		Social support
Clinical, psychosocial, and demographic variables					
Nakazawa et al (2018)[27]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 63 41.7 years 66.67 %	EDSS level	Resilience
Ciampi et al (2018)[28]	Cross-sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 43 57.2 years 65.1 %	EDSS level Fatigue Depression	
Fernández-Jiménez et al (2015)[32]	Cross-sectional	Functional Assessment of Multiple Sclerosis (FAMS)	N = 97 47.3 years 82.5 %	EDSS level Depression	
Klevan et al (2014)[29]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 93 41.8 years 69 %	EDSS (PCS) Fatigue Depression Apathy	
Williams et al (2014)[55]	Cross-sectional	Short-Form Health Survey 36 (SF-36) Short-Form Health Survey 12 (SF-12)	N = 447 49.3 years 70.02 %	Pain (PCS) Muscle spasms (PCS) Stiffness (PCS) Depression (MCS)	

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Protective factors
Hyncicova et al (2018)[40]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 67 32.3 years 53.7%	Number and severity of symptoms Fatigue Stress Depression Anxiety	
Shahrbanian et al (2015)[39]	Cross- sectional	Person Generated Index (PGI)	N = 188 43 years 74%	Pain Fatigue Irritability Anxiety Depression Sleep disorder Cognitive deficits	
Strober et al (2018)[51]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 69 40.4 years 89.5%	Pain Fatigue Behavioral disengagement Denial Depression Anxiety High neuroticism Low extroversion Low self-efficacy	Acceptance Growth Emotional social and instrumental support Planning Active coping Positive reinterpretation Humor
Dymecka et al (2018)[52]	Cross-sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 137 46.5 years 53.3 %	Fatigue Upper-limb disability Lower-limb disability Cognitive disorders Emotional problems	
Samartzis et al (2014)[66]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 100 40.5 years 64 %	Perceived planning/organization dysfunction Perceived retrospective memory dysfunction Depression	
Brola et al (2016)[31]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS) Multiple Sclerosis Impact Scale (MSIS-29)	N = 2385 37.8 years 69.7%	EDSS level MS duration Lack of DMD treatment Age	
Brola et al (2017)[30]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS) Multiple Sclerosis Impact Scale (MSIS-29)	N = 765 44.9 years 67.7 %	EDSS MS duration Be unemployed Age No immunomodulatory therapy	
Abdullah et al (2018)[54]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 200 35.1 years 68%	Motor symptoms Low resistance Sensory symptoms Low income Be unemployed	

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Risk factors
Nickel et al (2018)[33]	Cross-sectional	Multiple Sclerosis International Quality of Life (MusiQoL)	N = 1220 47.8 years 76 %	EDSS Comorbidity	High educational level High employment status
Campbell et al (2017)[67]	Cross-sectional	Functional assessment of multiple sclerosis (FAMS) EuroQol 5-Dimensions (EQ-5D)	N = 62 49.4 years 69.35%	Cognitive deficits Be unemployed	
Chiu et al (2015)[94]	Cross-sectional	Short Form Health Survey 12 (SF-12)	N = 157 43.8 years 86%	Be unemployed	Disability adjusted employment
Boogar et al (2018)[35]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 193 38.1 years 64.8 %	High disability Depression Low socioeconomic status	Positive story treatment
Bishop et al (2015)[41]	Cross-sectional	Quality of Life Scale (QOLS)	N = 1839 54 years 78.1 %	Number and severity of symptoms Perceived stress	High educational level High employment status Job satisfaction Job match
Cioncoloni et al (2014)[34]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 57 41.7 years 68.42%	EDSS level Fatigue Pain Bladder dysfunction Bowel dysfunction Depressive manifestations Sleeping problems Introverted personality Be unemployed	
Cichy et al (2016)[37]	Cross-sectional	Quality of Life Scale (QOLS)	N = 703 63 years 76 %	Progressive MS Progressive diagnosis Number and severity of symptoms Perceived stress Be male Not married/not living with significant other Unable to meet living expenses	
Mediational variables				*Mediator variable*	*Mediated relation*
Mikula et al (2016)[84]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 156 40 years 75 %	Coping strategies Problem focused Emotional focused Stopping	Personality type D and MCS
Mikula et al (2015)[83]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 154 40.05 years 76%	Coping strategies	Fatigue and MCS and PCS
Mikula et al (2017)[90]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 74 35.3 years 65.51%	Self-esteem	Social participation and MCS

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Risk factors	Main results Risk factors
Koelmel et al (2017)[87]	Longitudinal (T1 = basal level/ T2 = 10 weeks later/ T3 = 26 weeks later/ T4 = 52 weeks later)	Short Form Health Survey 8 (SF-8)	N = 163 52.2 years 87.1%	Resilience	Social support and MCS
Valvano et al (2016)[91]	Cross- sectional	Leeds MS Quality of Life Scale (MSQoL)	N = 128 45.5 years 85%	Cognitive fusion	Stigma and QoL

EDSS = expanded disability status scale; PCS = physical composite; RRMS = remittent remitting; SPMS = secondary progressive; MS= multiple sclerosis; MCS = mental composite score; DMD = disease modifying drug; QoL = quality of life

3.5 Disease history

Table 3 summarizes the characteristics of studies focusing on QoL at different ages and times in the disease history. Some of the selected studies examined QoL in MS in its early years. According to Possa et al.[95], QoL decreased in the first year of diagnosis, as assessed by the MCS and physical composite score (PCS). Stern et al.[96] found the worst QoL in the youngest group of MS patients.

Calandri et al.[97] found that during the first three years from diagnosis, problem-solving and avoidance coping strategies had a positive effect on QoL. Nourbakhsh et al.[98] also studied factors influencing the development of QoL in the first three years. Their results showed that higher baseline levels of fatigue and depression predicted worse QoL as assessed by the PCS, whereas lower cognitive functioning and higher fatigue predicted a worse MCS.

Another study on QoL in MS by Buhse et al.[99] focused on old age. These authors identified neurological impairment, physical disability, depression, and comorbidity with thyroid disease as risk factors for worse QoL as assessed by the PCS in a sample of elderly MS patients. On the contrary, being widowed and employed were identified as protective PCS factors.

In a longitudinal study, Kinkel et al.[100] showed that a second clinical event consistent with clinically defined MS, higher EDSS at the time of diagnosis and an earlier MS onset predicted a decrease in PCS 10 years after diagnosis. Bueno et al.[101] also showed that progression from benign MS to non-benign MS predicted a decrease in PCS 25-30 years after diagnosis.

Some longitudinal predictors of QoL identified have been: longer MS duration predicted worse QoL two years later,[102] and worse EDSS predicted worse QoL two,[102] six,[103] and ten[104] years later. Depression predicted worse QoL six[103] and ten[104] years later, and stronger pain[105] and cognitive impairment[104] predicted worse QoL ten years later.

.

Table 3
Characteristics of included studies

Authors, Publication year	Study design (T1: /T2:…)	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Years of diagnosis				
Possa et al (2017)[95]	Cross-sectional	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 38 32.9 years 58%	Decrease in MCS (38%) and PCS (19%) in the first year after diagnosis.
Calandri et al (2017)[97]	Cross-sectional	Short Form Health Survey 12 (SF-12)	N = 102 35.8 years 61.8%	Problem solving ($\beta = 0.28$) and avoidance ($\beta = 0.25$) was related to a higher MCS in the first 3 years of diagnosis.
Nourbakhsh et al (2016)[98]	Longitudinal (T1 = basal level/ T2 = 3 months after diagnosis/ T3 = 6 months after diagnosis/ T4 = 12 months after diagnosis/ T5 = 18 months after diagnosis/ T6 = 24 months after diagnosis / T6 = 36 months after diagnosis)	Short Form Health Survey 36 (SF-36)	N = 43 36 years 72%	Baseline severity of fatigue and depression predicts PCS and cognitive function and fatigue MCS in the first 3 years of diagnosis.
MS progression				
Kinkel et al (2015)[100]	Longitudinal (T1 = CIS diagnosis/T2 = 5 years after diagnosis/ T3 = 10 years after diagnosis)	Short Form Health Survey 36 (SF-36) Multiple Sclerosis Quality of Life Inventory (MSQLI)	N = 127 34.1 years 74%	A second clinic event consistent with CDMS, higher EDSS at the diagnosis and an earlier onset CDMS predicts a decrease QoL.
Bueno et al (2014)[101]	Cross-sectional (25-30 years after diagnosis)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 61 54.9 years 83.6%	Patient changing from benign (EDSS<3) to non-benign (EDSS>3) decreases PCS.
Years of MS duration				
Baumstarck et al (2015)[102]	Longitudinal (T1 = basal level/ T2 = 24 months later)	Multiple Sclerosis International Quality of Life questionnaire (MusiQol) Short-Form Health Survey 36 (SF-36)	N = 526 40.0 years 74.3%	Low levels of QoL, higher MS duration and higher EDSS level at T1 predicted worse QoL at T2.
Tepavcevic et al (2014)[103]	Longitudinal (T1 = basal level/ T2 = 3 years later/ T3 = 6 years later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 93 41.5 years 71%	Higher EDSS and depression at basal level predicted a decrease of QoL at T1 and T2.
Young et al (2017)[105]	Longitudinal (T1 = basal level/ T2 = 7 years later/ T3 = 10 years later)	Assessment of Quality of life (AQoL)	N = 70 59.8 years 71.6%	Higher pain predicts a decrease in QoL.
Chruzander et al (2014)[104]	Longitudinal (T1 = basal level/ T2 = 10 years later)	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analog Scale (EQ-VAS) Sickness Impact Profile (SIP)	N = 118 49 years 72%	Cognitive impairment, depressive symptoms and EDSS predicted a decrease in QoL at T2.
Group age				
Stern et al (2018)[96]	Cross-sectional	Multiple Sclerosis Quality of Life Instrument (MSQOL-54)	N = 57 50 years 73.7%	The youngest group (35-44) presents worst PCS vs the oldest (55-65).
Buhse et al (2014)[99]	Cross-sectional	Multiple Sclerosis Quality of Life–54 (MSQOL- 54)	N = 211 65.5 years 80%	Risk of neurologic impairment, physical disability, depression, and the comorbidity of thyroid disease was associated with decrease in PCS. Being widowed and employed was associated with increase in PCS.

MCS = mental composite score; PCS = physical composite score; CIS = clinical isolated syndrome; CDMS = clinical defined multiple sclerosis; EDSS = expanded disability status scale; QoL = quality of life.

3.6 Interventions

Details of the selected articles on psychological intervention are presented in Table 4.

3.6.1 Mindfulness-based therapies

All mindfulness-based therapy intervention programs showed improvement in QoL at some evaluation point and at least in some QoL domains. Body-affective mindfulness intervention increased the general QoL score up to six months after treatment.[106]

Of the three studies on mindfulness-based stress reduction programs, two showed a significant increase in QoL after treatment.[107-109] One study[109] only produced a small, insignificant increase after treatment and at the three-month follow-up.

A community-based mindfulness program resulted in a significant increase in MCS.[110]

Finally, mindfulness-based cognitive therapy did not show any significant difference in general QoL between the control and the experimental group, however, it did show significant differences in QoL: in health distress, mental well-being, role limitation due to emotional problems and cognitive performance.[111]

3.6.2 Cognitive-behavioral

A wide spectrum of cognitive behavioral interventions was analyzed.

In a study by Case et al.,[112] the experimental group attended 10 one-hour weekly sessions of healing light guided imagery. They found a greater increase in QoL in this group than with 10 hours of positive journaling in the active control group.

Blair et al.[113] focused intervention on emotion regulation. The design consisted of 16 1.5-hour biweekly sessions for eight weeks. The intervention resulted in a significant increase in QoL six months after treatment.

Interventions by Calandri et al.[114] and Graziano et al.[115] had a comparable design. Participants were divided into two subgroups by age. Intervention comprised four-five two-hour sessions over the course of two months, and one follow-up session six months after treatment. Calandri et al.[114] also included one follow-up session 12 months after treatment. At follow-up, the intervention groups in both studies had experienced an increase in QoL.

Three studies[116-118] focused intervention on depressive symptoms. Kiropoulos et al.[116] and Chruzander et al.[117] found improvement in QoL at post-treatment and follow-up assessments. Kikuchi et al.[118] also found a post-treatment improvement, but not significant.

Two of the studies based intervention on Acceptance and Commitment Therapy (ACT). Pakenham et al.[119] implemented an eight-week program aimed at training in resilience. QoL increased at treatment end and at three-month follow-up. Proctor et al.[120] implemented an eight-week intervention comprising telephone calls and self-help ACT books. No significant increase in QoL was observed.

3.6.3 Social and group support

The following social support and group interventions had an impact on QoL in MS.

Abolghasemi et al.[121] implemented a 12-session supportive-expressive therapy program, which improved QoL.

Jongen et al.[122] tested an intensive social-cognitive wellness program involving the partner or other significant informal caregiver. The results showed an increase in the MCS at one, three and six months from treatment, and in the

PCS six months after treatment. The results of the program were evaluated again 12 months after treatment. The relapsing-remittent MS group showed an increase in PCS and MCS.[123]

Eliášová et al.[124] found more improvement across several QoL domains in MS patients after self-help group sessions than in patients who did not attend the self-help groups. Liu et al.[125] detected an increase in physical and psychological QoL in women with MS after participating in a hope-based group therapy program for one-hour twice a week for eight weeks.

3.6.4 Symptom and self-management-based therapies

Two studies analyzed a fatigue self-management group therapy. Mulligan et al.[126] reported positive, but not significant, changes in QoL after their treatment. Thomas et al.[127] reported significant positive changes in physical health assessed by the Multiple Sclerosis Impact Scale (MSIS-29) and vitality as measured by the SF-36 in the intervention group 12 months after the treatment.

In addition to fatigue self-management, Ehde et al.[128] focused in their intervention on pain and depression self-management. The results were compared to an educational program. There was a higher QoL post-treatment and 12-month follow-up score in the self-management group. Feicke et al.[129] implemented a program focused on MS self-management. As in Ehde et al.,[128] improvements in QoL were still maintained at six-month follow up.

3.6.5 Other psychological intervention

LeClaire et al.[130] implemented a five-week positive psychology program. The results showed only a significant improvement in the SF-36 vitality subscale.

Table 4
Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Mindfulness-based therapies					
Carletto et al (2017)[106]	Body-affective mindfulness (BAM)	Longitudinal (T1 = basal level /T2 = post-treatment /T3 = 6 months later)	Functional Assessment of Multiple Sclerosis (FAMS)	N = 45 44.1 years 71.1%	Increase in general score FAMS from T1 to T2 (P< 0.001) and from T2 to T3 (P= 1).
Besharat et al (2017)[107]	Mindfulness-based stress reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Short Form Health Survey 36 (SF-36)	N intervention/ control= 22/ 11 35 years 100%	Increase in general QoL score in the intervention group (P< 0.05).
Blankespoor et al (2017)[108]	Mindfulness-based Stress Reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 25 52.6 years 84%	Increase PCS (P< 0.001).
Simpson et al (2017)[109]	Mindfulness-based Stress Reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 3 months later)	Multiple Sclerosis Quality of Life Inventory (MSQLI)	N = 25 43.6 years 92%	Small and insignificant increase QoL from T1 to T2 (P= 0.48) and insignificant increase from T2 to T3 (P= 0.71).
Spitzer et al (2018)[110]	Community-based group mindfulness	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 8 weeks later)	Short Form Health Survey 36 (SF-36)	N = 23 48.4 years 91.3%	Increase MCS from T1 to T2 (P= 0.008).
Ghodspour et al (2018)[111]	Mindfulness-based Cognitive Therapy (MBCT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 15/ 15 36 years 100%	Increase in health distress (P=0.032), mental well-being (P 0.001), role limitation due to emotional problems (P= 0.005) and cognitive performance (P= 0.04) subscales.
Cognitive behavioral					
Case et al (2018)[112]	Trial of healing light guided imagery (HLGI)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 9/ - 49.1 years -	Increase in PCS (P= 0.01) and MCS (P< 0.01) in the intervention group.
Blair et al (2017)[113]	Dialectical Behavior Group Therapy (TCD)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 6 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 10/ 10 40.4 years 90%	Increase in MSQoL-54 from T1 to T3 (P= 0.01).
Calandri et al (2017)[114]	Group-based cognitive behavioral therapy (CBT)	Longitudinal (T1 = pre-treatment/ T2 = 6 month post-treatment/ T3 = 1 year post-treatment)	Short Form Health Survey 12 (SF-12)	N intervention/ control= 54/ 31 38 years 61%	Increase in MCS T2 in the CBT group vs control (P= 0.036). Increase in MCS T3 in the CBT group vs control (P= 0.049).
Graziano et al (2014)[115]	Group-based cognitive behavioral therapy (CBT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 6 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 41/ 41 42.3 years	Increase in MSQoL-54 at T3 in the CBT group vs control group (P< 0.05).

Table 4
Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
				66%	
Kiropoulos et al (2016)[116]	Cognitive behavioral therapy (CBT) for depressive symptoms	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 20 weeks later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 15/15 34.6 years 86.7%	Differences between control and CBT group MCS and PCS in T2 and T3 (P< 0.001).
Chruzander et al (2016)[117]	Cognitive behavioral therapy (CBT) focused on depressive symptoms	Longitudinal (T1 = basal level/ T2 = 3 weeks post-treatment/ T3 = 3 months post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29) EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analog Scale (EQ-VAS)	N = 15 38 years 80%	Improvement in QoL from MSIS-29 and EQ-5D in T2 and T3 (P< 0.05).
Kikuchi et al (2019)[118]	Cognitive behavioral therapy (CBT) on depression	Longitudinal (T1 = pre-treatment/ T2 = mind-treatment/ T3 = post-treatment)	Functional Assessment of Multiple Sclerosis (FAMS)	N = 7 46.1 years 71.4%	Positive but not significant increase in FAMS (P> 0.05).
Pakenham et al (2018)[119]	Resilience Training Program (ACT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 3 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 37 39.4 years 73%	Increase in PCS (P< 0.001) and MCS (P< 0.006) from T1 to T2, maintained at T3, without significant changes.
Proctor et al (2018)[120]	Telephone-supported acceptance and commitment bibliotherapy (ACT)	Longitudinal (T1 = pre-randomization / T2 = 12 weeks after randomization)	EuroQol 5-Dimensions (EQ-5D)	N intervention/ control= 14/13 45.8 years 78%	No significant increase in QoL (P= 0.62).
Social and group support					
Liu (2017)[125]	Hope-Based Group Therapy (HBGT)	Longitudinal (T1 = pre-treatment / T2 = post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29)	N intervention/ control= 18/14 35.1 years 100%	Physical and psychological QoL increase in HBT group (P< 0.05).
Abolghasemi et al (2016)[121]	Supportive-Expressive Therapy (SE)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N intervention/ control= 16/16 31.8 years 41.7%	Increase QoL from T1 to T2 (P<0.001).
Jongen et al (2016)[122]	Intensive social cognitive treatment (can do treatment) with participation of support partners	Longitudinal (T1 = basal level/ T2 = 12 months post-treatment)	Multiple Sclerosis Quality of Life Instrument (MSQoL-54)	N = 38 - 65.8%	PCS increase (P= 0.032) and MCS (P= 0.087) in the RR group.
Jongen et al (2014)[122]	Intensive social cognitive wellness program with participation of support partners	Longitudinal (T1 = basal level/ T2 = 1 months post-treatment/T3 = 3 months post-treatment T4 = 6 months post-treatment	Multiple Sclerosis Quality of Life Instrument (MSQoL-54)	N = 44 45.7 years 79.5%	MCS increase at T2, T3 and T4 and PCS at T4 (P< 0.05).

Table 4
Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Eliášová et al (2015)[124]	Self-Help group (SH)	Cross-sectional (T1 = after the treatment)	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N intervention/ control = 46/ 35 42.2 years 59%	Increase in physical (P< 0.001), psychological (P< 0.001) and social relationships (P< 0.001) in the SH group.
Symptom and self-management-based therapies					
Mulligan et al (2016)[126]	Fatigue self-management program "Minimize Fatigue, Maximize Life: Creating Balance with Multiple Sclerosis (MFML)"	Longitudinal (T1 = 1 month pre-treatment/ T2 = pre-treatment/ T3 = post-treatment).	Short Form Health Survey 12 (SF-12)	N = 24 49.3 years 100%	Positive but not significant changes in SF-12 (P> 0.05).
Thomas et al (2014)[127]	Group-based fatigue management (FACETS)	Longitudinal (T1 = 1 week before treatment/ T2 = 1 month post-treatment/ T3 = 4 month post-treatment/ T4 = 12 month post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29) Short Form Health Survey 36 (SF-36)	N intervention/ control = 44/ 80 48 years 73%	Changes in physical health MSIS-29 (P= 0.046) and vitality SF-36 (P= 0.03) at T4.
Ehde et al (2015)[128]	Telephone-Delivered Self-Management (SM)	Longitudinal (T1 = before group randomization/ T2 = post-treatment/ T3 = 6 month post-treatment/ T4 = 12 month post-treatment)	Short Form Health Survey 8 (SF-8)	N intervention/ control = 53/ 88 51 years 89.3%	MCS and PCS increase at T2, T3 and T4 (P< 0.05).
Feicke et al (2014)[129]	Education program for self-management competencies (S.MS)	Longitudinal (T1 = 1 basal level/T2 = post-treatment /T3 = 6 month post-treatment)	Hamburg quality of life questionnaire in multiple sclerosis (HAQUAMS)	N intervention/ control = 31/ 33 41.9 years 87.1%	Stable positive changes in QoL (P= 0.007).
Other psychological intervention					
Leclaire et al (2018)[130]	Group Positive Psychology	Longitudinal (T1 = basal level /T2 = post-treatment)	Short Form Health Survey 36 (SF-36)	N = 11 53.5 years 100%	Increase in SF-36 vitality subscale score (P= 0.016). Increase in mental health SF-36 subscale (P= 0.098) that did not reach statistical significance.

FAMS = functional assessment of multiple sclerosis; QoL = quality of life; PCS = physical component score; MCS = mental component score; MSQoL-54 = multiple sclerosis quality of life instrument; CBT = cognitive behavioral therapy; SF-36 = short form health survey 36; MSIS-29 = multiple sclerosis impact scale; EQ-5D = euroqol 5-dimensions; HBT = hope-based group therapy; RR= relapsing-remitting; SH = self-help group; SF-12 = short-form health survey

4. Discussion

Firstly, the present systematic review was intended to identify risk and QoL protective factors in MS. The results showed that the EDSS was most employed for assessment of functional impairment.[25-35] As expected, the number and severity of symptoms and associated impairment appeared to play a crucial role in QoL. Fatigue,[28,29,39,40,42-52] cognitive impairment,[39,50,52,53,63,66,67] and pain[35,39,50,51,55,56], in particular, were the focus of a large number of studies, and were confirmed as important risk factors. Longitudinal studies suggested that greater fatigue,[98] pain,[105] and cognitive impairment[98,104] also predicted worse QoL up to 10 years later. This has important clinical implications, as treatment of the abovementioned symptoms should be prioritized. In general, functional impairment,[102-104] as well as longer duration of illness,[102] were predictors of QoL two to 10 years later, whereas disease progression[101] from benign to non-benign MS predicted QoL as measured by the PCS up to 30 years later.

Among the emotional symptoms, there was convincing evidence that depression,[28,29,32,34,35,39,40,51,55,66,69,71-75] along with depressive temperament[77] and anxiety,[38,40,51,69,71-74,76] were associated with lower QoL, and that depression also predicted QoL up to 10 years later.[104]

The coping strategies applied obviously influenced QoL in MS, however their effect depended on the specific circumstances of the disease history. For example, problem-solving and avoidance coping, normally classified as opposite strategies, both seemed to have a positive effect on the MCS in the first three years of diagnosis.[97] However, in general, strategies associated with denial[51,79] and avoidance of the challenges of the disease, such as problem avoidance,[71,81] behavioral disengagement, [51,80] distancing, [81] self-distraction,[79] social withdrawal,[71] wishful thinking,[71] were associated with a lower QoL. On the other hand, strategies based on acceptance and active commitment, such as active coping, humor, problem resolution, cognitive positive restructuring, and emotional expression, led to higher QoL in MS.[51,71,79-82] Obviously, there is a close connection between the active confrontation of the challenges of illness and specific personality-based convictions, such as a high self-efficacy. Thus, higher self-efficacy,[51,88] self-esteem,[88] and sense of coherence[89] improved QoL in MS.

Regarding sociodemographic influences on QoL, not surprisingly, unemployment, a low socioeconomic status[35] and financial difficulties[37] proved to be major risk factors[30,34,54,67,94]. In keeping with the negative influence of the scarcity of resources, lack of access to therapy was also identified as a risk factor.[30,31]

The second aim of this systematic review was to study QoL in MS patients at different times during their disease history. Two studies showed diminishing QoL in MS patients in its early stage.[95,96] This might have to do with the fact that patients being diagnosed with a severe chronic disease need a certain time to come to terms with this emotional shock. Oscillation between avoidance and problem-solving, which both have a positive influence in the first three years after diagnosis,[97] may be behind this inner struggle. In older patients, neurological impairment and physical disability,[97] which represent the age-associated increase in physical impairment, were identified as risk factors for QoL in MS.

Finally, the third aim of this review was to analyze psychological interventions for the improvement of QoL in MS. Symptomatic improvement of psychopathology usually at the center of psychotherapy outcome studies, was not the primary focus of our review.[131] Eight of the intervention studies specifically treated depressive symptomatology,[106,110-112,115,117-118] either with mindfulness-based or cognitive-behavioral approaches, both of which proved to be successful.

Three studies were specifically directed towards the treatment of fatigue[112,126,127] by light guided imagery or self-management programs. Both the imagery and self-management group intervention approaches were successful, whereas the individual self-management program did not show significant improvement.

A variety of mindfulness-based approaches[107-109] and a Community-based intervention were directed at stress reduction.[110] Three of the four studies showed some kind of improvement in QoL, including the only study with a control group.

Several of the interventions were designed to reinforce protective factors in MS patients. Graziano et al.[115] focused on identity redefinition, sense of coherence and self-efficacy. Pakenham et al.[119] implemented a program based on resilience training, and the program by Blair et al.[113] focused on the improvement of emotion regulation. All of them were successful in improving QoL, confirming the alternative focus on protective factors instead of risk factors.

A wide spectrum of interventions based on social support concentrated on reinforcement of the social network of MS patients, for example, self-help groups,[124] hope-based group therapy,[125] supportive-expressive therapy,[121] and social cognitive training with support partners.[122,123] All interventions aimed at helping people overcome MS barriers in daily living by strengthening their social support, improving some aspects of QoL. This is consistent with the studies mentioned above [92,93] and emphasizes the importance of social support and participation as a protective factor for QoL.

5. Limitations

The main limitation of this study was the impossibility of carrying out a quantitative synthesis of the results, due to the heterogeneity of methodologies and designs in the articles included. Due to the vast number of topics and limited resources our search was restricted to a five-year period through January 2019.

6. Conclusions

This review was intended to give a broad overview of QoL in MS. The findings show the importance of clinical, psychosocial and demographic variables as QoL risk and protective factors. A variety of psychological interventions ranging from mindfulness-based and cognitive-behavioral approaches to self-help groups addressing these factors were identified as promising options for improving QoL. These findings have important clinical implications. A sound biopsychosocial assessment of MS patients in daily clinical practice is necessary to ensure the possibility of early identification of QoL risk factors and evidence-based psychological intervention is recommended to improve or stabilize QoL.

Authors Contribution

Irene Gil-González: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

Agustín Martín-Rodríguez: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

Rupert Conrad: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

María Ángeles Pérez-San-Gregorio: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

This study was financially supported by the program of Formation of University Professor of Ministry of Education, Culture and Sport of Spain grant number: FPU 17/04240.

Data sharing statement

All relevant data appear in the study manuscript. No additional data available.

Patient and public involvement

No patient involved.

References

[1] World Health Organisation. Governance. Basic documents. World Health Organisation. https://www.who.int/about/who-we-are/constitution. Published 2019.Accesed December 15, 2019.
[2] Patti F, Pappalardo A. Quality of life in patients affected by multiple sclerosis: a systematic review. In: Preedy V.R., Watson R.R., eds. Handbook of Disease Burdens and Quality of Life Measures. New York: Springer, New York (NY) 2010:3769-3783. doi:10.1007/978-0-387-78665-0_218
[3] Bernstein U. The World Health Organization Quality of Life Assessment (WHOQOL): Position Paper from the World Helath Organization. *SocSciMed* 1995;41(10):1403-1409.
[4] Marcel W.M. Definitions of quality of life: What has happened and how to move on. *Top Spinal Cord Inj Rehabil* 2014;20:167-180.doi:10.1310/sci2003-167
[5] Gellert GA. The importance of quality of life research for health care reform in the USA and the future of public health. *Qual Life Res* 1993;2:357-361.doi:10.1007/BF00449431
[6] Benito-León J, Morales JM, Rivera-Navarro J, Mitchell AJ. A review about the impact of multiple sclerosis on health-related quality of life. *Disabil Rehabil* 2003;25:1291-1303.doi:10.1080/09638280310001608591
[7] Hyarat SY, Subih M, Rayan A, Salami I, Harb A. Health related quality of life among patients with multiple sclerosis: The role of psychosocial adjustment to illness. Arch Psychiatr Nurs. 2019;33(1):11-16. doi:10.1016/j.apnu.2018.08.006
[8] Yalachkov Y, Soydaş D, Bergmann J, et al. Determinants of quality of life in relapsing-remitting and progressive multiple sclerosis. *Mult Scler Relat Disord.* 2019;30:33-37.doi:10.1016/j.msard.2019.01.049
[9] Amtmann D, Bamer AM, Kim J, Chung H, Salem R. People with multiple sclerosis report significantly worse symptoms and health related quality of life than the US general population as measured by PROMIS and NeuroQoL outcome measures. *Disabil Health J.* 2018;11(1):99-107. doi:10.1016/j.dhjo.2017.04.008
[10] Pittock SJ, Mayr WT, McClelland RL, et al. Quality of life is favorable for most patients with multiple sclerosis: A population-based cohort study. *Arch Neurol.* 2004;61(5):679-686. doi:10.1001/archneur.61.5.679
[11] McCabe MP, McKern S. Quality of life and multiple sclerosis: Comparison between people with multiple sclerosis and people from the general population. *J Clin Psychol Med Settings.* 2002;9(4):287-295. doi:10.1023/A:1020734901150
[12] Schmidt S, Vilagut G, Garin O, et al. Reference guidelines for the 12-item short-form health survey version 2 based on the catalan general population. *Med Clin.* 2012;139(14):613-625. doi:10.1016/j.medcli.2011.10.024
[13] Petrović N, Prlić N, Gašparić I, Placento H, Gvozdanović Z. Quality of life among persons suffering from multiple sclerosis. *Medica Jadertina.* 2019;49(3-4):217-226.
[14] Algahtani HA, Shirah BH, Alzahrani FA, Abobaker HA, Alghanaim NA, Manlangit Js Jr. Quality of life among multiple sclerosis patients in Saudi Arabia. *Neurosci.* 2017;22(4):261-266. doi:10.17712/nsj.2017.4.20170273
[15] Wilski M, Gabryelski J, Brola W, Tomasz T. Health-related quality of life in multiple sclerosis: Links to acceptance, coping strategies and disease severity. *Disabil Health J.* 2019;12(4):608-614. doi:10.1016/j.dhjo.2019.06.003
[16] Pérez De Heredia-Torres M, Huertas-Hoyas E, Sánchez-Camarero C, et al. Occupational performance in multiple sclerosis and its relationship with quality of life and fatigue. *Eur J Phys Rehabil Med.* 2020;56(2):148-154. doi:10.23736/S1973-9087.20.05914-6
[17] Ochoa-Morales A, Hernández-Mojica T, Paz-Rodríguez F, et al. Quality of life in patients with multiple sclerosis and its association with depressive symptoms and physical disability. *Mult Scler Relat Disord.* 2019;36. doi:10.1016/j.msard.2019.101386
[18] Dorstyn DS, Roberts RM, Murphy G, Haub R. Employment and multiple sclerosis: A meta-analytic review of psychological correlates. *J Health Psychol.* 2019;24(1):38-51. doi:10.1177/1359105317691587

[19] Schmidt S, Jöstingmeyer P. Depression, fatigue and disability are independently associated with quality of life in patients with multiple sclerosis: Results of a cross-sectional study. *Mult Scler Relat Disord.* 2019;35:262-269. doi:10.1016/j.msard.2019.07.029
[20] Ysrraelit MC, Fiol MP, Gaitán MI, Correale J. Quality of life assessment in multiple sclerosis: Different perception between patients and neurologists. *Front Neurol.* 2018;8:1-6. doi:10.3389/fneur.2017.00729
[21] Revicki DA, Osoba D, Fairclough D, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. *Qual Life Res.* 2000;9:887-900. doi:10.1023/A:1008996223999
[22] Baumstarck K, Boyer L, Boucekine M, Michel P, Pelletier J, Auquier P. Measuring the quality of life in patients with multiple sclerosis in clinical practice: a necessary challenge. *Mult Scler Int.* 2013;2013:1-8. doi:10.1155/2013/524894
[23] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
[24] Chacón-Moscos S, Sanduvete-Chaves S, Sánchez-Martín M. The development of a checklist to enhance methodological quality in intervention programs. *Front Psychol* 2016;7:1811.doi:10.3389/fpsyg.2016.01811
[25] Gupta S, Goren A, Phillips AL, Dangond F, Stewart M. Self-reported severity among patients with multiple sclerosis in the U . S . and its association with health outcomes. *Mult Scler Relat Disord* 2014;3:78-88.doi:10.1016/j.msard.2013.06.002
[26] Rezapour A, Kia AA, Goodarzi S, Hasoumi M, Motlagh SN, Vahedi S. The impact of disease characteristics on multiple sclerosis patients ' quality of life. *Epidemiol Health* 2017;39:1-7.doi:10.4178/epih.e2017008
[27] Nakazawa K, Noda T, Ichikura K, Okamoto T. Resilience and depression / anxiety symptoms in multiple sclerosis and neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord* 2018;25:309-315.doi:10.1016/j.msard.2018.08.023
[28] Ciampi E, Uribe-San-Martin R, Vásquez M, et al. Relationship between Social Cognition and traditional cognitive impairment in Progressive Multiple Sclerosis and possible implicated neuroanatomical regions. *Mult Scler Relat Disord* 2018;20:122-128.doi:10.1016/j.msard.2018.01.013
[29] Klevan G, Jacobsen CO, Aarseth JH, et al. Health related quality of life in patients recently diagnosed with multiple sclerosis. *Acta Neurol Scand* 2014;129:21-26.doi:10.1111/ane.12142
[30] Brola W, Sobolewski P, Jantarski K. Multiple sclerosis: patient-reported quality of life in the Świętokrzyskie Region. *Med Stud Med* 2017;33:191-198.
[31] Brola W, Sobolewski P, Fudala M et al. Self-reported quality of life in multiple sclerosis patients : preliminary results based on the Polish MS Registry. *Patient Prefer Adherence* 2016;10:1647-1656.
[32] Fernández-Jiménez E, Arnett PA. Impact of neurological impairment, depression, cognitive function and coping on quality of life of people with multiple sclerosis: a relative importance analysis. *Mult Scler J* 2015;21(11):1468-1472.doi:10.1177/1352458514562439
[33] Nickel S, Kofahl OVKC, Kofahl C. Assessments and determinants of HRQoL in a German MS population. *Acta Neurol Scand* 2018; 137(2): 174-180.doi:10.1111/ane.12854
[34] Cioncoloni D, Innocenti I, Bartalini S, et al. Individual factors enhance poor health-related quality of life outcome in multiple sclerosis patients. Significance of predictive determinants. *J Neurol Sci* 2014;345:213-219.doi:10.1016/j.jns.2014.07.050
[35] Boogar IR, Talepasand S, Jabari M. Psychosocial and Medical Determinants of Health-related Quality of Life in Patients with Relapsing-Remitting Multiple Sclerosis. *Noro Psikiyatr Ars* 2018;13:29-35.doi:10.29399/npa.16983
[36] Gross HJ, Watson C. Characteristics, burden of illness, and physical functioning of patients with relapsing-remitting and secondary progressive multiple sclerosis: a cross-sectional US survey. *Neuropsychiatr Dis Treat* 2017;13:1349-1357.doi:10.2147/NDT.S132079
[37] Cichy KE, Li J, Rumrill PD, Bishop M, Roessler RT. Non-vocational health-related correlates of quality of life for older adults living with multiple sclerosis. *J Rehabil* 2016;82:36-44.
[38] Zhang Y, Taylor BV, Simpson SJ, Blizzard L, van der Mei I. Patient-reported outcomes are worse for progressive-onset multiple sclerosis than relapse-onset multiple sclerosis, particularly early in the disease process. *Eur J Neurol* 2019;26: 155-161. doi:10.1111/ene.13786
[39] Shahrbanian S, Duquette P, Kuspinar A, Mayo NE. Contribution of symptom clusters to multiple sclerosis consequences. *Qual Life Res* 2015;24: 617-629.doi:10.1007/s11136-014-0804-7
[40] Hyncicova E, Kalina A, Vyhnalek M, et al. Health-related quality of life , neuropsychiatric symptoms and structural brain changes in clinically isolated syndrome. *PLoS ONE* 2018;13:1-13.doi:10.1371/journal.pone.0200254.
[41] Bishop M, Rumrill PD, Roessler RT. Quality of life among people with multiple sclerosis: replication of a three-factor prediction model. *Work* 2015;52:757-765.doi:10.3233/WOR-152203
[42] Leonavicius R, Ph DMD. Among multiple sclerosis and fatigue. *Neurol Psychiatry Brain Res* 2016;22:141-145.doi:10.1016/j.npbr.2016.08.002
[43] Garg H, Bush S, Gappmaier E. Associations between fatigue and disability, functional mobility, depression, and quality of life in people with multiple sclerosis. *Int J MS Care* 2016:18:71-77.doi:10.7224/1537-2073.2015-013
[44] Fernández-Muñoz, JJ, Morón-Verdasco A, Cigarán-Méndez M, Muñoz-Hellín E, Pérez-de-Heredia-Torres M, Fernández-de-las-Peñas C. Disability, quality of life, personality, cognitive and psychological variables associated with fatigue in patients with multiple sclerosis. *Acta Neurol Scand* 2015;132:118-124.doi:10.1111/ane.12370
[45] Weiland TJ, Jelinek GA, Marck CH, Hadgkiss EJ. Clinically significant fatigue: prevalence and associated factors in an international sample of adults with multiple sclerosis recruited via the internet. *PLoS ONE* 2015;10:1-18.doi:10.1371/journal.pone.0115541
[46] Aygünoğlu SK, ÇelebİA, Vardar N, Gürsoy E. Correlation of fatigue with depression, disability level and quality of life

in patients with multiple sclerosis. *Noro Psikiyatr Ars* 2015;52:247-251.doi:10.5152/npa.2015.8714
[47] Vister E, Tijsma ME, Hoang PD, Lord SR. Fatigue, physical activity, quality of life, and fall risk in people with multiple sclerosis. *Int J MS Care* 2017;19(2):91-98.doi:10.7224/1537-2073.2015-077
[48] Tabrizi FM, Radfar M. Fatigue, sleep quality, and disability in relation to quality of life in multiple sclerosis. *Int J MS Care* 2015;17:268-274.doi:10.7224/1537-2073.2014-046
[49] Barin L, Salmen A, Disanto G, et al. The disease burden of multiple sclerosis from the individual and population perspective: which symptoms matter most? *Mult Scler Relat Disord* 2018;25:112–121.doi:10.1016/j.msard.2018.07.013.
[50] Kratz AL, Ehde DM, Hanley MA, Jensen MP, Osborne TL, Kraft GH. Cross sectional examination of the associations between symptoms, community integration, and mental health in Multiple Sclerosis. *Arch Phys Med Rehabil*. 2016;97:11-13.doi:10.1016/j.apmr.2015.10.093
[51] Strober LB. Quality of life and psychological well-being in the early stages of multiple sclerosis (MS): Importance of adopting a biopsychosocial model. *Disabil Health J* 2018;11:555-561.doi:10.1016/j.dhjo.2018.05.003
[52] Dymecka J. Biomedical variables and adaptation to disease and health-related quality of life in polish patients with MS. *Int J Environ Res Public Health* 2018; 15: 2678.doi:10.3390/ijerph15122678.
[53] Colbeck M. Sensory processing, cognitive fatigue, and quality of life in multiple sclerosis. *Can J Occup Ther* 2018;85:169-175.doi:10.1177/0008417417727298
[54] Abdullah EJ, Badr HE. Assessing the quality of life in patients with multiple sclerosis in Kuwait: a cross sectional study. *Psychol Heal Med*. 2018;23:391-399.doi:10.1080/13548506.2017.1366660
[55] Williams AE, Vietri JT, Isherwood G, Flor A. Symptoms and Association with Health Outcomes in Relapsing-Remitting Multiple Sclerosis : Results of a US Patient Survey. *Mult Scler Int*. 2014;2014:203183.doi: 10.1155/2014/203183
[56] Marck CH, Livera AM De, Weiland TJ, Jelinek PL. Pain in people with multiple sclerosis : associations with modifiable lifestyle factors, fatigue, depression, anxiety, and mental health quality of life. *Front Neurol* 2017;8:1-7.doi:10.3389/fneur.2017.00461
[57] Milinis K, Tennant A, Young CA. Spasticity in multiple sclerosis: associations with impairments and overall quality of life. *Mult Scler Relat Disord* 2016;5:34-39.doi:10.1016/j.msard.2015.10.007
[58] Zettl UK, Henze T, Essner U, Flachenecker P. Burden of disease in multiple sclerosis patients with spasticity in Germany: Mobility improvement study (Move I). *Eur J Heal Econ* 2014;15:953-966.doi:10.1007/s10198-013-0537-5
[59] Khalaf KM, Coyne KS, Globe DR, et al. The impact of lower urinary tract symptoms on health-related quality of life among patients with multiple sclerosis. *Neurourol Urodyn* 2016;54:48-54.doi:10.1002/nau
[60] Vitkova M, Rosenberger J, Krokavcova M, et al. Health-related quality of life in multiple sclerosis patients with bladder, bowel and sexual dysfunction. *Disabil Rehabil* 2014;36:987-992.doi:10.3109/09638288.2013.825332
[61] Qaderi K, Merghati Khoei E. Sexual problems and quality of life in women with multiple sclerosis. *Sex Disabil* 2014;32:35-43.doi:10.1007/s11195-013-9318-4
[62] Schairer LC, Foley FW, Zemon V, et al. The impact of sexual dysfunction on health-related quality of life in people with multiple sclerosis. *Mult Scler J* 2014;20:610-616.doi:10.1177/1352458513503598
[63] Ma S, Rui X, Qi P, Liu G, Yang J. Sleep disorders in patients with multiple sclerosis in China. *Sleep Breath* 2017;21:149-154.doi:10.1007/s11325-016-1416-y
[64] White EK, Sullivan AB, Drerup M. Impact of sleep disorders on depression and patient-perceived health-related quality of life in multiple sclerosis. *Int J MS Care* 2019;21: 10-14.doi:10.7224/1537-2073.2017-068
[65] Grech LB, Kiropoulos LA, Kirby KM, Butler E, Paine M, Hester R. The effect of executive function on stress, depression, anxiety, and quality of life in multiple sclerosis. *J Clin Exp Neuropsychol* 2015;37:549-562.doi:10.1080/13803395.2015.1037723
[66] Samartzis L, Gavala E, Zoukos Y, Aspiotis A, Thomaides T. Perceived cognitive decline in multiple sclerosis impacts quality of life independently of depression. *Rehabil Res Pract* 2014;2014:128751.doi: 10.1155/2014/128751.
[67] Campbell J, Rashid W, Cercignani M, Langdon D. Cognitive impairment among patients with multiple sclerosis : associations with employment and quality of life. *Postgrad Med J* 2017;93:143-147. doi: 10.1136/postgradmedj-2016-134071.
[68] Sgaramella TM, Carrieri L, Stenta G, Bortolon F, Perini F, Soresi S. Self-reported executive functioning and satisfaction for quality of life dimensions in adults with multiple sclerosis. *Int J Child Heal Hum Dev* 2014;7:167.
[69] Paziuc LC, Radu MR. The influence of mixed anxiety-depressive disorder on the perceived quality of life in multiple sclerosis patients. *Bulletin of the Transilvania University of Brasov, Seriels VI: Medical Sciences* 2018;11:41–50.
[70] Phillips LH, Henry JD, Nouzova E, et al. Difficulties with emotion regulation in multiple sclerosis: links to executive function, mood, and quality of life. *J Clin Exp Neuropsychol* 2014;36:831-842.doi:10.1080/13803395.2014.946891
[71] Ledesma ALH., Méndez AJR, Vidal LSG, Cruz GT, García-Solís P, Esquivel FDJD. Coping strategies and quality of life in mexican multiple sclerosis patients: physical, psychological and social factors relationship. *Mult Scler Relat Disord* 2018;25:122-127.doi:10.1016/j.msard.2018.06.001
[72] Prisnie JC, Sajobi TT, Wang M, et al. CR. Effects of depression and anxiety on quality of life in five common neurological disorders. *Gen Hosp Psychiatry* 2018;52:58-63.doi:10.1016/j.genhosppsych.2018.03.009
[73] Alsaadi T, Hammasi K El, Shahrour TM, et al. Depression and anxiety as determinants of health-related quality of life in patients with multiple sclerosis - United Arab Emirates. *Neurol Int* 2017;9:75-78.doi:10.4081/ni.2017
[74] Labiano-fontcuberta A, Mitchell AJ, Moreno-garcía S, Puertas-martín V. Impact of anger on the health-related quality of life of multiple sclerosis patients. *Mult Scler J* 2015;21:630-641.doi:10.1177/1352458514549399.
[75] Fernández-muñoz JJ, Cigarán-méndez M, Navarro-pardo E, Pérez-de-heredia-torres M, Parás-bravo P. Is the association between health- related quality of life and fatigue mediated by depression in patients with multiple sclerosis ? A Spanish

cross- sectional study. *BMJ Open* 2018; 8:1-6.doi:10.1136/bmjopen-2017-016297
[76] Pham T, Jetté N, Bulloch AGM, Burton JM, Wiebe S, Patten SB. The prevalence of anxiety and associated factors in persons with multiple sclerosis. *Mult Scler Relat Disord* 2018;19:35-39.doi:10.1016/j.msard.2017.11.003
[77] Salhofer-Polanyi S, Friedrich F, Löffler S, et al. Health-related quality of life in multiple sclerosis: temperament outweighs EDSS. *BMC Psychiatry* 2018;18:1-6. doi:10.1186/s12888-018-1719-6
[78] Demirci S, Demirci K, Demirci S. The Effect of type D personality on quality of life in patients with multiple sclerosis. *Noropsikiyatri Arsivi.* 2017;54:272-276.doi:10.5152/npa.2016.12764
[79] Zengin O, Erbay E, Yıldırım B, Altındağ Ö. Quality of life, coping, and social support in patients with multiple sclerosis: a pilot study. *Turk J Neurol* 2017;23: 211–218. https://doi.org/10.4274/tnd.37074
[80] Grech LB, Kiropoulos LA, Kirby KM, Butler E, Paine M, Hester R. Target coping strategies for interventions aimed at maximizing psychosocial adjustment in people with multiple sclerosis. *Int J MS Care* 2018;20:109-119.doi:10.7224/1537-2073.2017-008
[81] Farran N, Ammar D, Darwish H. Quality of life and coping strategies in lebanese multiple sclerosis patients: a pilot study. *Mult Scler Relat Disord* 2016;6:21-27.doi:10.1016/j.msard.2015.12.003
[82] Mikula P, Nagyova I, Krokavcova M, et al. Coping and its importance for quality of life in patients with multiple sclerosis. *Disabil Rehabil* 2014;36:732-736.doi:10.3109/09638288.2013.808274
[83] Mikula P, Nagyova I, Krokavcova M, et al. The mediating effect of coping on the association between fatigue and quality of life in patients with multiple sclerosis. *Psychol Health Med* 2015;20:653-661.doi:10.1080/13548506.2015.1032310
[84] Mikula P, Nagyova I, Krokavcova M, et al. Do coping strategies mediate the association between Type D personality and quality of life among people with multiple sclerosis ? *J Health Psychol* 2016;23:1557-1565.doi:10.1177/1359105316660180
[85] Van Damme S, De Waegeneer A, Debruyne J. Do flexible goal adjustment and acceptance help preserve quality of life in patients with Multiple Sclerosis? *Int J Behav Med* 2016;23, 333-339.
[86] Nery-hurwit M, Yun J, Ebbeck V. Examining the roles of self-compassion and resilience on health-related quality of life for individuals with Multiple Sclerosis. *Disabil Health J* 2018;11:256-261.doi:10.1016/j.dhjo.2017.10.010
[87] Koelmel E, Hughes AJ, Alschuler KN, Ehde DM. Resilience mediates the longitudinal relationships between social support and mental health outcomes in multiple sclerosis. *Arch Phys Med Rehabil* 2017;98:1139-1148. doi:10.1016/j.apmr.2016.09.127
[88] Wilski M, Tasiemski T. Health-related quality of life in multiple sclerosis: role of cognitive appraisals of self , illness and treatment. *Qual Life Res* 2016;25:1761-1770.doi:10.1007/s11136-015-1204-3
[89] Calandri E, Graziano F, Borghi M, Bonino, S. Depression, positive and negative affect, optimism and health-related quality of life in recently diagnosed multiple sclerosis patients: the role of identity, sense of coherence, and self-efficacy. *J Happiness Stud* 2018;19:277-295.doi:10.1007/s10902-016-9818-x
[90] Mikula P, Nagyova I, Krokavcova M, et al. Self-esteem, social participation, and quality of life in patients with multiple sclerosis. *J Health Psychol* 2017;22:984-992.doi:10.1177/1359105315621778
[91] Valvano A, Floyd RM, Penwell-waines L, Stepleman L, Lewis K, House A. The relationship between cognitive fusion, stigma, and well-being in people with multiple sclerosis. *J Context Behav Sci* 2016;5:266-270.doi:10.1016/j.jcbs.2016.07.003
[92] Costa DC, Sá, MJ , Calheiros JM. Social support network and quality of life in multiple sclerosis patients. *Arq Neuropsiquiatr* 2017;75:267-271.https://doi.org/10.1590/0004-282x20170036
[93] Mikula P, Nagyova I, Krokavcova M, et al. Social participation and health-related quality of life in people with multiple sclerosis. *Disabil Health J* 2015;8:29-34.doi:10.1016/j.dhjo.2014.07.002
[94] Chiu C, Chan F, Edward S, Dutta A, Hartman E, Bezyak J. Employment as a health promotion intervention for persons with multiple sclerosis. *Work* 2015;52:749-756.doi:10.3233/WOR-152202
[95] Possa MF, Minacapelli E, Canale S, et al. The first year after diagnosis : psychological impact on people with multiple sclerosis. *Psychol Health Med* 2017;22:1063-1701.doi:10.1080/13548506.2016.1274043
[96] Stern BZ, Strober L, DeLuca J, Goverover Y. Subjective well-being differs with age in multiple sclerosis: A brief report. *Rehabil Psychol* 2018;63:474-478.doi:10.1037/rep0000220
[97] Calandri E, Graziano F, Borghi M, Bonino S. Coping strategies and adjustment to multiple sclerosis among recently diagnosed patients: The mediating role of sense of coherence. *Clin Rehabil* 2017;31:1386-1395.doi:10.1177/0269215517695374
[98] Nourbakhsh B, Julian L, Waubant E. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. *Eur J Neurol* 2016;23:1482-1486.doi:10.1111/ene.13102
[99] Buhse M, Banker WM, Clement LM. Factors associated with health-related quality of life among older people with multiple sclerosis. *Int J MS Care* 2014;16:10-19. doi:10.7224/1537-2073.2012-046
[100] Kinkel RP, Laforet G, You X. Disease-Related Determinants of quality of life 10 years after clinically isolated syndrome. *Int J MS Care* 2015;17:26-34.doi:10.7224/1537-2073.2013-041
[101] Bueno AM, Sayao AL, Yousefi M, Devonshire V, Traboulsee A, Tremlett H. Health-related quality of life in patients with longstanding "benign multiple sclerosis." *Mult Scler Relat Disord* 2015;4:31-38.doi:10.1016/j.msard.2014.09.211
[102] Baumstarck K, Pelletier J, Boucekine M, Auquier P. Predictors of quality of life in patients with relapsing-remitting multiple sclerosis: a 2-year longitudinal study. *Rev Neurol* 2015;171:173-180.doi:10.1016/j.neurol.2014.09.005
[103] Tepavcevic DK, Pekmezovic T, Stojsavljevic N, et al. Change in quality of life and predictors of change among patients with multiple sclerosis: a prospective cohort study. *Qual Life Res* 2014;23:1027-1037.doi:10.1007/s11136-013-0535-1
[104] Chruzander C, Ytterberg C, Gottberg K, Einarsson U, Widén L, Johansson S. A 10-year follow-up of a population-based

study of people with multiple sclerosis in Stockholm , Sweden: changes in health-related quality of life and the value of different factors in predicting health-related qualit. *J Neurol Sci* 2014;339:57-63.doi:10.1016/j.jns.2014.01.020
[105] Young J, Amatya B, Galea MP, Khan F. Chronic pain in multiple sclerosis: a 10-year longitudinal study. *Scand J Pain* 2017;16:198-203.doi:10.1016/j.sjpain.2017.04.070
[106] Carletto S, Tesio V, Borghi M, et al. The effectiveness of a body-affective mindfulness intervention for multiple sclerosis patients with depressive symptoms : a randomized controlled clinical trial. *Front Psychol* 2017;8:1-13.doi:10.3389/fpsyg.2017.02083
[107] Besharat M, massood Nabavi S, Geranmayepour S, Morsali D, Haghani S. Mindfulness-based Stress Reduction (MBSR) program: the effect of a novel psycho-interventional method on quality of life, mental health, and self-efficacy in female patients with multiple sclerosis: a randomized clinical trial. *J Biol Today's World* 2017;06:211-215. doi:10.15412/j.jbtw.01061101
[108] Blankespoor RJ, Schellekens MPJ, Vos SH, Speckens AEM, Jong BA De. The effectiveness of mindfulness-based stress reduction on psychological distress and cognitive functioning in patients with multiple sclerosis : a pilot study. *Mindfulness (N Y)* 2017;8:1251-1258.doi:10.1007/s12671-017-0701-6
[109] Simpson R, Mair FS, Mercer SW. Mindfulness-based stress reduction for people with multiple sclerosis – a feasibility randomised controlled trial. *BMC Neurol* 2017;17:1-12.doi:10.1186/s12883-017-0880-8
[110] Spitzer E, Pakenham KI. Evaluation of a brief community-based mindfulness intervention for people with multiple sclerosis: a pilot study. *Clin Psychol* 2018;22:182-191.doi:10.1111/cp.12108
[111] Ghodspour Z, Najafi M, Boogar IR, Boogar R. Research paper: effectiveness of mindfulness-based cognitive therapy on psychological aspects of quality of life, depression, anxiety, and stress among patients with multiple sclerosis. *J Pract Clin Psychol* 2018;6:215-222.
[112] Case LK, Jackson P, Kinkel R, Mills PJ. Guided imagery improves mood, fatigue, and quality of life in individuals with multiple sclerosis : an exploratory efficacy trial of healing light guided imagery. *Evid Base Integr Med* 2018;23:1-8.doi:10.1177/2515690X17748744
[113] Blair M, Ferreria G, Gill S, et al. Dialectical behavior group therapy is feasible and reduces emotional dysfunction in multiple sclerosis. *Int J Group Psychother* 2017;67:500-518.doi:10.1080/00207284.2016.1260457
[114] Calandri E, Graziano F, Borghi M, Bonino S. Improving the quality of life and psychological well-being of recently diagnosed multiple sclerosis patients: preliminary evaluation of a group-based cognitive behavioral intervention. *Disabil Rehabil* 2017;39:1474-1481.doi:10.1080/09638288.2016.1198430
[115] Graziano F, Calandri E, Borghi M, Bonino S. The effects of a group-based cognitive behavioral therapy on people with multiple sclerosis: a randomized controlled trial. *Clin Rehabil* 2014;28:264-274.doi:10.1177/0269215513501525
[116] Kiropoulos LA, Kilpatrick T, Holmes A, Threader J. A pilot randomized controlled trial of a tailored cognitive behavioural therapy based intervention for depressive symptoms in those newly diagnosed with multiple sclerosis. *BMC Psychiatry* 2016;16:1-10.doi:10.1186/s12888-016-1152-7
[117] Chruzander C, Gottberg K, Ytterberg C, et al. A single-group pilot feasibility study of cognitive behavioural therapy in people with multiple sclerosis with depressive symptoms. *Disabil Rehabil* 2016;38:2383-2391. doi:10.3109/09638288.2015.1130179
[118] Kikuchi, H., Niino, M., Hirotani, M., Miyazaki, Y, Kikuchi, S. Pilot study on the effects of cognitive behavioral therapy on depression among japanese patients with multiple sclerosis. *Clin Exp Neuroimmunol* 2019;10: 180-185.doi:10.1111/cen3.12529
[119] Pakenham KI, Mawdsley M, Brown FL, Burton NW. (2018). Pilot evaluation of a resilience training program for people with multiple sclerosis. *Rehabil Psychol 2018;63*:29-42.doi:10.1037/rep0000167
[120] Proctor BJ, Moghaddam NG, Evangelou N. Telephone-supported acceptance and commitment bibliotherapy for people with multiple sclerosis and psychological distress: a pilot randomised controlled trial. *J Context Behav Sci* 2018;9:103-109.doi:10.1016/j.jcbs.2018.07.006
[121] Abolghasemi A, Farhang S, Taherifard M, Kiamarsi A. The effect of supportive-expressive therapy on hope and quality of life in patients with multiple sclerosis (MS). *Archives of Psychiatry and Psychotherapy* 2016;18:20-27. doi:10.12740/APP/64975
[122] Jongen PJ, Ruimschotel R, Heerings M, et al. Improved self-efficacy in persons with relapsing remitting multiple sclerosis after an intensive social cognitive wellness program with participation of support partners: a 6-months observational study. *Health Qual Life Outcomes.* 2014;12:1-9.doi:10.1186/1477-7525-12-40
[123] Jongen PJ, Heerings M, Ruimschotel R, et al. Intensive social cognitive treatment (can do treatment) with participation of support partners in persons with relapsing remitting multiple sclerosis: observation of improved self-efficacy, quality of life, anxiety and depression 1 year later. *BMC Res Notes* 2016;9:1-8.doi:10.1186/s13104-016-2173-5
[124] Eliášová A, Majerníková L, Hudáková A, Kaščáková M. Self-help group and the quality of life of patients with multiple sclerosis - pilot study. *Cent Eur J Nurs Midwifery* 2015;6:336-342.doi:10.15452/CEJNM.2015.06.0025
[125] Liu Y. A hope-based group therapy program to women with multiple sclerosis: quality of life. *Neuroquantology* 2017;15:127-132. doi:10.14704/nq.2017.15.4.1135
[126] Mulligan H, Wilkinson A, Barclay A, Whiting H, Heynike C, Snowdon J. Evaluation of a fatigue self-management program for people with multiple sclerosis. *Int J MS Care* 2016;18:116-121.doi:10.7224/1537-2073.2015-019
[127] Thomas PW, Thomas S, Kersten P, et al. One year follow-up of a pragmatic multi-centre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *BMC Neurol* 2014;14:1-6.doi:10.1186/1471-2377-14-109
[128] Ehde DM, Elzea JL, Verrall AM, Gibbons LE, Smith AE, Amtmann D. Efficacy of a telephone-delivered self-

management intervention for persons with multiple sclerosis : a randomized controlled trial with a one-year follow-up. *Arch Phys Med Rehabil* 2015;96:1945-1958.e2.doi:10.1016/j.apmr.2015.07.015

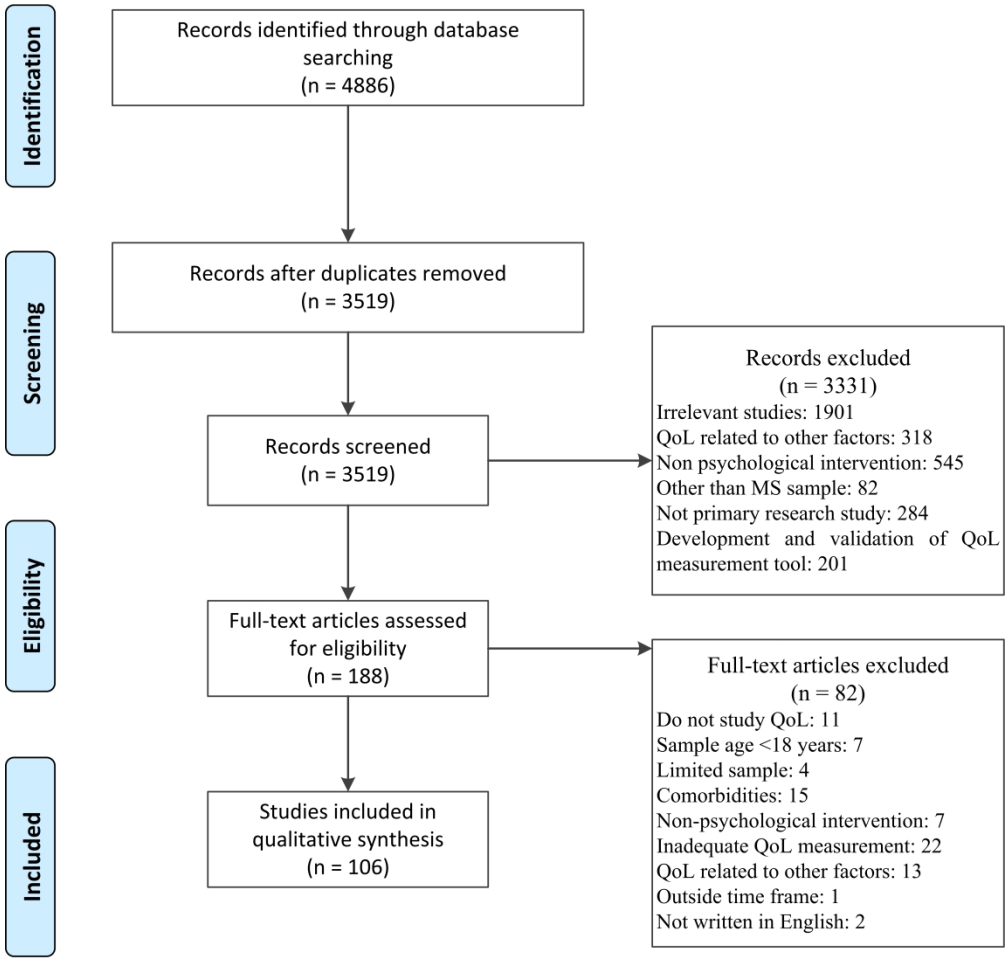
[129] Feicke J, Spörhase U, Köhler J, Busch C, Wirtz M. A multicenter, prospective, quasi-experimental evaluation study of a patient education program to foster multiple sclerosis self-management competencies. *Patient Educ Couns* 2014;97:361-369. doi:10.1016/j.pec.2014.09.005

[130] Leclaire K, Cecil A, Larussa A, et al. A pilot study of a group positive psychology intervention for patients with multiple sclerosis. *Int J MS Care* 2018;20:136-141.doi:10.7224/1537-2073.2017-002

[131] Geiser F, Imbierowicz K, Conrad R, Schilling G, Liedtke R. Differences between patients classified as "recovered" or "improved" and "unchanged" or "deteriorated" in a psychotherapy outcome study. *Z Psychosom Med Psychother* 2001;47(3):250-61. doi.org/10.13109/zptm.2001.47.3.250

Figure Legend 1

PRISMA flow diagram of selection process.



PRISMA flow diagram of selection process

167x160mm (800 x 800 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	4
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.	4-5
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.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-5
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).	5
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.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
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.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable

PRISMA 2009 Checklist

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.	Not applicable

Section/topic	#	Checklist item	Reported on page #
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).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
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.	6
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.	11-17, 19,22-24
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).	7
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.	11-17, 19,22-24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
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).	25-26
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).	26
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			

PRISMA 2009 Checklist

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.	26

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Quality of life in adults with Multiple Sclerosis: a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041249.R2
Article Type:	Original research
Date Submitted by the Author:	04-Nov-2020
Complete List of Authors:	Gil-González, Irene; Universidad de Sevilla, Personality, Assessment, and Psychological Treatment Martín-Rodríguez, Agustín; Universidad de Sevilla, Department of Personality, Assessment, and Psychological Treatment Conrad, Rupert; Department of Psychosomatic Medicine and Psychotherapy, University of Bonn, Bonn, Germany Pérez-San-Gregorio, María Ángeles; Universidad de Sevilla Facultad de Psicologia, Personality, Assessment, and Psychological Treatment
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Global health
Keywords:	Multiple sclerosis < NEUROLOGY, MENTAL HEALTH, Adult neurology < NEUROLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Quality of life in adults with Multiple Sclerosis: a systematic review

Irene Gil-González[a*], MD, igil2@us.es

Agustín Martín-Rodríguez[a*], PhD, amartinr@us.es

Rupert Conrad[b*], MD, Rupert.Conrad@ukbonn.de

María Ángeles Pérez-San-Gregorio[a*], PhD, anperez@us.es

[*]All authors have contributed equally.

[a]Department of Personality, Assessment, and Psychological Treatment, University of Seville, Seville, Spain.

[b]Department of Psychosomatic Medicine and Psychotherapy, University of Bonn, Bonn, Germany.

Corresponding author: Irene Gil-González. Department of Personality, Assessment, and Psychological Treatment. Faculty of Psychology, Camilo José Cela s/n, 41018-Seville (Spain).

Phone: +34954556939. E-mail: igil2@us.es.

ABSTRACT

Objective

In recent years, quality of life (QoL) in multiple sclerosis (MS) has been gaining considerable importance in clinical research and practice. Against this backdrop, this systematic review aimed to provide a broad overview of clinical, sociodemographic and psychosocial risk and protective factors for QoL in adults with MS and analyze psychological interventions for improving QoL.

Method

The literature search was conducted in the Scopus, Web of Science and ProQuest electronic databases. Document type was limited to articles written in English, published from January 1, 2014 to January 31, 2019. Information from the selected articles was extracted using a coding sheet and then qualitatively synthesized.

Results

The search identified 4886 records. After duplicate removal and screening, 106 articles met the inclusion and exclusion criteria for qualitative synthesis and were assessed for study quality. Disability, fatigue, depression, cognitive impairment, and unemployment were consistently identified as QoL risk factors, whereas higher self-esteem, self-efficacy, resilience and social support proved to be protective. The review analyzed a wide spectrum of approaches for QoL psychological intervention, such as mindfulness, cognitive-behavioral therapy, self-help groups and self-management. The majority of interventions were successful in improving various aspects of QoL.

Conclusion

Adequate biopsychosocial assessment is of vital importance to treat risk and promote protective factors to improve QoL in patients with MS in general care practice.

Key words

Multiple sclerosis, quality of life, protective and risk factors, mental and physical quality of life.

Abbreviation

QoL= Quality of life, MS= multiple sclerosis, EDSS= Expanded Disability Status Scale, WHO= World Health Organization, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SF-36= Short Form Health Survey 36, MSQoL-54= Multiple Sclerosis Quality of Life-54, MCS= mental composite score, PCS= physical composite score, ACT= acceptance and commitment therapy, MSIS-29= multiple sclerosis impact scale.

Strengths and limitations of this study

-This is the first systematic review of risk factors and psychological intervention for quality of life in multiple sclerosis in over a decade.

-A comprehensive and robust search strategy and strict inclusion criteria were employed to cover all the relevant evidence.

-Careful standardized risk of bias was assessed in all 106 studies included.

-Due to heterogeneity of the studies only qualitative synthesis of results was possible.

-The huge number of publications made it necessary to limit the time span to the five-year period from January 1, 2014 to January 31, 2019.

1. Introduction

The Constitution of the World Health Organization (WHO) declares health to be "…a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[1] Quality of life (QoL) is a multidimensional concept that encompasses the domains included in this definition of health.[2,3] Its introduction in medical literature dates back to 1960[4], with its importance continuously growing to date.[5]

Multiple Sclerosis (MS) is a chronic neurodegenerative condition, characterized by a wide range of symptoms and a highly unpredictable prognosis, which can severely affect patient QoL.[6-8] MS patients tend to report lower QoL than the general population.[9-12] This diminished QoL may be due to their impaired functioning in daily living, more so if the help of caregivers is required, impeding family relations, work and social dynamics. [13,14] The impact of MS on QoL can be affected by numerous disease-related factors, such as disability level or MS type, and individual factors such as social support, education, age or employment.[15-18]

Identification of risk and protective factors is a key point in implementing strategies to improve patient QoL.[7] In this context, all influences must be considered to contribute to QoL in MS.[7,19] In addition to providing practitioners with useful information on the impact of symptoms and therapy on the patient's life, QoL is also an indicator of treatment success and a predictor of disease progression.[20-22]

In view of its relevance in healthcare research, the need to compile and condense available scientific evidence on the subject is urgent. Against this backdrop, this systematic review gives a comprehensive overview of risk and protective factors related to QoL in MS as well as relevant psychological interventions. The growing number of studies on this subject[2,22] provides a vast amount of data, which due to the inconsistency of findings, needs careful assessment to come to evidence-based conclusions.

2. Methodology

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] As a review of prior publications, ethical approval (or informed consent) was unnecessary. A review protocol is available from the corresponding author upon request.

2.1 *Search strategy*

The systematic search focused on journal articles published between January 1, 2014 to January 31, 2019. The Scopus, Web of Science and ProQuest databases were searched in February and March 2019. The key words used were ("multiple sclerosis") AND ("quality of life" OR "health-related quality of life" OR "well-being" OR "wellbeing" OR "life satisfaction"). The search terms were intentionally broad to ensure wide coverage of the literature. The search field was limited to "title/abstract" and language was limited to "English". The complete research string is reported under Supplement Digital Content A.

There is no published systematic review on this topic in the Cochrane Library.

2.2 *Study selection*

First, title and abstract were screened to identify suitable articles for full text review. The screening process was performed independently by two researchers. Any disagreement about study selection was resolved by consensus with a third reviewer.

Inclusion criteria were the following:

1. Studies primarily focusing on QoL determinants and psychological intervention to improve it.
2. Study participants aged over 18 with a confirmed MS diagnosis.

The following exclusion criteria were applied:

1. Nonpsychological intervention.
2. Not primary research studies (systematic reviews, meta-analyses, protocols and clinical guidelines were excluded).
3. Studies on the development and validation of QoL measurement instruments.
4. QoL risk or intervention studies for healthy behavior, cognitive rehabilitation, physical activity or pharmacological treatment.
5. Studies on comorbidity with another illness or mental health diagnosis.
6. Sample selection based on a special condition (for example: only employees or MS patients under certain pharmacological treatment).
7. Studies not using a validated QoL measurement tool.

2.3 *Quality assessment*

The methodological quality of the studies was appraised with a well-established standardized 12-item checklist,[24] in which every item represents a methodological feature: inclusion/exclusion criteria, methodology/design, attrition rate, attrition between-groups, exclusions after, follow-up, occasion of measurements, pre/post measures, dependent variables, control techniques, construct definition and imputing missing data. The codification criteria proposed by the checklist authors was used. No article was excluded from quality appraisal.

2.4 *Data abstraction*

Data were extracted from selected articles based on a previously designed coding sheet. The pilot study was approved by consensus. The information extracted included: title, authors and publication year, country (city), design, sample characteristics, study variables and measurement tools, main results and conclusions. After extraction, the information was independently reviewed by two authors to avoid errors or omitting data.

A meta-analysis was not possible due to the heterogeneity of study designs and outcomes, so a narrative synthesis was undertaken.

3. Results

3.1 Literature screening

A total of 4886 articles were initially identified from SCOPUS, Web of Science and ProQuest. After removal of duplicates and abstract analysis, 188 studies were eligible for full text review. Finally, 106 were selected for the narrative analysis. The selection process is detailed below in a PRISMA flow diagram (Figure 1).

Figure 1 around here

3.2 Methodological quality

Methodological quality scores using the 12-item checklist are summarized in Table 1.

Table 1

Methodological quality of articles (n = 106)

Inclusion criteria		Design			Attrition		Attrition between groups		Exclusion after		Follow up period		Occasion of measurement		Same pre-post measurement	Normalization of D.V. measurement	Control techniques		Construct definition	Imputing missing data	
Yes	No or N/A*	Pre-experimental	Quasi experimental	Experimental	Yes	No or N/A*	Yes	No or N/A*	Yes	No or N/A*	Yes	No or N/A*	One	Two or more	Yes		Yes	No or N/A*		Yes	No or N/A*
99	1	7.7	33.7	58.7	48.1	51.9	28.9	62.9	22.1	77.9	32.7	67.3	70.2	29.8	70.2	100	70.2	29.8	100	19.2	80.8

No or N/A* = the item is not proceeded or does not appear

3.3 Study characteristics

The articles included were analyzed by their primary and secondary outcomes. Seventy studies analyzed QoL risk and protective factors (Table 2), 11 focused on the development of QoL at different ages and times in the disease (Table 3), and 25 studied the effect of psychological intervention on QoL in MS (Table 4).

All the articles included employed standardized and validated QoL measurement instruments; 64 studies evaluated QoL with a generic measure and 50 studies made use of a disease-specific measure. The Short Form Health Survey 36 (SF-36) was mainly used (n = 29) as a generic measure and Multiple Sclerosis Quality of Life-54 (MSQoL-54) (n = 28) as a disease-specific measure. Finally, 11 studies used more than one measure to evaluate QoL. The study designs were mostly cross-sectional (n = 74), and sample sizes ranged from 7 to 74451 participants.

The main findings of the articles are summarized below.

3.4 Risk and protective MS QoL factors

Factors influencing MS patients QoL are summarized in Table 2.

3.4.1 Clinical factors

Functional impairment, as assessed by the EDSS level was one of the leading causes of diminished QoL.[25-35] Disease duration, [30,31] progressive type,[26,36,37] progressive MS onset[38] and relapses in the last three months were further relevant factors negatively affecting QoL.[26]

Several studies found a significant association between the severity and number of symptoms and the decline of QoL in MS.[33,37,38-41] Fatigue was identified as a main risk factor.[28,29,39,40,42-52]

A number of articles stated the importance of sensory[53,54] and motor[49,52,54,55] dysfunction on quality of life, including paralysis, walking difficulties, balance, stiffness, and spasms as motor problems, specifically emphasizing pain[34,39,50,51,55,56] and spasticity[49,57,58], and low sensory sensitivity and sensation avoidance as sensory problems.

Bladder dysfunction,[34,59,60] bowel dysfunction,[34] sexual,[60-62] and sleeping[34,39,48,63,64] problems contributed to deterioration of QoL.

A diversity of cognitive impairments, for instance, cognitive fatigue, memory loss and planning/organizational dysfunction, were recognized as risk factors by a number of studies.[39,50,52,53,65-67] Sgaramella et al.[68] showed that maintaining executive functioning was a protective factor of QoL. This was also the only study on the important subject of cognitive reserve and QoL.

3.4.2 Psychosocial factors

3.4.2.1 Emotional symptoms

Some studies reported the beneficial effect of emotional stability on QoL,[69] and the harmful effect of emotional problems.[52,70] The emotional symptom studied most was depression[28,29,32,34,35,39,40,51,55,65,69,71-75] followed by anxiety.[39,40,51,69,71-74,76] Both symptoms were confirmed as risk factors for QoL in MS. Similarly, high levels of perceived stress,[37,40,41] anger expression-in[74] and apathy[29] were identified as factors related to emotional regulation negatively affecting QoL in MS.

3.4.2.2 Personality domains

The role of personality domains was explored in several studies. Cyclothymic and depressive temperament were associated with a lower QoL in MS, in contrast to hyperthymic temperament, which was associated with higher QoL.[77] Another study recognized extraversion as a personality trait related to higher QoL levels.[69] Cioncoloni et al.[34] recognized introverted personality as a risk factor for QoL in MS, and finally, type D personality was another relevant factor.[78]

3.4.2.3 Coping strategies

Results with regard to coping strategies were consistent. Active coping, problem resolution, planning problem-solving, cognitive positive restructuring, emotional and instrumental social support, emotional expression, acceptance, and growth were related to a higher QoL in MS.[51,71,79-82] In addition, Grech et al.[80] found a similar connection with restrained coping, Strober[51] with humor, and Mikula et al.[82] with stopping unpleasant emotion coping strategies. On the contrary, problem avoidance,[71,81] behavioral disengagement,[51,80] distancing,[81] self-distraction,[79] denial,[51,79] emotion-focused and venting coping strategies,[80] social withdrawal,[71] wishful thinking,[71] self-criticism,[71,81] suppression,[80] and self-controlling coping[70] were associated with lower QoL.

Coping strategies were also identified as relevant mediator variables. Problem-focused, emotion-focused, and stopping unpleasant emotion coping strategies were partial mediators between fatigue[83] or type D personality[84] and QoL as measured by the mental composite score (MCS).

3.4.2.4 Other psychological factors

According to Van Damme et al.,[85] acceptance of the illness is a protective factor for QoL. The role of flexible adjustment and tenacious goal pursuit in achieving personally blocked goals was not as clear, although their findings showed a trend towards a positive relationship.

Resilience was confirmed as a protective factor of QoL in MS.[27,86] Moreover, Koelmel et al.[87] highlighted its role as a mediator variable in the relationship between social support and MCS.

High levels of self-efficacy,[51,88] self-esteem,[88] illness identity[88] and sense of coherence[89] correlated with higher QoL, and self-esteem mediated in the relationship of social support with MCS.[90] Ultimately, cognitive fusion, the extent to which people feel fused with or attached to their thoughts, mediated the relationship between stigma and QoL in MS.[91]

3.4.2.5 Social factors

Social support[92] and participation[93] were positively related with QoL. Several mediators in this relationship were mentioned above.

3.4.3 Demographic factors

Employment was found to be the leading sociodemographic factor influencing QoL. Several studies displayed an association between unemployment and lower QoL.[30,34,54,67,94] Others showed a positive correlation between jobs adapted to disability,[94] job match and job satisfaction,[41] high employment status,[33,41] and QoL in MS. Low socioeconomic status[35] and financial straits[37] were also risk factors for lower QoL.

Brola et al.[30,31] noted that not having access to an adequate pharmacological treatment put QoL in danger. Congruent with this finding, Boogar et al.[35] found a positive treatment experience to be a protective factor.

Other sociodemographic variables related to poorer QoL in MS were male sex,[37] old age,[30,31] unmarried or living with significant others,[37] whereas a higher education was a protective factor.[33]

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (mean) Sex (Female%)	Main results: Risk factors	Main results: Protective factors
Clinical variables					
Gupta et al (2014)[25]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 74451 47.9 years 51.3 %	EDSS (PCS)	
Gross et al (2017)[36]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 810 RRMS 48.9years SPMS 55.7 years RRMS 71.6 % SPMS 56.2 %	Progressive MS type (PCS)	
Zhang et al (2019)[38]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D)	N = 1958 55.3 years 78.1%	Progressive MS type, Onset	
Rezapour et al (2017)[26]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 171 35.7 years 76.6%	Relapses in the last 3 months	Mild EDSS RRMS Type
Marck et al (2017)[56]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 2296 45.5 years 82.2%	Pain	
Milinis et al (2016)[57]	Cross- sectional	Leeds MS Quality of Life Scale (MSQoL)	N = 701 48.8 years 72%	Spasticity	
Zettl et al (2014)[58]	Cross- sectional	EuroQol 5-Dimensions (EQ-5D) Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 414 48.6 years 64.3 %	Spasticity	
Leonavicius et al (2016)[42]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 137 44.7 years 72.3%	Fatigue (MCS)	
Garg et al (2016)[43]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 89 54.26 years 66%	Fatigue	
Fernández-Muñoz et al (2015)[44]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 108 44 years 55%	Fatigue	
Weiland et al (2015)[45]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 2738 45.5 years 82.3%	Fatigue	
Aygünoğlu et al (2015)[46]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 120 34.24 years 70 %	Fatigue	
Vister et al (2015)[47]	Cross- sectional	World Health Organization Disability Assessment Schedule (WHODAS) 2.0	N = 210 50.8 years 72.4 %	Fatigue	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results	
				Risk factors	Protective factors
Tabrizi et al (2015)[48]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 217 36.2 years 79 %	Fatigue Poor sleep quality Low MCS (PCS)	
White et al (2019)[64]	Cross- sectional	EuroQol 5-Dimensiones (EQ-5D)	N = 531 51.60 years 70.1 %	Sleep disorder	
Barin et al (2018)[49]	Cross- sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS)	N = 855 48 years 72.7 %	Fatigue Balance Spasticity Paralysis Walking difficulty	
Kratz et al (2016)[50]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 180 50.5 years 78 %	Fatigue (MCS) Pain (MCS) Memory loss (MCS)	
Colbeck et al (2018)[53]	Cross- sectional	RAND-36 Health Item Survey (RAND-36)	N = 30 - 73.33%	Cognitive fatigue Low sensory sensitivity Sensation avoiding	
Grech et al (2015)[65]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 107 48.8 years 77.6 %	Cognitive inflexibility	
Sgaramella et al (2014)[68]	Cross- sectional	Quality of life questionnaire (QoL)	N = 39 42.2 years 71.8 %		Executive function
Khalaf et al (2016)[59]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 1048 47.8 years 81%	Lower urinary tract symptoms	
Vitkova et al (2014)[60]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 223 38.4 years 67.3 %	Bladder dysfunction (PCS) Sexual dysfunction (MCS)	
Qaderi et al (2014)[61]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 132 36.9 years 100 %	Sexual problems (PCS and MCS)	
Schairer et al (2014)[62]	Cross- sectional	Short-Form Health Survey 12 (SF-12)	N = 6138 50.6 years 74.7 %	Sexual dysfunction	
Ma et al (2017)[63]	Cross- sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 231 40.2 years 58.4 %	Sleep disorders	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results: Risk factors	Main results: Protective factors
Psychosocial variables					
Ledesma et al (2018)[71]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 26 39.2 years 57.5%	Problem avoidance Social withdrawal Wishful thinking Self-criticism Anxiety Depression	Problem resolution Cognitive restructuring Emotional social and instrumental support Emotional expression
Grech et al (2018)[80]	Cross- sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 107 48.8 years 77.57%	Behavioral disengagement Suppression and lack control Emotional venting	Acceptance Growth Restrain
Zengin et al (2017)[79]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 214 36-46 years 53.2%	Self-distraction Denial Substance use	Planning Active coping Acceptance Positive reinterpretation Social support
Farran et al (2016)[81]	Cross- sectional	Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL)	N = 34 36 years 56%	Self-criticism Escape avoidance Distancing Self-controlling	Emotional social support Instrumental social support Planful problem solving Positive reappraisal
Mikula et al (2014)[82]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 113 40.8 years 77 %		Problem focused coping Stopping unpleasant emotion Getting support
Van Damme et al (2016)[85]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 117 41 years 70.2 %		Acceptance (PCS and MCS) Tenacious goal pursuit (PCS) Flexible goal adjustment (MCS)
Wilski et al (2016)[88]	Cross- sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 257 47.9 years 69.93%		Self-efficacy Self-esteem Illness identity
Nery-Hurwit et al (2018)[86]	Cross- sectional	Function Neutral Health-Related Quality of Life Short Form (FuNHRQOL-SF)	N = 259 48.6 years 84.23%		Resilience Self-compassion
Calandri et al (2018)[89]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 90 37 years 61.1 %		Sense of Coherence
Fernández-Muñoz et al (2018)[75]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 108 44 years 55 %	Depression	
Pham et al (2018)[76]	Cross- sectional	Short Form Health Survey 12 (SF-12)	N = 310 49 years 73.6 %	Anxiety	
Prisnie et al (2018)[72]	Longitudinal (T1 = basal level/ T2 = 2 weeks later)	Short Form Health Survey 12 (SF-12)	N = 139 40 years 70.5%	Anxiety Depression	

Table 2

Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Protective factors
Alsaadi et al (2018)[73]	Cross- sectional	World Health Organization Quality of Life Questionnaire (WHOQoL-BREF)	N = 80 35.1 years 65 %	Anxiety Depression	Alsaadi et al (2018)[62]
Labiano-Fontcuberta et al (2015)[74]	Cross- sectional	Functional Assessment of Multiple Sclerosis (FAMS)	N = 157 41.7 years 66.9%	Depression Anxiety Anger expression-in	
Paziuc et al (2018)[69]	Cross- sectional	Short-Form Health Survey 36 (SF-36)	N = 60 46 years 85 %	Trait anxiety State anxiety Depression	Extraversion Emotional Stability
Phillips et al (2014)[70]	Cross-seccional	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N = 32 44.0 years 75 %	Emotional problems	
Salhofer-Polanyi et al (2018)[77]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 139 40.0 years 70.5%	Depressive temperament Cyclothymic temperament	Hyperthymic temperament
Demirci et al (2017)[78]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 74 35.3 years 65.51%	Type D personality	
Mikula et al (2015)[93]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 116 40.4 years 72.4%		Social participation (MCS y PCS)
Costa et al (2017)[92]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 150 41.7 years 70.7%		Social support
Clinical, psychosocial, and demographic variables					
Nakazawa et al (2018)[27]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 63 41.7 years 66.67 %	EDSS level	Resilience
Ciampi et al (2018)[28]	Cross-sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 43 57.2 years 65.1 %	EDSS level Fatigue Depression	
Fernández-Jiménez et al (2015)[32]	Cross-sectional	Functional Assessment of Multiple Sclerosis (FAMS)	N = 97 47.3 years 82.5 %	EDSS level Depression	
Klevan et al (2014)[29]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 93 41.8 years 69 %	EDSS (PCS) Fatigue Depression Apathy	
Williams et al (2014)[55]	Cross-sectional	Short-Form Health Survey 36 (SF-36) Short-Form Health Survey 12 (SF-12)	N = 447 49.3 years 70.02 %	Pain (PCS) Muscle spasms (PCS) Stiffness (PCS) Depression (MCS)	

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Protective factors
Hyncicova et al (2018)[40]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 67 32.3 years 53.7%	Number and severity of symptoms Fatigue Stress Depression Anxiety	
Shahrbanian et al (2015)[39]	Cross- sectional	Person Generated Index (PGI)	N = 188 43 years 74%	Pain Fatigue Irritability Anxiety Depression Sleep disorder Cognitive deficits	
Strober et al (2018)[51]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 69 40.4 years 89.5%	Pain Fatigue Behavioral disengagement Denial Depression Anxiety High neuroticism Low extroversion Low self-efficacy	Acceptance Growth Emotional social and instrumental support Planning Active coping Positive reinterpretation Humor
Dymecka et al (2018)[52]	Cross-sectional	Multiple Sclerosis Impact Scale (MSIS-29)	N = 137 46.5 years 53.3 %	Fatigue Upper-limb disability Lower-limb disability Cognitive disorders Emotional problems	
Samartzis et al (2014)[66]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 100 40.5 years 64 %	Perceived planning/organization dysfunction Perceived retrospective memory dysfunction Depression	
Brola et al (2016)[31]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS) Multiple Sclerosis Impact Scale (MSIS-29)	N = 2385 37.8 years 69.7%	EDSS level MS duration Lack of DMD treatment Age	
Brola et al (2017)[30]	Cross-sectional	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analogue Scale (EQ-VAS) Multiple Sclerosis Impact Scale (MSIS-29)	N = 765 44.9 years 67.7 %	EDSS MS duration Be unemployed Age No immunomodulatory therapy	
Abdullah et al (2018)[54]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 200 35.1 years 68%	Motor symptoms Low resistance Sensory symptoms Low income Be unemployed	

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Risk factors
Nickel et al (2018)[33]	Cross-sectional	Multiple Sclerosis International Quality of Life (MusiQoL)	N = 1220 47.8 years 76 %	EDSS Comorbidity	High educational level High employment status
Campbell et al (2017)[67]	Cross-sectional	Functional assessment of multiple sclerosis (FAMS) EuroQol 5-Dimensions (EQ-5D)	N = 62 49.4 years 69.35%	Cognitive deficits Be unemployed	
Chiu et al (2015)[94]	Cross-sectional	Short Form Health Survey 12 (SF-12)	N = 157 43.8 years 86%	Be unemployed	Disability adjusted employment
Boogar et al (2018)[35]	Cross-sectional	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	N = 193 38.1 years 64.8 %	High disability Depression Low socioeconomic status	Positive story treatment
Bishop et al (2015)[41]	Cross-sectional	Quality of Life Scale (QOLS)	N = 1839 54 years 78.1 %	Number and severity of symptoms Perceived stress	High educational level High employment status Job satisfaction Job match
Cioncoloni et al (2014)[34]	Cross-sectional	Short Form Health Survey 36 (SF-36)	N = 57 41.7 years 68.42%	EDSS level Fatigue Pain Bladder dysfunction Bowel dysfunction Depressive manifestations Sleeping problems Introverted personality Be unemployed	
Cichy et al (2016)[37]	Cross-sectional	Quality of Life Scale (QOLS)	N = 703 63 years 76 %	Progressive MS Progressive diagnosis Number and severity of symptoms Perceived stress Be male Not married/not living with significant other Unable to meet living expenses	
Mediational variables				*Mediator variable*	*Mediated relation*
Mikula et al (2016)[84]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 156 40 years 75 %	Coping strategies Problem focused Emotional focused Stopping	Personality type D and MCS
Mikula et al (2015)[83]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 154 40.05 years 76%	Coping strategies	Fatigue and MCS and PCS
Mikula et al (2017)[90]	Cross- sectional	Short Form Health Survey 36 (SF-36)	N = 74 35.3 years 65.51%	Self-esteem	Social participation and MCS

Table 2
Characteristics of included articles

Authors, Publication year	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results Risk factors	Risk factors
Koelmel et al (2017)[87]	Longitudinal (T1 = basal level/ T2 = 10 weeks later/ T3 = 26 weeks later/ T4 = 52 weeks later)	Short Form Health Survey 8 (SF-8)	N = 163 52.2 years 87.1%	Resilience	Social support and MCS
Valvano et al (2016)[91]	Cross- sectional	Leeds MS Quality of Life Scale (MSQoL)	N = 128 45.5 years 85%	Cognitive fusion	Stigma and QoL

EDSS = expanded disability status scale; PCS = physical composite; RRMS = remittent remitting; SPMS = secondary progressive; MS= multiple sclerosis; MCS = mental composite score; DMD = disease modifying drug; QoL = quality of life

3.5 Disease history

Table 3 summarizes the characteristics of studies focusing on QoL at different ages and times in the disease history. Some of the selected studies examined QoL in MS in its early years. According to Possa et al.[95], QoL decreased in the first year of diagnosis, as assessed by the MCS and physical composite score (PCS). Stern et al.[96] found the worst QoL in the youngest group of MS patients.

Calandri et al.[97] found that during the first three years from diagnosis, problem-solving and avoidance coping strategies had a positive effect on QoL. Nourbakhsh et al.[98] also studied factors influencing the development of QoL in the first three years. Their results showed that higher baseline levels of fatigue and depression predicted worse QoL as assessed by the PCS, whereas lower cognitive functioning and higher fatigue predicted a worse MCS.

Another study on QoL in MS by Buhse et al.[99] focused on old age. These authors identified neurological impairment, physical disability, depression, and comorbidity with thyroid disease as risk factors for worse QoL as assessed by the PCS in a sample of elderly MS patients. On the contrary, being widowed and employed were identified as protective PCS factors.

In a longitudinal study, Kinkel et al.[100] showed that a second clinical event consistent with clinically defined MS, higher EDSS at the time of diagnosis and an earlier MS onset predicted a decrease in PCS 10 years after diagnosis. Bueno et al.[101] also showed that progression from benign MS to non-benign MS predicted a decrease in PCS 25-30 years after diagnosis.

Some longitudinal predictors of QoL identified have been: longer MS duration predicted worse QoL two years later,[102] and worse EDSS predicted worse QoL two,[102] six,[103] and ten[104] years later. Depression predicted worse QoL six[103] and ten[104] years later, and stronger pain[105] and cognitive impairment[104] predicted worse QoL ten years later.

.

Table 3
Characteristics of included studies

Authors, Publication year	Study design (T1: /T2:…)	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Years of diagnosis				
Possa et al (2017)[95]	Cross-sectional	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 38 32.9 years 58%	Decrease in MCS (38%) and PCS (19%) in the first year after diagnosis.
Calandri et al (2017)[97]	Cross-sectional	Short Form Health Survey 12 (SF-12)	N = 102 35.8 years 61.8%	Problem solving ($\beta = 0.28$) and avoidance ($\beta = 0.25$) was related to a higher MCS in the first 3 years of diagnosis.
Nourbakhsh et al (2016)[98]	Longitudinal (T1 = basal level/ T2 = 3 months after diagnosis/ T3 = 6 months after diagnosis/ T4 = 12 months after diagnosis/ T5 = 18 months after diagnosis/ T6 = 24 months after diagnosis / T6 = 36 months after diagnosis)	Short Form Health Survey 36 (SF-36)	N = 43 36 years 72%	Baseline severity of fatigue and depression predicts PCS and cognitive function and fatigue MCS in the first 3 years of diagnosis.
MS progression				
Kinkel et al (2015)[100]	Longitudinal (T1 = CIS diagnosis/T2 = 5 years after diagnosis/ T3 = 10 years after diagnosis)	Short Form Health Survey 36 (SF-36) Multiple Sclerosis Quality of Life Inventory (MSQLI)	N = 127 34.1 years 74%	A second clinic event consistent with CDMS, higher EDSS at the diagnosis and an earlier onset CDMS predicts a decrease in
Bueno et al (2014)[101]	Cross-sectional (25-30 years after diagnosis)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 61 54.9 years 83.6%	Patient changing from benign (EDSS<3) to non-benign (EDSS>3) decreases PCS.
Years of MS duration				
Baumstarck et al (2015)[102]	Longitudinal (T1 = basal level/ T2 = 24 months later)	Multiple Sclerosis International Quality of Life questionnaire (MusiQol) Short-Form Health Survey 36 (SF-36)	N = 526 40.0 years 74.3%	Low levels of QoL, higher MS duration and higher EDSS level at T1 predicted worse QoL at T2.
Tepavcevic et al (2014)[103]	Longitudinal (T1 = basal level/ T2 = 3 years later/ T3 = 6 years later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 93 41.5 years 71%	Higher EDSS and depression at basal level predicted a decrease of QoL at T1 and T2.
Young et al (2017)[105]	Longitudinal (T1 = basal level/ T2 = 7 years later/ T3 = 10 years later)	Assessment of Quality of life (AQoL)	N = 70 59.8 years 71.6%	Higher pain predicts a decrease in QoL.
Chruzander et al (2014)[104]	Longitudinal (T1 = basal level/ T2 = 10 years later)	EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analog Scale (EQ-VAS) Sickness Impact Profile (SIP)	N = 118 49 years 72%	Cognitive impairment, depressive symptoms and EDSS predicted a decrease in QoL at T2.
Group age				
Stern et al (2018)[96]	Cross-sectional	Multiple Sclerosis Quality of Life Instrument (MSQOL-54)	N = 57 50 years 73.7%	The youngest group (35-44) presents worst PCS vs the oldest (55-65).
Buhse et al (2014)[99]	Cross-sectional	Multiple Sclerosis Quality of Life–54 (MSQOL- 54)	N = 211 65.5 years 80%	Risk of neurologic impairment, physical disability, depression, and the comorbidity of thyroid disease was associated with decrease in PCS. Being widowed and employed was associated with increase in PCS.

MCS = mental composite score; PCS = physical composite score; CIS = clinical isolated syndrome; CDMS = clinical defined multiple sclerosis; EDSS = expanded disability status scale; QoL = quality of life.

3.6 Interventions

Details of the selected articles on psychological intervention are presented in Table 4.

3.6.1 Mindfulness-based therapies

All mindfulness-based therapy intervention programs showed improvement in QoL at some evaluation point and at least in some QoL domains. Body-affective mindfulness intervention increased the general QoL score up to six months after treatment.[106]

Of the three studies on mindfulness-based stress reduction programs, two showed a significant increase in QoL after treatment.[107-109] One study[109] only produced a small, insignificant increase after treatment and at the three-month follow-up.

A community-based mindfulness program resulted in a significant increase in MCS.[110]

Finally, mindfulness-based cognitive therapy did not show any significant difference in general QoL between the control and the experimental group, however, it did show significant differences in QoL: in health distress, mental well-being, role limitation due to emotional problems and cognitive performance.[111]

3.6.2 Cognitive-behavioral

A wide spectrum of cognitive behavioral interventions was analyzed.

In a study by Case et al.,[112] the experimental group attended 10 one-hour weekly sessions of healing light guided imagery. They found a greater increase in QoL in this group than with 10 hours of positive journaling in the active control group.

Blair et al.[113] focused intervention on emotion regulation. The design consisted of 16 1.5-hour biweekly sessions for eight weeks. The intervention resulted in a significant increase in QoL six months after treatment.

Interventions by Calandri et al.[114] and Graziano et al.[115] had a comparable design. Participants were divided into two subgroups by age. Intervention comprised four-five two-hour sessions over the course of two months, and one follow-up session six months after treatment. Calandri et al.[114] also included one follow-up session 12 months after treatment. At follow-up, the intervention groups in both studies had experienced an increase in QoL.

Three studies[116-118] focused intervention on depressive symptoms. Kiropoulos et al.[116] and Chruzander et al.[117] found improvement in QoL at post-treatment and follow-up assessments. Kikuchi et al.[118] also found a post-treatment improvement, but not significant.

Two of the studies based intervention on Acceptance and Commitment Therapy (ACT). Pakenham et al.[119] implemented an eight-week program aimed at training in resilience. QoL increased at treatment end and at three-month follow-up. Proctor et al.[120] implemented an eight-week intervention comprising telephone calls and self-help ACT books. No significant increase in QoL was observed.

3.6.3 Social and group support

The following social support and group interventions had an impact on QoL in MS.

Abolghasemi et al.[121] implemented a 12-session supportive-expressive therapy program, which improved QoL.

Jongen et al.[122] tested an intensive social-cognitive wellness program involving the partner or other significant informal caregiver. The results showed an increase in the MCS at one, three and six months from treatment, and in the

PCS six months after treatment. The results of the program were evaluated again 12 months after treatment. The relapsing-remittent MS group showed an increase in PCS and MCS.[123]

Eliášová et al.[124] found more improvement across several QoL domains in MS patients after self-help group sessions than in patients who did not attend the self-help groups. Liu et al.[125] detected an increase in physical and psychological QoL in women with MS after participating in a hope-based group therapy program for one-hour twice a week for eight weeks.

3.6.4 Symptom and self-management-based therapies

Two studies analyzed a fatigue self-management group therapy. Mulligan et al.[126] reported positive, but not significant, changes in QoL after their treatment. Thomas et al.[127] reported significant positive changes in physical health assessed by the Multiple Sclerosis Impact Scale (MSIS-29) and vitality as measured by the SF-36 in the intervention group 12 months after the treatment.

In addition to fatigue self-management, Ehde et al.[128] focused in their intervention on pain and depression self-management. The results were compared to an educational program. There was a higher QoL post-treatment and 12-month follow-up score in the self-management group. Feicke et al.[129] implemented a program focused on MS self-management. As in Ehde et al.,[128] improvements in QoL were still maintained at six-month follow up.

3.6.5 Other psychological intervention

LeClaire et al.[130] implemented a five-week positive psychology program. The results showed only a significant improvement in the SF-36 vitality subscale.

Table 4
Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Mindfulness-based therapies					
Carletto et al (2017)[106]	Body-affective mindfulness (BAM)	Longitudinal (T1 = basal level /T2 = post-treatment /T3 = 6 months later)	Functional Assessment of Multiple Sclerosis (FAMS)	N = 45 44.1 years 71.1%	Increase in general score FAMS from T1 to T2 (P< 0.001) and from T2 to T3 (P= 1).
Besharat et al (2017)[107]	Mindfulness-based stress reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Short Form Health Survey 36 (SF-36)	N intervention/ control= 22/ 11 35 years 100%	Increase in general QoL score in the intervention group (P< 0.05).
Blankespoor et al (2017)[108]	Mindfulness-based Stress Reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 25 52.6 years 84%	Increase PCS (P< 0.001).
Simpson et al (2017)[109]	Mindfulness-based Stress Reduction (MBSR)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 3 months later)	Multiple Sclerosis Quality of Life Inventory (MSQLI)	N = 25 43.6 years 92%	Small and insignificant increase QoL from T1 to T2 (P= 0.48) and insignificant increase from T2 to T3 (P= 0.71).
Spitzer et al (2018)[110]	Community-based group mindfulness	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 8 weeks later)	Short Form Health Survey 36 (SF-36)	N = 23 48.4 years 91.3%	Increase MCS from T1 to T2 (P= 0.008).
Ghodspour et al (2018)[111]	Mindfulness-based Cognitive Therapy (MBCT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 15/ 15 36 years 100%	Increase in health distress (P=0.032), mental well-being (P 0.001), role limitation due to emotional problems (P= 0.005) and cognitive performance (P= 0.04) subscales.
Cognitive behavioral					
Case et al (2018)[112]	Trial of healing light guided imagery (HLGI)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 9/ - 49.1 years -	Increase in PCS (P= 0.01) and MCS (P< 0.01) in the intervention group.
Blair et al (2017)[113]	Dialectical Behavior Group Therapy (TCD)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 6 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 10/ 10 40.4 years 90%	Increase in MSQoL-54 from T1 to T3 (P= 0.01).
Calandri et al (2017)[114]	Group-based cognitive behavioral therapy (CBT)	Longitudinal (T1 = pre-treatment/ T2 = 6 month post-treatment/ T3 = 1 year post-treatment)	Short Form Health Survey 12 (SF-12)	N intervention/ control= 54/ 31 38 years 61%	Increase in MCS T2 in the CBT group vs control (P= 0.036). Increase in MCS T3 in the CBT group vs control (P= 0.049).
Graziano et al (2014)[115]	Group-based cognitive behavioral therapy (CBT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 6 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 41/ 41 42.3 years	Increase in MSQoL-54 at T3 in the CBT group vs control group (P< 0.05).

Table 4
Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
				66%	
Kiropoulos et al (2016)[116]	Cognitive behavioral therapy (CBT) for depressive symptoms	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 20 weeks later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N intervention/ control= 15/15 34.6 years 86.7%	Differences between control and CBT group MCS and PCS in T2 and T3 (P< 0.001).
Chruzander et al (2016)[117]	Cognitive behavioral therapy (CBT) focused on depressive symptoms	Longitudinal (T1 = basal level/ T2 = 3 weeks post-treatment/ T3 = 3 months post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29) EuroQol 5-Dimensions (EQ-5D) EuroQol Visual Analog Scale (EQ-VAS)	N = 15 38 years 80%	Improvement in QoL from MSIS-29 and EQ-5D in T2 and T3 (P< 0.05).
Kikuchi et al (2019)[118]	Cognitive behavioral therapy (CBT) on depression	Longitudinal (T1 = pre-treatment/ T2 = mind-treatment/ T3 = post-treatment)	Functional Assessment of Multiple Sclerosis (FAMS)	N = 7 46.1 years 71.4%	Positive but not significant increase in FAMS (P> 0.05).
Pakenham et al (2018)[119]	Resilience Training Program (ACT)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment/ T3 = 3 months later)	Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54)	N = 37 39.4 years 73%	Increase in PCS (P< 0.001) and MCS (P< 0.006) from T1 to T2, maintained at T3, without significant changes.
Proctor et al (2018)[120]	Telephone-supported acceptance and commitment bibliotherapy (ACT)	Longitudinal (T1 = pre-randomization / T2 = 12 weeks after randomization)	EuroQol 5-Dimensions (EQ-5D)	N intervention/ control= 14/13 45.8 years 78%	No significant increase in QoL (P= 0.62).
Social and group support					
Liu (2017)[125]	Hope-Based Group Therapy (HBGT)	Longitudinal (T1 = pre-treatment / T2 = post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29)	N intervention/ control= 18/14 35.1 years 100%	Physical and psychological QoL increase in HBT group (P< 0.05).
Abolghasemi et al (2016)[121]	Supportive-Expressive Therapy (SE)	Longitudinal (T1 = pre-treatment/ T2 = post-treatment	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N intervention/ control= 16/16 31.8 years 41.7%	Increase QoL from T1 to T2 (P<0.001).
Jongen et al (2016)[122]	Intensive social cognitive treatment (can do treatment) with participation of support partners	Longitudinal (T1 = basal level/ T2 = 12 months post-treatment)	Multiple Sclerosis Quality of Life Instrument (MSQoL-54)	N = 38 - 65.8%	PCS increase (P= 0.032) and MCS (P= 0.087) in the RR group.
Jongen et al (2014)[122]	Intensive social cognitive wellness program with participation of support partners	Longitudinal (T1 = basal level/ T2 = 1 months post-treatment/T3 = 3 months post-treatment T4 = 6 months post-treatment	Multiple Sclerosis Quality of Life Instrument (MSQoL-54)	N = 44 45.7 years 79.5%	MCS increase at T2, T3 and T4 and PCS at T4 (P< 0.05).

Table 4
Characteristics of the included articles

Authors, Publication year	Program name	Study design	Quality of life measurement	Sample size (N) Age (media) Sex (Female%)	Main results
Eliášová et al (2015)[124]	Self-Help group (SH)	Cross-sectional (T1 = after the treatment)	World Health Organization Quality of Life questionnaire (WHOQoL-BREF)	N intervention/ control = 46/ 35 42.2 years 59%	Increase in physical (P< 0.001), psychological (P< 0.001) and social relationships (P< 0.001) in the SH group.
Symptom and self-management-based therapies					
Mulligan et al (2016)[126]	Fatigue self-management program "Minimize Fatigue, Maximize Life: Creating Balance with Multiple Sclerosis (MFML)"	Longitudinal (T1 = 1 month pre-treatment/ T2 = pre-treatment/ T3 = post-treatment).	Short Form Health Survey 12 (SF-12)	N = 24 49.3 years 100%	Positive but not significant changes in SF-12 (P> 0.05).
Thomas et al (2014)[127]	Group-based fatigue management (FACETS)	Longitudinal (T1 = 1 week before treatment/ T2 = 1 month post-treatment/ T3 = 4 month post-treatment/ T4 = 12 month post-treatment)	Multiple Sclerosis Impact Scale (MSIS-29) Short Form Health Survey 36 (SF-36)	N intervention/ control = 44/ 80 48 years 73%	Changes in physical health MSIS-29 (P= 0.046) and vitality SF-36 (P= 0.03) at T4.
Ehde et al (2015)[128]	Telephone-Delivered Self-Management (SM)	Longitudinal (T1 = before group randomization/ T2 = post-treatment/ T3 = 6 month post-treatment/ T4 = 12 month post-treatment)	Short Form Health Survey 8 (SF-8)	N intervention/ control = 75/ 88 51 years 89.3%	MCS and PCS increase at T2, T3 and T4 (P< 0.05).
Feicke et al (2014)[129]	Education program for self-management competencies (S.MS)	Longitudinal (T1 = 1 basal level/T2 = post-treatment /T3 = 6 month post-treatment)	Hamburg quality of life questionnaire in multiple sclerosis (HAQUAMS)	N intervention/ control = 31/ 33 41.9 years 87.1%	Stable positive changes in QoL (P= 0.007).
Other psychological intervention					
Leclaire et al (2018)[130]	Group Positive Psychology	Longitudinal (T1 = basal level /T2 = post-treatment)	Short Form Health Survey 36 (SF-36)	N = 11 53.5 years 100%	Increase in SF-36 vitality subscale score (P= 0.016). Increase in mental health SF-36 subscale (P= 0.098) that did not reach statistical significance.

FAMS = functional assessment of multiple sclerosis; QoL = quality of life; PCS = physical component score; MCS = mental component score; MSQoL-54 = multiple sclerosis quality of life instrument; CBT = cognitive behavioral therapy; SF-36 = short form health survey 36; MSIS-29 = multiple sclerosis impact scale; EQ-5D = euroqol 5-dimensions; HBT = hope-based group therapy; RR= relapsing-remitting; SH = self-help group; SF-12 = short-form health survey

4. Discussion

Firstly, the present systematic review was intended to identify risk and QoL protective factors in MS. The results showed that the EDSS was most employed for assessment of functional impairment.[25-35] As expected, the number and severity of symptoms and associated impairment appeared to play a crucial role in QoL. Fatigue,[28,29,39,40,42-52] cognitive impairment,[39,50,52,53,63,66,67] and pain[35,39,50,51,55,56], in particular, were the focus of a large number of studies, and were confirmed as important risk factors. Longitudinal studies suggested that greater fatigue,[98] pain,[105] and cognitive impairment[98,104] also predicted worse QoL up to 10 years later. This has important clinical implications, as treatment of the abovementioned symptoms should be prioritized. In general, functional impairment,[102-104] as well as longer duration of illness,[102] were predictors of QoL two to 10 years later, whereas disease progression[101] from benign to non-benign MS predicted QoL as measured by the PCS up to 30 years later.

Among the emotional symptoms, there was convincing evidence that depression,[28,29,32,34,35,39,40,51,55,66,69,71-75] along with depressive temperament[77] and anxiety,[38,40,51,69,71-74,76] were associated with lower QoL, and that depression also predicted QoL up to 10 years later.[104]

The coping strategies applied obviously influenced QoL in MS, however their effect depended on the specific circumstances of the disease history. For example, problem-solving and avoidance coping, normally classified as opposite strategies, both seemed to have a positive effect on the MCS in the first three years of diagnosis.[97] However, in general, strategies associated with denial[51,79] and avoidance of the challenges of the disease, such as problem avoidance,[71,81] behavioral disengagement, [51,80] distancing, [81] self-distraction,[79] social withdrawal,[71] wishful thinking,[71] were associated with a lower QoL. On the other hand, strategies based on acceptance and active commitment, such as active coping, humor, problem resolution, cognitive positive restructuring, and emotional expression, led to higher QoL in MS.[51,71,79-82] Obviously, there is a close connection between the active confrontation of the challenges of illness and specific personality-based convictions, such as a high self-efficacy. Thus, higher self-efficacy,[51,88] self-esteem,[88] and sense of coherence[89] improved QoL in MS.

Regarding sociodemographic influences on QoL, not surprisingly, unemployment, a low socioeconomic status[35] and financial difficulties[37] proved to be major risk factors[30,34,54,67,94]. In keeping with the negative influence of the scarcity of resources, lack of access to therapy was also identified as a risk factor.[30,31]

The second aim of this systematic review was to study QoL in MS patients at different times during their disease history. Two studies showed diminishing QoL in MS patients in its early stage.[95,96] This might have to do with the fact that patients being diagnosed with a severe chronic disease need a certain time to come to terms with this emotional shock. Oscillation between avoidance and problem-solving, which both have a positive influence in the first three years after diagnosis,[97] may be behind this inner struggle. In older patients, neurological impairment and physical disability,[97] which represent the age-associated increase in physical impairment, were identified as risk factors for QoL in MS.

Finally, the third aim of this review was to analyze psychological interventions for the improvement of QoL in MS. Symptomatic improvement of psychopathology usually at the center of psychotherapy outcome studies, was not the primary focus of our review.[131] Eight of the intervention studies specifically treated depressive symptomatology,[106,110-112,115,117-118] either with mindfulness-based or cognitive-behavioral approaches, both of which proved to be successful.

Three studies were specifically directed towards the treatment of fatigue[112,126,127] by light guided imagery or self-management programs. Both the imagery and self-management group intervention approaches were successful, whereas the individual self-management program did not show significant improvement.

A variety of mindfulness-based approaches[107-109] and a Community-based intervention were directed at stress reduction.[110] Three of the four studies showed some kind of improvement in QoL, including the only study with a control group.

Several of the interventions were designed to reinforce protective factors in MS patients. Graziano et al.[115] focused on identity redefinition, sense of coherence and self-efficacy. Pakenham et al.[119] implemented a program based on resilience training, and the program by Blair et al.[113] focused on the improvement of emotion regulation. All of them were successful in improving QoL, confirming the alternative focus on protective factors instead of risk factors.

A wide spectrum of interventions based on social support concentrated on reinforcement of the social network of MS patients, for example, self-help groups,[124] hope-based group therapy,[125] supportive-expressive therapy,[121] and social cognitive training with support partners.[122,123] All interventions aimed at helping people overcome MS barriers in daily living by strengthening their social support, improving some aspects of QoL. This is consistent with the studies mentioned above [92,93] and emphasizes the importance of social support and participation as a protective factor for QoL.

5. Limitations

The main limitation of this study was the impossibility of carrying out a quantitative synthesis of the results, due to the heterogeneity of methodologies and designs in the articles included. Due to the vast number of topics and limited resources our search was restricted to a five-year period through January 2019.

6. Conclusions

This review was intended to give a broad overview of QoL in MS. The findings show the importance of clinical, psychosocial and demographic variables as QoL risk and protective factors. A variety of psychological interventions ranging from mindfulness-based and cognitive-behavioral approaches to self-help groups addressing these factors were identified as promising options for improving QoL. These findings have important clinical implications. A sound biopsychosocial assessment of MS patients in daily clinical practice is necessary to ensure the possibility of early identification of QoL risk factors and evidence-based psychological intervention is recommended to improve or stabilize QoL.

Authors Contribution

Irene Gil-González: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

Agustín Martín-Rodríguez: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

Rupert Conrad: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

María Ángeles Pérez-San-Gregorio: Conceptualization, Investigation, Methodology, Validation, Writing-original draft, and Writing-Review & Editing.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

This study was financially supported by the program of Formation of University Professor of Ministry of Education, Culture and Sport of Spain grant number: FPU 17/04240.

Data sharing statement

All relevant data appear in the study manuscript. No additional data available.

Patient and public involvement

No patient involved.

References

[1] World Health Organisation. Governance. Basic documents. World Health Organisation. https://www.who.int/about/who-we-are/constitution. Published 2019.Accesed December 15, 2019.
[2] Patti F, Pappalardo A. Quality of life in patients affected by multiple sclerosis: a systematic review. In: Preedy V.R., Watson R.R., eds. Handbook of Disease Burdens and Quality of Life Measures. New York: Springer, New York (NY) 2010:3769-3783. doi:10.1007/978-0-387-78665-0_218
[3] Bernstein U. The World Health Organization Quality of Life Assessment (WHOQOL): Position Paper from the World Helath Organization. *SocSciMed* 1995;41(10):1403-1409.
[4] Marcel W.M. Definitions of quality of life: What has happened and how to move on. *Top Spinal Cord Inj Rehabil* 2014;20:167-180.doi:10.1310/sci2003-167
[5] Gellert GA. The importance of quality of life research for health care reform in the USA and the future of public health. *Qual Life Res* 1993;2:357-361.doi:10.1007/BF00449431
[6] Benito-León J, Morales JM, Rivera-Navarro J, Mitchell AJ. A review about the impact of multiple sclerosis on health-related quality of life. *Disabil Rehabil* 2003;25:1291-1303.doi:10.1080/09638280310001608591
[7] Hyarat SY, Subih M, Rayan A, Salami I, Harb A. Health related quality of life among patients with multiple sclerosis: The role of psychosocial adjustment to illness. Arch Psychiatr Nurs. 2019;33(1):11-16. doi:10.1016/j.apnu.2018.08.006
[8] Yalachkov Y, Soydaş D, Bergmann J, et al. Determinants of quality of life in relapsing-remitting and progressive multiple sclerosis. *Mult Scler Relat Disord.* 2019;30:33-37.doi:10.1016/j.msard.2019.01.049
[9] Amtmann D, Bamer AM, Kim J, Chung H, Salem R. People with multiple sclerosis report significantly worse symptoms and health related quality of life than the US general population as measured by PROMIS and NeuroQoL outcome measures. *Disabil Health J.* 2018;11(1):99-107. doi:10.1016/j.dhjo.2017.04.008
[10] Pittock SJ, Mayr WT, McClelland RL, et al. Quality of life is favorable for most patients with multiple sclerosis: A population-based cohort study. *Arch Neurol.* 2004;61(5):679-686. doi:10.1001/archneur.61.5.679
[11] McCabe MP, McKern S. Quality of life and multiple sclerosis: Comparison between people with multiple sclerosis and people from the general population. *J Clin Psychol Med Settings.* 2002;9(4):287-295. doi:10.1023/A:1020734901150
[12] Schmidt S, Vilagut G, Garin O, et al. Reference guidelines for the 12-item short-form health survey version 2 based on the catalan general population. *Med Clin.* 2012;139(14):613-625. doi:10.1016/j.medcli.2011.10.024
[13] Petrović N, Prlić N, Gašparić I, Placento H, Gvozdanović Z. Quality of life among persons suffering from multiple sclerosis. *Medica Jadertina.* 2019;49(3-4):217-226.
[14] Algahtani HA, Shirah BH, Alzahrani FA, Abobaker HA, Alghanaim NA, Manlangit Js Jr. Quality of life among multiple sclerosis patients in Saudi Arabia. *Neurosci.* 2017;22(4):261-266. doi:10.17712/nsj.2017.4.20170273
[15] Wilski M, Gabryelski J, Brola W, Tomasz T. Health-related quality of life in multiple sclerosis: Links to acceptance, coping strategies and disease severity. *Disabil Health J.* 2019;12(4):608-614. doi:10.1016/j.dhjo.2019.06.003
[16] Pérez De Heredia-Torres M, Huertas-Hoyas E, Sánchez-Camarero C, et al. Occupational performance in multiple sclerosis and its relationship with quality of life and fatigue. *Eur J Phys Rehabil Med.* 2020;56(2):148-154. doi:10.23736/S1973-9087.20.05914-6
[17] Ochoa-Morales A, Hernández-Mojica T, Paz-Rodríguez F, et al. Quality of life in patients with multiple sclerosis and its association with depressive symptoms and physical disability. *Mult Scler Relat Disord.* 2019;36. doi:10.1016/j.msard.2019.101386
[18] Dorstyn DS, Roberts RM, Murphy G, Haub R. Employment and multiple sclerosis: A meta-analytic review of psychological correlates. *J Health Psychol.* 2019;24(1):38-51. doi:10.1177/1359105317691587

[19] Schmidt S, Jöstingmeyer P. Depression, fatigue and disability are independently associated with quality of life in patients with multiple sclerosis: Results of a cross-sectional study. *Mult Scler Relat Disord.* 2019;35:262-269. doi:10.1016/j.msard.2019.07.029
[20] Ysrraelit MC, Fiol MP, Gaitán MI, Correale J. Quality of life assessment in multiple sclerosis: Different perception between patients and neurologists. *Front Neurol.* 2018;8:1-6. doi:10.3389/fneur.2017.00729
[21] Revicki DA, Osoba D, Fairclough D, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. *Qual Life Res.* 2000;9:887-900. doi:10.1023/A:1008996223999
[22] Baumstarck K, Boyer L, Boucekine M, Michel P, Pelletier J, Auquier P. Measuring the quality of life in patients with multiple sclerosis in clinical practice: a necessary challenge. *Mult Scler Int.* 2013;2013:1-8. doi:10.1155/2013/524894
[23] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
[24] Chacón-Moscos S, Sanduvete-Chaves S, Sánchez-Martín M. The development of a checklist to enhance methodological quality in intervention programs. *Front Psychol* 2016;7:1811.doi:10.3389/fpsyg.2016.01811
[25] Gupta S, Goren A, Phillips AL, Dangond F, Stewart M. Self-reported severity among patients with multiple sclerosis in the U . S . and its association with health outcomes. *Mult Scler Relat Disord* 2014;3:78-88.doi:10.1016/j.msard.2013.06.002
[26] Rezapour A, Kia AA, Goodarzi S, Hasoumi M, Motlagh SN, Vahedi S. The impact of disease characteristics on multiple sclerosis patients ' quality of life. *Epidemiol Health* 2017;39:1-7.doi:10.4178/epih.e2017008
[27] Nakazawa K, Noda T, Ichikura K, Okamoto T. Resilience and depression / anxiety symptoms in multiple sclerosis and neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord* 2018;25:309-315.doi:10.1016/j.msard.2018.08.023
[28] Ciampi E, Uribe-San-Martin R, Vásquez M, et al. Relationship between Social Cognition and traditional cognitive impairment in Progressive Multiple Sclerosis and possible implicated neuroanatomical regions. *Mult Scler Relat Disord* 2018;20:122-128.doi:10.1016/j.msard.2018.01.013
[29] Klevan G, Jacobsen CO, Aarseth JH, et al. Health related quality of life in patients recently diagnosed with multiple sclerosis. *Acta Neurol Scand* 2014;129:21-26.doi:10.1111/ane.12142
[30] Brola W, Sobolewski P, Jantarski K. Multiple sclerosis: patient-reported quality of life in the Świętokrzyskie Region. *Med Stud Med* 2017;33:191-198.
[31] Brola W, Sobolewski P, Fudala M et al. Self-reported quality of life in multiple sclerosis patients : preliminary results based on the Polish MS Registry. *Patient Prefer Adherence* 2016;10:1647-1656.
[32] Fernández-Jiménez E, Arnett PA. Impact of neurological impairment, depression, cognitive function and coping on quality of life of people with multiple sclerosis: a relative importance analysis. *Mult Scler J* 2015;21(11):1468-1472.doi:10.1177/1352458514562439
[33] Nickel S, Kofahl OVKC, Kofahl C. Assessments and determinants of HRQoL in a German MS population. *Acta Neurol Scand* 2018; 137(2): 174-180.doi:10.1111/ane.12854
[34] Cioncoloni D, Innocenti I, Bartalini S, et al. Individual factors enhance poor health-related quality of life outcome in multiple sclerosis patients. Significance of predictive determinants. *J Neurol Sci* 2014;345:213-219.doi:10.1016/j.jns.2014.07.050
[35] Boogar IR, Talepasand S, Jabari M. Psychosocial and Medical Determinants of Health-related Quality of Life in Patients with Relapsing-Remitting Multiple Sclerosis. *Noro Psikiyatr Ars* 2018;13:29-35.doi:10.29399/npa.16983
[36] Gross HJ, Watson C. Characteristics, burden of illness, and physical functioning of patients with relapsing-remitting and secondary progressive multiple sclerosis: a cross-sectional US survey. *Neuropsychiatr Dis Treat* 2017;13:1349-1357.doi:10.2147/NDT.S132079
[37] Cichy KE, Li J, Rumrill PD, Bishop M, Roessler RT. Non-vocational health-related correlates of quality of life for older adults living with multiple sclerosis. *J Rehabil* 2016;82:36-44.
[38] Zhang Y, Taylor BV, Simpson SJ, Blizzard L, van der Mei I. Patient-reported outcomes are worse for progressive-onset multiple sclerosis than relapse-onset multiple sclerosis, particularly early in the disease process. *Eur J Neurol* 2019;26: 155-161. doi:10.1111/ene.13786
[39] Shahrbanian S, Duquette P, Kuspinar A, Mayo NE. Contribution of symptom clusters to multiple sclerosis consequences. *Qual Life Res* 2015;24: 617-629.doi:10.1007/s11136-014-0804-7
[40] Hyncicova E, Kalina A, Vyhnalek M, et al. Health-related quality of life , neuropsychiatric symptoms and structural brain changes in clinically isolated syndrome. *PLoS ONE* 2018;13:1-13.doi:10.1371/journal.pone.0200254.
[41] Bishop M, Rumrill PD, Roessler RT. Quality of life among people with multiple sclerosis: replication of a three-factor prediction model. *Work* 2015;52:757-765.doi:10.3233/WOR-152203
[42] Leonavicius R, Ph DMD. Among multiple sclerosis and fatigue. *Neurol Psychiatry Brain Res* 2016;22:141-145.doi:10.1016/j.npbr.2016.08.002
[43] Garg H, Bush S, Gappmaier E. Associations between fatigue and disability, functional mobility, depression, and quality of life in people with multiple sclerosis. *Int J MS Care* 2016:18:71-77.doi:10.7224/1537-2073.2015-013
[44] Fernández-Muñoz, JJ, Morón-Verdasco A, Cigarán-Méndez M, Muñoz-Hellín E, Pérez-de-Heredia-Torres M, Fernández-de-las-Peñas C. Disability, quality of life, personality, cognitive and psychological variables associated with fatigue in patients with multiple sclerosis. *Acta Neurol Scand* 2015;132:118-124.doi:10.1111/ane.12370
[45] Weiland TJ, Jelinek GA, Marck CH, Hadgkiss EJ. Clinically significant fatigue: prevalence and associated factors in an international sample of adults with multiple sclerosis recruited via the internet. *PLoS ONE* 2015;10:1-18.doi:10.1371/journal.pone.0115541
[46] Aygünoğlu SK, ÇelebİA, Vardar N, Gürsoy E. Correlation of fatigue with depression, disability level and quality of life

in patients with multiple sclerosis. *Noro Psikiyatr Ars* 2015;52:247-251.doi:10.5152/npa.2015.8714
[47] Vister E, Tijsma ME, Hoang PD, Lord SR. Fatigue, physical activity, quality of life, and fall risk in people with multiple sclerosis. *Int J MS Care* 2017;19(2):91-98.doi:10.7224/1537-2073.2015-077
[48] Tabrizi FM, Radfar M. Fatigue, sleep quality, and disability in relation to quality of life in multiple sclerosis. *Int J MS Care* 2015;17:268-274.doi:10.7224/1537-2073.2014-046
[49] Barin L, Salmen A, Disanto G, et al. The disease burden of multiple sclerosis from the individual and population perspective: which symptoms matter most? *Mult Scler Relat Disord* 2018;25:112–121.doi:10.1016/j.msard.2018.07.013.
[50] Kratz AL, Ehde DM, Hanley MA, Jensen MP, Osborne TL, Kraft GH. Cross sectional examination of the associations between symptoms, community integration, and mental health in Multiple Sclerosis. *Arch Phys Med Rehabil*. 2016;97:11-13.doi:10.1016/j.apmr.2015.10.093
[51] Strober LB. Quality of life and psychological well-being in the early stages of multiple sclerosis (MS): Importance of adopting a biopsychosocial model. *Disabil Health J* 2018;11:555-561.doi:10.1016/j.dhjo.2018.05.003
[52] Dymecka J. Biomedical variables and adaptation to disease and health-related quality of life in polish patients with MS. *Int J Environ Res Public Health* 2018; 15: 2678.doi:10.3390/ijerph15122678.
[53] Colbeck M. Sensory processing, cognitive fatigue, and quality of life in multiple sclerosis. *Can J Occup Ther* 2018;85:169-175.doi:10.1177/0008417417727298
[54] Abdullah EJ, Badr HE. Assessing the quality of life in patients with multiple sclerosis in Kuwait: a cross sectional study. *Psychol Heal Med*. 2018;23:391-399.doi:10.1080/13548506.2017.1366660
[55] Williams AE, Vietri JT, Isherwood G, Flor A. Symptoms and Association with Health Outcomes in Relapsing-Remitting Multiple Sclerosis : Results of a US Patient Survey. *Mult Scler Int*. 2014;2014:203183.doi: 10.1155/2014/203183
[56] Marck CH, Livera AM De, Weiland TJ, Jelinek PL. Pain in people with multiple sclerosis : associations with modifiable lifestyle factors, fatigue, depression, anxiety, and mental health quality of life. *Front Neurol* 2017;8:1-7.doi:10.3389/fneur.2017.00461
[57] Milinis K, Tennant A, Young CA. Spasticity in multiple sclerosis: associations with impairments and overall quality of life. *Mult Scler Relat Disord* 2016;5:34-39.doi:10.1016/j.msard.2015.10.007
[58] Zettl UK, Henze T, Essner U, Flachenecker P. Burden of disease in multiple sclerosis patients with spasticity in Germany: Mobility improvement study (Move I). *Eur J Heal Econ* 2014;15:953-966.doi:10.1007/s10198-013-0537-5
[59] Khalaf KM, Coyne KS, Globe DR, et al. The impact of lower urinary tract symptoms on health-related quality of life among patients with multiple sclerosis. *Neurourol Urodyn* 2016;54:48-54.doi:10.1002/nau
[60] Vitkova M, Rosenberger J, Krokavcova M, et al. Health-related quality of life in multiple sclerosis patients with bladder, bowel and sexual dysfunction. *Disabil Rehabil* 2014;36:987-992.doi:10.3109/09638288.2013.825332
[61] Qaderi K, Merghati Khoei E. Sexual problems and quality of life in women with multiple sclerosis. *Sex Disabil* 2014;32:35-43.doi:10.1007/s11195-013-9318-4
[62] Schairer LC, Foley FW, Zemon V, et al. The impact of sexual dysfunction on health-related quality of life in people with multiple sclerosis. *Mult Scler J* 2014;20:610-616.doi:10.1177/1352458513503598
[63] Ma S, Rui X, Qi P, Liu G, Yang J. Sleep disorders in patients with multiple sclerosis in China. *Sleep Breath* 2017;21:149-154.doi:10.1007/s11325-016-1416-y
[64] White EK, Sullivan AB, Drerup M. Impact of sleep disorders on depression and patient-perceived health-related quality of life in multiple sclerosis. *Int J MS Care* 2019;21: 10-14.doi:10.7224/1537-2073.2017-068
[65] Grech LB, Kiropoulos LA, Kirby KM, Butler E, Paine M, Hester R. The effect of executive function on stress, depression, anxiety, and quality of life in multiple sclerosis. *J Clin Exp Neuropsychol* 2015;37:549-562.doi:10.1080/13803395.2015.1037723
[66] Samartzis L, Gavala E, Zoukos Y, Aspiotis A, Thomaides T. Perceived cognitive decline in multiple sclerosis impacts quality of life independently of depression. *Rehabil Res Pract* 2014;2014:128751.doi: 10.1155/2014/128751.
[67] Campbell J, Rashid W, Cercignani M, Langdon D. Cognitive impairment among patients with multiple sclerosis : associations with employment and quality of life. *Postgrad Med J* 2017;93:143-147. doi: 10.1136/postgradmedj-2016-134071.
[68] Sgaramella TM, Carrieri L, Stenta G, Bortolon F, Perini F, Soresi S. Self-reported executive functioning and satisfaction for quality of life dimensions in adults with multiple sclerosis. *Int J Child Heal Hum Dev* 2014;7:167.
[69] Paziuc LC, Radu MR. The influence of mixed anxiety-depressive disorder on the perceived quality of life in multiple sclerosis patients. *Bulletin of the Transilvania University of Brasov, Seriels VI: Medical Sciences* 2018;11:41–50.
[70] Phillips LH, Henry JD, Nouzova E, et al. Difficulties with emotion regulation in multiple sclerosis: links to executive function, mood, and quality of life. *J Clin Exp Neuropsychol* 2014;36:831-842.doi:10.1080/13803395.2014.946891
[71] Ledesma ALH., Méndez AJR, Vidal LSG, Cruz GT, García-Solís P, Esquivel FDJD. Coping strategies and quality of life in mexican multiple sclerosis patients: physical, psychological and social factors relationship. *Mult Scler Relat Disord* 2018;25:122-127.doi:10.1016/j.msard.2018.06.001
[72] Prisnie JC, Sajobi TT, Wang M, et al. CR. Effects of depression and anxiety on quality of life in five common neurological disorders. *Gen Hosp Psychiatry* 2018;52:58-63.doi:10.1016/j.genhosppsych.2018.03.009
[73] Alsaadi T, Hammasi K El, Shahrour TM, et al. Depression and anxiety as determinants of health-related quality of life in patients with multiple sclerosis - United Arab Emirates. *Neurol Int* 2017;9:75-78.doi:10.4081/ni.2017
[74] Labiano-fontcuberta A, Mitchell AJ, Moreno-garcía S, Puertas-martín V. Impact of anger on the health-related quality of life of multiple sclerosis patients. *Mult Scler J* 2015;21:630-641.doi:10.1177/1352458514549399.
[75] Fernández-muñoz JJ, Cigarán-méndez M, Navarro-pardo E, Pérez-de-heredia-torres M, Parás-bravo P. Is the association between health- related quality of life and fatigue mediated by depression in patients with multiple sclerosis ? A Spanish

cross- sectional study. *BMJ Open* 2018; 8:1-6.doi:10.1136/bmjopen-2017-016297
[76] Pham T, Jetté N, Bulloch AGM, Burton JM, Wiebe S, Patten SB. The prevalence of anxiety and associated factors in persons with multiple sclerosis. *Mult Scler Relat Disord* 2018;19:35-39.doi:10.1016/j.msard.2017.11.003
[77] Salhofer-Polanyi S, Friedrich F, Löffler S, et al. Health-related quality of life in multiple sclerosis: temperament outweighs EDSS. *BMC Psychiatry* 2018;18:1-6. doi:10.1186/s12888-018-1719-6
[78] Demirci S, Demirci K, Demirci S. The Effect of type D personality on quality of life in patients with multiple sclerosis. *Noropsikiyatri Arsivi.* 2017;54:272-276.doi:10.5152/npa.2016.12764
[79] Zengin O, Erbay E, Yıldırım B, Altındağ Ö. Quality of life, coping, and social support in patients with multiple sclerosis: a pilot study. *Turk J Neurol* 2017;23: 211–218. https://doi.org/10.4274/tnd.37074
[80] Grech LB, Kiropoulos LA, Kirby KM, Butler E, Paine M, Hester R. Target coping strategies for interventions aimed at maximizing psychosocial adjustment in people with multiple sclerosis. *Int J MS Care* 2018;20:109-119.doi:10.7224/1537-2073.2017-008
[81] Farran N, Ammar D, Darwish H. Quality of life and coping strategies in lebanese multiple sclerosis patients: a pilot study. *Mult Scler Relat Disord* 2016;6:21-27.doi:10.1016/j.msard.2015.12.003
[82] Mikula P, Nagyova I, Krokavcova M, et al. Coping and its importance for quality of life in patients with multiple sclerosis. *Disabil Rehabil* 2014;36:732-736.doi:10.3109/09638288.2013.808274
[83] Mikula P, Nagyova I, Krokavcova M, et al. The mediating effect of coping on the association between fatigue and quality of life in patients with multiple sclerosis. *Psychol Health Med* 2015;20:653-661.doi:10.1080/13548506.2015.1032310
[84] Mikula P, Nagyova I, Krokavcova M, et al. Do coping strategies mediate the association between Type D personality and quality of life among people with multiple sclerosis ? *J Health Psychol* 2016;23:1557-1565.doi:10.1177/1359105316660180
[85] Van Damme S, De Waegeneer A, Debruyne J. Do flexible goal adjustment and acceptance help preserve quality of life in patients with Multiple Sclerosis? *Int J Behav Med* 2016;23, 333-339.
[86] Nery-hurwit M, Yun J, Ebbeck V. Examining the roles of self-compassion and resilience on health-related quality of life for individuals with Multiple Sclerosis. *Disabil Health J* 2018;11:256-261.doi:10.1016/j.dhjo.2017.10.010
[87] Koelmel E, Hughes AJ, Alschuler KN, Ehde DM. Resilience mediates the longitudinal relationships between social support and mental health outcomes in multiple sclerosis. *Arch Phys Med Rehabil* 2017;98:1139-1148. doi:10.1016/j.apmr.2016.09.127
[88] Wilski M, Tasiemski T. Health-related quality of life in multiple sclerosis: role of cognitive appraisals of self , illness and treatment. *Qual Life Res* 2016;25:1761-1770.doi:10.1007/s11136-015-1204-3
[89] Calandri E, Graziano F, Borghi M, Bonino, S. Depression, positive and negative affect, optimism and health-related quality of life in recently diagnosed multiple sclerosis patients: the role of identity, sense of coherence, and self-efficacy. *J Happiness Stud* 2018;19:277-295.doi:10.1007/s10902-016-9818-x
[90] Mikula P, Nagyova I, Krokavcova M, et al. Self-esteem, social participation, and quality of life in patients with multiple sclerosis. *J Health Psychol* 2017;22:984-992.doi:10.1177/1359105315621778
[91] Valvano A, Floyd RM, Penwell-waines L, Stepleman L, Lewis K, House A. The relationship between cognitive fusion, stigma, and well-being in people with multiple sclerosis. *J Context Behav Sci* 2016;5:266-270.doi:10.1016/j.jcbs.2016.07.003
[92] Costa DC, Sá, MJ , Calheiros JM. Social support network and quality of life in multiple sclerosis patients. *Arq Neuropsiquiatr* 2017;75:267-271.https://doi.org/10.1590/0004-282x20170036
[93] Mikula P, Nagyova I, Krokavcova M, et al. Social participation and health-related quality of life in people with multiple sclerosis. *Disabil Health J* 2015;8:29-34.doi:10.1016/j.dhjo.2014.07.002
[94] Chiu C, Chan F, Edward S, Dutta A, Hartman E, Bezyak J. Employment as a health promotion intervention for persons with multiple sclerosis. *Work* 2015;52:749-756.doi:10.3233/WOR-152202
[95] Possa MF, Minacapelli E, Canale S, et al. The first year after diagnosis : psychological impact on people with multiple sclerosis. *Psychol Health Med* 2017;22:1063-1701.doi:10.1080/13548506.2016.1274043
[96] Stern BZ, Strober L, DeLuca J, Goverover Y. Subjective well-being differs with age in multiple sclerosis: A brief report. *Rehabil Psychol* 2018;63:474-478.doi:10.1037/rep0000220
[97] Calandri E, Graziano F, Borghi M, Bonino S. Coping strategies and adjustment to multiple sclerosis among recently diagnosed patients: The mediating role of sense of coherence. *Clin Rehabil* 2017;31:1386-1395.doi:10.1177/0269215517695374
[98] Nourbakhsh B, Julian L, Waubant E. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. *Eur J Neurol* 2016;23:1482-1486.doi:10.1111/ene.13102
[99] Buhse M, Banker WM, Clement LM. Factors associated with health-related quality of life among older people with multiple sclerosis. *Int J MS Care* 2014;16:10-19. doi:10.7224/1537-2073.2012-046
[100] Kinkel RP, Laforet G, You X. Disease-Related Determinants of quality of life 10 years after clinically isolated syndrome. *Int J MS Care* 2015;17:26-34.doi:10.7224/1537-2073.2013-041
[101] Bueno AM, Sayao AL, Yousefi M, Devonshire V, Traboulsee A, Tremlett H. Health-related quality of life in patients with longstanding "benign multiple sclerosis." *Mult Scler Relat Disord* 2015;4:31-38.doi:10.1016/j.msard.2014.09.211
[102] Baumstarck K, Pelletier J, Boucekine M, Auquier P. Predictors of quality of life in patients with relapsing-remitting multiple sclerosis: a 2-year longitudinal study. *Rev Neurol* 2015;171:173-180.doi:10.1016/j.neurol.2014.09.005
[103] Tepavcevic DK, Pekmezovic T, Stojsavljevic N, et al. Change in quality of life and predictors of change among patients with multiple sclerosis: a prospective cohort study. *Qual Life Res* 2014;23:1027-1037.doi:10.1007/s11136-013-0535-1
[104] Chruzander C, Ytterberg C, Gottberg K, Einarsson U, Widén L, Johansson S. A 10-year follow-up of a population-based

study of people with multiple sclerosis in Stockholm , Sweden: changes in health-related quality of life and the value of different factors in predicting health-related qualit. *J Neurol Sci* 2014;339:57-63.doi:10.1016/j.jns.2014.01.020
[105] Young J, Amatya B, Galea MP, Khan F. Chronic pain in multiple sclerosis: a 10-year longitudinal study. *Scand J Pain* 2017;16:198-203.doi:10.1016/j.sjpain.2017.04.070
[106] Carletto S, Tesio V, Borghi M, et al. The effectiveness of a body-affective mindfulness intervention for multiple sclerosis patients with depressive symptoms : a randomized controlled clinical trial. *Front Psychol* 2017;8:1-13.doi:10.3389/fpsyg.2017.02083
[107] Besharat M, massood Nabavi S, Geranmayepour S, Morsali D, Haghani S. Mindfulness-based Stress Reduction (MBSR) program: the effect of a novel psycho-interventional method on quality of life, mental health, and self-efficacy in female patients with multiple sclerosis: a randomized clinical trial. *J Biol Today's World* 2017;06:211-215. doi:10.15412/j.jbtw.01061101
[108] Blankespoor RJ, Schellekens MPJ, Vos SH, Speckens AEM, Jong BA De. The effectiveness of mindfulness-based stress reduction on psychological distress and cognitive functioning in patients with multiple sclerosis : a pilot study. *Mindfulness (N Y)* 2017;8:1251-1258.doi:10.1007/s12671-017-0701-6
[109] Simpson R, Mair FS, Mercer SW. Mindfulness-based stress reduction for people with multiple sclerosis – a feasibility randomised controlled trial. *BMC Neurol* 2017;17:1-12.doi:10.1186/s12883-017-0880-8
[110] Spitzer E, Pakenham KI. Evaluation of a brief community-based mindfulness intervention for people with multiple sclerosis: a pilot study. *Clin Psychol* 2018;22:182-191.doi:10.1111/cp.12108
[111] Ghodspour Z, Najafi M, Boogar IR, Boogar R. Research paper: effectiveness of mindfulness-based cognitive therapy on psychological aspects of quality of life, depression, anxiety, and stress among patients with multiple sclerosis. *J Pract Clin Psychol* 2018;6:215-222.
[112] Case LK, Jackson P, Kinkel R, Mills PJ. Guided imagery improves mood, fatigue, and quality of life in individuals with multiple sclerosis : an exploratory efficacy trial of healing light guided imagery. *Evid Base Integr Med* 2018;23:1-8.doi:10.1177/2515690X17748744
[113] Blair M, Ferreria G, Gill S, et al. Dialectical behavior group therapy is feasible and reduces emotional dysfunction in multiple sclerosis. *Int J Group Psychother* 2017;67:500-518.doi:10.1080/00207284.2016.1260457
[114] Calandri E, Graziano F, Borghi M, Bonino S. Improving the quality of life and psychological well-being of recently diagnosed multiple sclerosis patients: preliminary evaluation of a group-based cognitive behavioral intervention. *Disabil Rehabil* 2017;39:1474-1481.doi:10.1080/09638288.2016.1198430
[115] Graziano F, Calandri E, Borghi M, Bonino S. The effects of a group-based cognitive behavioral therapy on people with multiple sclerosis: a randomized controlled trial. *Clin Rehabil* 2014;28:264-274.doi:10.1177/0269215513501525
[116] Kiropoulos LA, Kilpatrick T, Holmes A, Threader J. A pilot randomized controlled trial of a tailored cognitive behavioural therapy based intervention for depressive symptoms in those newly diagnosed with multiple sclerosis. *BMC Psychiatry* 2016;16:1-10.doi:10.1186/s12888-016-1152-7
[117] Chruzander C, Gottberg K, Ytterberg C, et al. A single-group pilot feasibility study of cognitive behavioural therapy in people with multiple sclerosis with depressive symptoms. *Disabil Rehabil* 2016;38:2383-2391. doi:10.3109/09638288.2015.1130179
[118] Kikuchi, H., Niino, M., Hirotani, M., Miyazaki, Y, Kikuchi, S. Pilot study on the effects of cognitive behavioral therapy on depression among japanese patients with multiple sclerosis. *Clin Exp Neuroimmunol* 2019;10: 180-185.doi:10.1111/cen3.12529
[119] Pakenham KI, Mawdsley M, Brown FL, Burton NW. (2018). Pilot evaluation of a resilience training program for people with multiple sclerosis. *Rehabil Psychol 2018;63*:29-42.doi:10.1037/rep0000167
[120] Proctor BJ, Moghaddam NG, Evangelou N. Telephone-supported acceptance and commitment bibliotherapy for people with multiple sclerosis and psychological distress: a pilot randomised controlled trial. *J Context Behav Sci* 2018;9:103-109.doi:10.1016/j.jcbs.2018.07.006
[121] Abolghasemi A, Farhang S, Taherifard M, Kiamarsi A. The effect of supportive-expressive therapy on hope and quality of life in patients with multiple sclerosis (MS). *Archives of Psychiatry and Psychotherapy* 2016;18:20-27. doi:10.12740/APP/64975
[122] Jongen PJ, Ruimschotel R, Heerings M, et al. Improved self-efficacy in persons with relapsing remitting multiple sclerosis after an intensive social cognitive wellness program with participation of support partners: a 6-months observational study. *Health Qual Life Outcomes.* 2014;12:1-9.doi:10.1186/1477-7525-12-40
[123] Jongen PJ, Heerings M, Ruimschotel R, et al. Intensive social cognitive treatment (can do treatment) with participation of support partners in persons with relapsing remitting multiple sclerosis: observation of improved self-efficacy, quality of life, anxiety and depression 1 year later. *BMC Res Notes* 2016;9:1-8.doi:10.1186/s13104-016-2173-5
[124] Eliášová A, Majerníková L, Hudáková A, Kaščáková M. Self-help group and the quality of life of patients with multiple sclerosis - pilot study. *Cent Eur J Nurs Midwifery* 2015;6:336-342.doi:10.15452/CEJNM.2015.06.0025
[125] Liu Y. A hope-based group therapy program to women with multiple sclerosis: quality of life. *Neuroquantology* 2017;15:127-132. doi:10.14704/nq.2017.15.4.1135
[126] Mulligan H, Wilkinson A, Barclay A, Whiting H, Heynike C, Snowdon J. Evaluation of a fatigue self-management program for people with multiple sclerosis. *Int J MS Care* 2016;18:116-121.doi:10.7224/1537-2073.2015-019
[127] Thomas PW, Thomas S, Kersten P, et al. One year follow-up of a pragmatic multi-centre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *BMC Neurol* 2014;14:1-6.doi:10.1186/1471-2377-14-109
[128] Ehde DM, Elzea JL, Verrall AM, Gibbons LE, Smith AE, Amtmann D. Efficacy of a telephone-delivered self-

management intervention for persons with multiple sclerosis : a randomized controlled trial with a one-year follow-up. *Arch Phys Med Rehabil* 2015;96:1945-1958.e2.doi:10.1016/j.apmr.2015.07.015

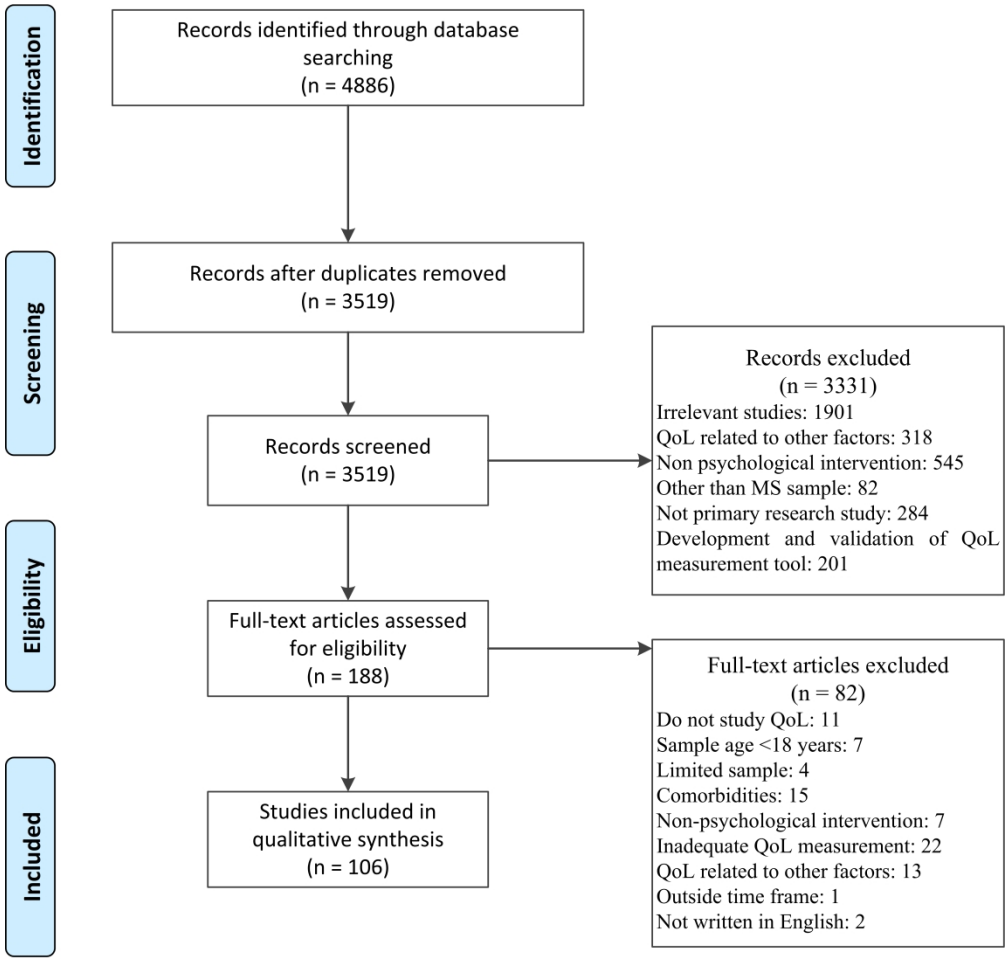
[129] Feicke J, Spörhase U, Köhler J, Busch C, Wirtz M. A multicenter, prospective, quasi-experimental evaluation study of a patient education program to foster multiple sclerosis self-management competencies. *Patient Educ Couns* 2014;97:361-369. doi:10.1016/j.pec.2014.09.005

[130] Leclaire K, Cecil A, Larussa A, et al. A pilot study of a group positive psychology intervention for patients with multiple sclerosis. *Int J MS Care* 2018;20:136-141.doi:10.7224/1537-2073.2017-002

[131] Geiser F, Imbierowicz K, Conrad R, Schilling G, Liedtke R. Differences between patients classified as "recovered" or "improved" and "unchanged" or "deteriorated" in a psychotherapy outcome study. *Z Psychosom Med Psychother* 2001;47(3):250-61. doi.org/10.13109/zptm.2001.47.3.250

Figure Legend 1

PRISMA flow diagram of selection process.



PRISMA flow diagram of selection process

167x160mm (800 x 800 DPI)

Supplement Digital Content A: Search strategy for data bases

SCOPUS

TITLE-ABS-KEY ("MULTIPLE SCLEROSIS") AND TITLE-ABS-KEY ("QUALITY OF LIFE" OR "Health-related quality of life" OR "Well-being" OR "Wellbeing" OR "Life satisfaction") AND (LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014)) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))

WEB OF SCIENCE

(TS= (“MULTIPLE SCLEROSIS”) AND TS= (“QUALITY OF LIFE” OR “Health-related quality of life” OR “Well-being” OR “Wellbeing” OR “Life satisfaction)) AND SEARCH LANGUAGE: (English) AND DOCUMENT TYPE: (Article)

Timespan: 2014-2019.

PROQUEST

ab("MULTIPLE SCLEROSIS") AND "QUALITY OF LIFE" OR "HEALTH-RELATED QUALITY OF LIFE" OR "WELL-BEING" OR "WELLBEING" OR "LIFE SATISFACTION"

Date: From 2014 January 01 to 2019 January 31
Source type: Scholarly journal
Document type: Article
Language: English
Age group: Adult (19-44 years), Middle aged (45-64 years), Aged (65+ years), Aged (80+ years)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	4
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.	4-5
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.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement Digital Content A
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).	5
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.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
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.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable

bmjopen-2020-041249 on 30 November 2020. Downloaded from

PRISMA 2009 Checklist

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.	Not applicable

Section/topic	#	Checklist item	Reported on page #
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).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
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.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICO, follow-up period) and provide the citations.	11-17, 19,22-24
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).	7
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.	11-17, 19,22-24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
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).	25-26
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).	26
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			

PRISMA 2009 Checklist

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.	26

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.