Review article

Psychological impacts of COVID-19 pandemic on individuals living with multiple sclerosis: A rapid systematic review

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ABSTRACT

Introduction: The global spread of COVID-19 has raised concerns about its possible impact on mental health. People living with multiple sclerosis (PwMS) are considered potentially vulnerable to the mental health effects of the pandemic, as they may be subject to increased social isolation.
Aim: To systematically review the current evidence on the impact of the COVID-19 pandemic on mental health outcomes among PwMS.
Method: We searched four major databases (Medline, EMBASE, PsychInfo and Scopus) and the WHO Global Health COVID-19 research database. We included peer-reviewed primary research studies using validated health-related quality of life (HRQOL) and psychometric screening tools to evaluate mental health outcomes among PwMS during the COVID-19 pandemic. Studies reporting data on the prevalence of mental health disorders, severity of psychological symptoms and contributing demographic and clinical factors for PwMS during the COVID-19 pandemic were included.
Results: Our initial search yielded 268 records; 19 studies (13 cross-sectional, 6 longitudinal) were included. Most were conducted during a peak in the pandemic in the host country via an online platform. The main mental health outcomes were depression, anxiety, stress, sleep quality and HRQOL. The included studies used a variety of outcome assessment tools and study designs. The prevalence of mental health issues such as depression, anxiety and stress were high among PwMS during the pandemic. In addition, compared to control populations, PwMS experienced more severe symptoms of depression and stress during the COVID-19 outbreak. However, results from longitudinal studies demonstrate that the severity of mental health symptoms among PwMS during the pandemic were not significantly different compared with the pre-pandemic period.
Conclusion: Although mental health issues such as anxiety and depression were common among PwMS during the pandemic, current evidence suggests that mental health among PwMS has not been significantly affected by pandemic-related restrictive measures. Instead, the observed differences may be the result of pre-pandemic differences in prevalence and severity. Where possible, future studies should seek to address the methodological issues identified in the included studies to ensure that data collected during the pandemic can be synthesized into recommendations for policy and practice.

1. Introduction

On March 11, 2020, the World Health organization (WHO) officially declared a COVID-19 pandemic (WHO 2020). To date, the pandemic has affected 223 countries, areas or territories, and has caused > 113 million known cases and almost 2.5 million confirmed deaths (WHO 2021). In response to this global health threat and the unprecedented pressures placed on healthcare systems, nearly every country has initiated social distancing measures, gradual or immediate lockdowns, border closures, and/or travel bans. However, these methods, which are aimed at stemming the spread of the virus, have also affected the lives of billions of people, directly and indirectly, by restricting social gatherings, travel, employment, and education. In addition to the social and economic impact of COVID-19, the unpredictability of the situation, unavailability of vaccination, overflow of information, and the dissemination of myths and inaccurate information via social media have led to an increase in

concern and confusion for the public (Bao et al., 2020; Krishnamoorthy et al., 2020).

Research from previous and ongoing outbreaks, such as severe acute respiratory syndrome (SARS) (De Brier et al., 2020; Rogers et al., 2020), Middle East respiratory syndrome (MERS) (De Brier et al., 2020; Rogers et al., 2020), H1N1 influenza (H1N1) (Han et al., 2020), Ebola virus (Cenat et al., 2020), and the current COVID-19 pandemic (Krishnamoorthy et al., 2020; Rogers et al., 2020), demonstrate that outbreaks increase the risk of mental health issues among patients and healthcare providers, and amongst various subpopulations, including people with chronic health conditions (Wu et al., 2020), quarantined people (Hossain et al., 2020), older people (Sepulveda-Loyola et al., 2020), children and adolescents (Nearchou et al., 2020), and pregnant and post-partum women (Yan et al., 2020). A recent meta-analysis reported that the global prevalence of depression, anxiety, and distress during the COVID-19 pandemic was 31.4%, 31.9%, and 41.1%, respectively. Notably, the risk of depression and anxiety were found to be substantially higher among non-infectious chronic disease patients, quarantined people and COVID-19 patients than in other subpopulations (Wu et al., 2020). Similarly, results from a national cohort study in UK demonstrated that the prevalence of clinically significant levels of mental health distress increased from 18.9% in 2018–19 to 27.3% by late April 2020, one month into the UK's lockdown (Pierce et al., 2021).

People with multiple sclerosis (PwMS) may be more vulnerable to the neuropsychiatric impacts of the COVID-19 pandemic than the general population (Haji Akhoundi et al., 2020). Psychiatric comorbidities such as depression and anxiety are more common in PwMS compared to the general population, and these conditions are often considered to be part of the spectrum of MS symptoms (Marrie et al., 2015). A recent meta-analysis of pre-pandemic studies reported that in the early phase of MS, the prevalence of anxiety and depression (as measured by HADS) was 35% (95%CI: 28–41%) and 17% (95%CI: 9–25%), respectively (Rintala et al., 2019). Psychiatric comorbidities are major contributors to psychological distress and can influence the disease course, level of fatigue, disability progression and quality of life (QoL) in affected PwMS (Berrigan et al., 2016; McKay et al., 2018).

As described above, restrictive measures that curtail personal freedoms such as quarantine, social isolation, and social distancing have been imposed to protect society from the rapid spread of COVID-19. However, such laudable preventative measures may impact both the physical and psychosocial well-being of PwMS. PwMS may face disruptions in lifestyle and increased stress as a result of COVID-19 containment measures, such as increased social isolation and delays in medical appointments. This could ultimately lead to adverse effects on their neuropsychological state, adherence to treatment and overall QoL (Motl et al., 2020; Pedrosa et al., 2020). Results from a large online survey among PwMS in the United States showed considerable disruptions in multiple health behaviours and access to MS-related health care during the COVID-19 pandemic. More than two-thirds of respondents reported that they had to cancel a clinical appointment during this period and almost 20% missed an MRI or laboratory test. Furthermore, about 10% reported some level of disease-modifying therapy treatment (DMT) change, including delayed dosage. Importantly, the same cohort reported that COVID-19 has had a significant economic impact on their lives, causing them to change employment, reduce work hours, or even lose their job (Vogel et al., 2020). Similar findings on the economic consequences of COVID-19 for PwMS have also been found in surveys from Spain and China (Zhang et al., 2021). Notably, previous studies have demonstrated the adverse impact of unemployment on mental health (Dorstyn et al., 2019), and the negative effect of DMT non-adherence on disease activity and health resource utilization (Burks et al., 2017) among PwMS.

Several systematic reviews and meta-analyses have reported the prevalence of common mental health conditions among the general population and various subpopulations during previous outbreaks such as SARS, MERS, H1N1, as well as the COVID-19 pandemic (Cabarkapa

et al., 2020; Hossain et al., 2020; Xiong et al., 2020). However, no review has evaluated the current evidence in PwMS. Therefore, the aim of this study is to conduct a rapid systematic review of the existing evidence on impact of the COVID-19 pandemic on mental health outcomes among PwMS.

2. Methods

2.1. Search methodology and study design

We conducted a systematic literature search in four biomedical databases (MEDLINE, PsycInfo, EMBASE and Scopus) for studies published prior to 25 June 2021. The full list of search strategies and the retrieved records are described in Supplementary Table 1. We utilized a combination of terms relating to COVID-19 (e.g., "SARS-CoV-2″ and "coronavirus"), mental health outcomes (e.g., "psychiatric" and "mental health") and MS-related disease and disease course. We used several keywords for each of the main concepts. We did not limit our search to specific psychiatric disorders; by selecting more general Medical Subject Headings (MeSH) or Map terms, we considered broader outcomes and determinants of mental health and wellbeing. We also conducted a search in the WHO Global Health research database on COVID-19 for additional articles. Duplicate records were removed, and titles and abstracts were reviewed by one reviewer (AZ). The full text of the remaining records was then reviewed by one reviewer (AZ). Study selection was conducted based on the inclusion and exclusion criteria summarized in Table 1, which follows the PICOS convention (population; intervention/exposure; comparison; outcome; study design) (Methley et al., 2014).

2.2. Data extraction

The following items were extracted from the included studies using a standardized spreadsheet: author name, year of publication, country, study design, sample size, recruitment location, study participants, type of MS, sex, average age, average disease duration, average Expanded Disability Status Scale (EDSS) score, history of psychiatric comorbidity and results of psychometric screening tools. We also recorded the timeframe of the study with respect to the COVID-19 pandemic and related lockdowns (early/during/at the peak), as stated in the included articles. The WHO defines a pandemic peak as the number of new cases rising to the highest observed levels and the peak of the

Table 1
Summary of inclusion and exclusion criteria according to PICOS acronym.

	Inclusion criteria	Exclusion criteria
Population	People living with MS including pediatric and adult-onset types	–
Intervention/ exposure	COVID-19 pandemic and related social distancing and lockdown measures	Conducted prior to the COVID-19 pandemic
Comparison	Any control population was acceptable. Having no control group was also acceptable	–
Outcome	Prevalence of psychiatric disorders, or the level of psychological symptoms or wellbeing measured by a valid psychometric assessment tool, or measurement determinants of mental health outcomes	Used questionnaires that have not been validated to assess mental health-related outcomes
Study design	Observational studies, including cross-sectional studies	Reported the effect of any therapeutic or behavioural intervention; expert opinion; or case report
Language	English language	Not written in English
Setting	All	–

epidemic curve beginning to drop following implementation of adequate surveillance (WHO). It is noteworthy that the working definition of a pandemic peak and the severity of social and health-related containment and prevention measures depend on country/territory policies and may vary from each other.

2.3. Quality assessment

Two reviewers (AZ and CE) conducted the risk of bias assessment independently, and any conflicts were resolved by a third reviewer (SC). Methodological quality assessment was carried out using the Newcastle-Ottawa Scale (NOS), which contains separate quality assessment instruments for cohort studies (Wells et al., 2022), and an adapted form of the NOS for cross-sectional studies (Herzog et al., 2013). The quality of each study was determined for three main domains (selection, comparability, and outcome) according to the tool's assessment criteria (Supplementary Tables 2 and 3). A cohort study could be awarded a maximum of one star for each numbered item within the "Selection" and "Outcome" domains. A maximum of two stars can be awarded for the "Comparability" domain. The final score for each study was calculated as the total number of awarded stars. The higher total number stars indicate better research quality (Wells et al., 2022). The maximum number of stars for cohort and cross-sectional studies is 9 and 10, respectively. In addition, we used the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting this study (Supplementary Table 4).

2.4. Data synthesis

The included studies were too heterogeneous for a meta-analysis; a small number of studies assessed each outcome, and a wide range of psychometric screening tools were used. Consequently, we conducted a narrative synthesis focused on five major mental health-related outcomes as common themes: anxiety, depression, HRQOL, stress and sleep quality. For each outcome, we discuss the prevalence or frequency of the outcome, the severity of symptoms as measured by psychometric scales, comparisons between PwMS and controls and the comparison over time.

3. Results

Fig. 1 illustrates the flow of studies into this review. In summary, a total of 268 records were returned from the initial searches. After removing duplicate articles, the titles and abstract of 197 records were screened. Of these, 37 articles (18.8%) were deemed eligible for full-text review. Of these, 19 articles (51.3%) were included.

3.1. Characteristics of included studies

Table 2 presents the characteristics of the included studies. Of the 19 included studies, 13 were cross-sectional, four were longitudinal, and two included both longitudinal and cross-sectional analyses. The included studies assessed a total of 5816 adult MS cases and 30 pediatric (aged $\leq$ 18 years) MS cases. Eleven studies were conducted in European countries and the remainder were based in Iran ($n = 4$), the USA ($n = 1$)
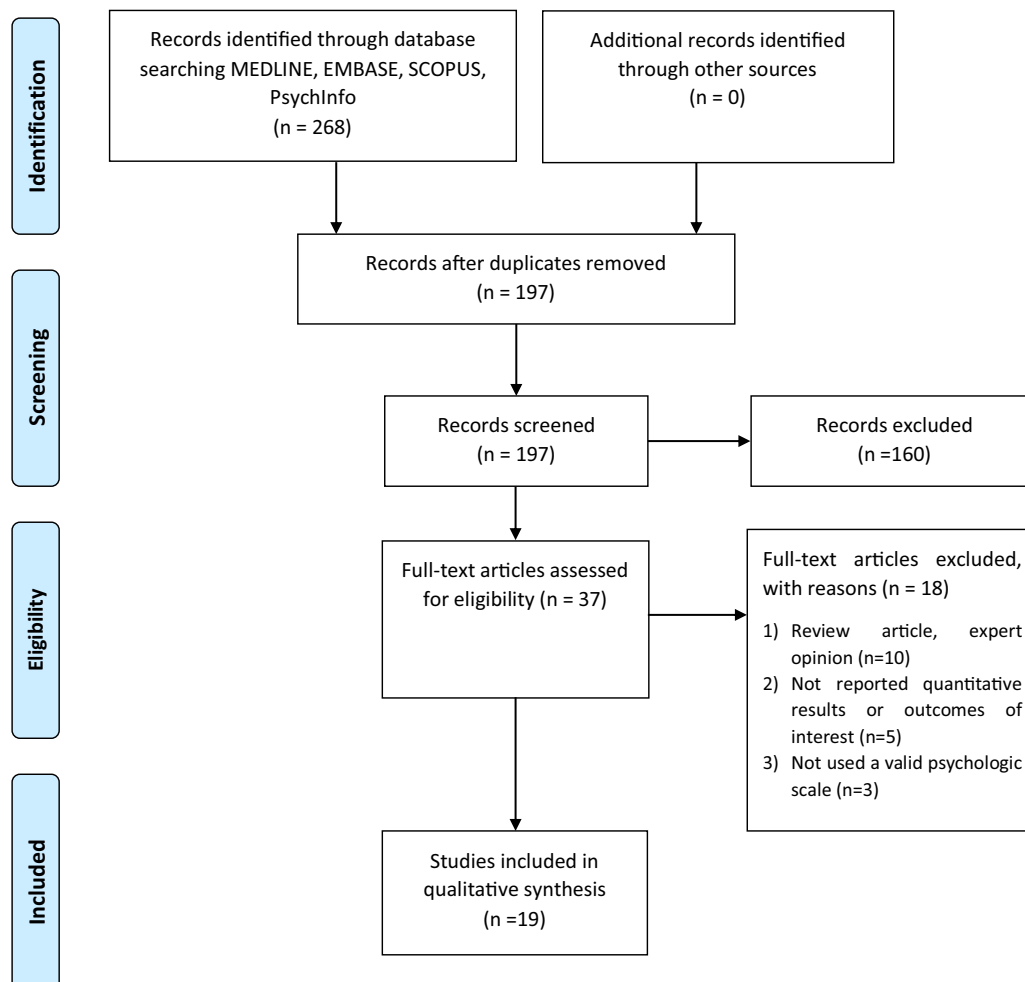

Fig. 1. PRISMA Flowchart of citations selection.

Table 2
Characteristics of the articles included in this review.

AuthorsDate	Country	Study design	COVID-19 pandemic Time frame	State of lockdown#	Sample size and participant type	Recruitment source	Age* (years)	Female casesn (%)	MS duration* (years)	Psychiatric comorbidities	Data collection	Outcomes	Psychometric scale	Overall quality score
Andreu-Caravaca et al. (2021)	Spain	Longitudinal	During	Before/after	18 PwMS[1]	NA	43.5 (11.2)	10(55.5)	NA	NA	Online survey	Anxiety	State-Trait Anxiety Inventory (STAI)	4
Capuano et al. (2021)	Italy	Longitudinal	Before/during	Yes	67 RRMS[2]	MS center	37.5 (11.1)	37(55.2)	7.6(8.1)	NA	Online survey	Anxiety, depression, quality of life	State-Trait Anxiety Inventory (STAI), Beck Depression Inventory second edition (BDI-II), Multiple Sclerosis Quality of Life-54 (MSQoL-54)	4
Chiaravalloti et al. (2021)	Belgium, Canada, Denmark, Italy, UK, USA	Longitudinal	Before/during	Yes	131 PMS[3]	Ongoing clinical trial (sourced from in and outpatient MS clinics)	52.1(6.9)	83(63.4)	14.4(9.1)	Exclusion criterion	Telephonic/online, in-person survey	Anxiety, depression, impact of MS on psychological scale, quality of life	The Hospital Anxiety Depression Scale (HADS), The Beck Depression Inventory-II (BDI-II), Multiple Sclerosis Impact Scale (MSIS-29), EuroQol (EQ-5D-5 L)	5
Demir et al. (2020)	Turkey	Longitudinal	Early/during	No	50 PwMS[1]	Web-based	30.0(7.0)	42(84.0)	NA	Exclusion criterion	Online survey	Anxiety, depression, sleep quality, quality of life	Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI), Multiple Sclerosis Quality of Life-54 (MSQoL-54)	5
Garjani et al. (2021)	UK	Longitudinal/cross-sectional	Before/during	Before/during	2010 PwMS[1], 380 controls	UK MS Register cohort	median: 56 (48–63)	1488 (74.3)	median: 12 (6–20)	Baseline anxiety and depression were reported.	Online survey	Anxiety, depression, post-traumatic stress disorder (PTSD)	The Hospital Anxiety Depression Scale (HADS), General Anxiety Disorder 7-item (GAD-7), Patient Health Questionnaire 9-question (PHQ-9), Impact of Event Scale–Revised (IES-R)	Longitudinal (6) Cross-sectional(8)
Stojanov et al. (2020)	Serbia	Longitudinal/cross-sectional	Before/during	Yes	95 RRMS[2], 99 HC[4]	MS clinic	43.4(9.7)	89(67.6)	median: 8.2	Exclusion criterion	In-person survey	Anxiety, depression, quality of life	Hamilton scales for anxiety (HAM-A), and depression (HAM-D), Multiple Sclerosis Quality of Life-54 Instrument (MSQOL-54),	Longitudinal (5) Cross-sectional(6)
Alschuler et al. (2021)	USA	Cross-sectional	During	No	491 PwMS[1]	Online	55.8 (12.6)	399 (81.3)	16.7(11.2)	NA	Online survey	Anxiety, depression, positive affect and well-being	PROMIS Short Form v1.0 – Depression 6a and Anxiety 6a, Quality of Life in Neurological Disorders (Neuro-QoL) Short Form v1.0	7
Altunan et al. (2021)	Turkey	Cross-sectional	During	No	205 PwMS[1]	Outpatient clinic	37.7 (10.0)	152 (74.1)	7.4(6.5)	Exclusion criterion	Online survey	Stress, quality of life	Perceived Stress Scale (PSS),SF-12	4
	Italy	Cross-sectional	During	No		Online	43(10)		median: 10	NA		Stress, depression		5

(*continued on next page*)

Table 2 (*continued*)

AuthorsDate	Country	Study design	COVID-19 pandemic Time frame	State of lockdown[#]	Sample size and participant type	Recruitment source	Age* (years)	Female casesn (%)	MS duration* (years)	Psychiatric comorbidities	Data collection	Outcomes	Psychometric scale	Overall quality score
Bonavita et al., 2021					612 PwMS[1], 674 controls			465 (76.0)			Online survey		Perceived Stress Scale (PSS), Patient Health Questionnaire 2(PHQ-2)	
Broche-Perez et al. (2021)	Argentina, Mexico, Spain, Dominican Republic, Venezuela, Cuba	Cross-sectional	During	NA	202 PwMS[1]	Online and medical record	42,8 (12,7)	154 (76.2)	9.6(8.5)	NA	Online survey	Anxiety, depression	Beck Depression Inventory-II (BDI-II), Generalized Anxiety Disorder Scale (GAD-7)	5
Costabile et al., 2021	Italy	Cross-sectional	During	Yes	497 PwMS[1], 348 controls+	Web-based	42.4 (10.7)	351 (70.6)	NA	Reported and controlled for comparisons	Online survey	Mental distress	Quality of Life in Neurological Disorders (Neuro-QoL),	7
Dilek et al. (2021)	Turkey	Cross-sectional	During	NA	30 children with MS, 49 age-sex matched HC[4]	University hospital	15.6(2.1)	19(63.3)	2.5(1.3)	NA	Online survey	Anxiety	State-Trait Anxiety Inventory (STAI)	7
Motolese et al. (2020)	Italy	Cross-sectional	During	Yes	60 PwMS[1], 50 HC[4]	Outpatient clinic	NA	41(68.3)	5.1(5.9)	Reported	Online survey	Anxiety, depression, sleep quality	Beck Depression Inventory II (BDI-II) and the Generalized Anxiety Disease 7 (GAD-7), the Pittsburgh Sleep Quality Index (PSQI)	5
Naser Moghadasi (2020)	Iran	Cross-sectional	During	NA	33 PwMS[1]	MS clinic	33.5(5.2)	27(81.8)	6.1(4.2)	NA	In-person survey	Anxiety	Beck Anxiety Inventory (BAI)	4
Ramezani et al. (2021)	Iran	Cross-sectional	During	NA	410 PwMS[1]	MS clinic	38.6 (10.3)	326 (79.5)	NA	Reported	In-person survey	Anxiety, depression	Hospital Anxiety and Depression Scale (HADS)	4
Shaygannejad et al. (2021b)	Iran	Cross-sectional	During	NA	165 PwMS[1]	MS clinic	35.3(8.6)	136 (82.4)	7.1(5)	NA	In-person survey	Anxiety, depression, stress	Depression Anxiety Stress Scales-21 (DASS-21)	4
Shaygannejad et al. (2021a)	Iran	Cross-sectional	During	Yes	223 PwMS[1], 245 HC[4]	MS clinic	35.9(7.5)	183 (82.1)	6.4(5.2)	Reported	Online survey	Anxiety, depression, stress	Depression Anxiety Stress Scales-21 (DASS-21)	5
Talaat et al. (2020)	Egypt	Cross-sectional	During	NA	115 PwMS[1], 129 HC[4]	University hospital	34.4(8.5)	89(77.4)	6.8(5.5)	NA	Online survey	Anxiety, depression, stress	Depression Anxiety Stress Scales-21 (DASS-21)	5
Zanghi et al. (2020)	Italy	Cross-sectional	During	After ease of lockdown	432 RRMS[2]	MS center	40.4 (12.4)	277 (64.1)	5.3(3.2)	Reported	Telephonic interview	Anxiety, depression, stress, Post-Traumatic Stress Disorder (PTSD), Sleep quality	Depression Anxiety Stress Scales-21 (DASS-21), Short Screening Scale for DSM-IV (SSS DSM-IV), Insomnia Severity Index (ISI).	6

*Data are mean(SD) unless otherwise stated. 1.PwMS: People Living with Multiple Sclerosis, 2. RRMS: Relapsing Remitting MS, 3.PMS: Progressive MS, 4. HC: Healthy controls, NA: Not available. # Study conducted during the local or national state of lockdown + Control group in this study was selected from family members and/or friends not affected by MS.

and Egypt ($n = 1$). There were two multicentre studies; one recruited participant from six countries across North America and Europe (Chiaravalloti et al., 2021) and the other recruited participants from five Central and South American countries and Spain (Broche-Perez et al., 2021). All were conducted during the COVID-19 outbreak but a subset was done during a period of lockdown in the host country. About half of the studies ($n = 9$) described concurrent public health attempts to limit COVID-19 spread, with governments enforcing a regional or nationwide lockdown/quarantine in the state or country (Andreu-Caravaca et al., 2021; Capuano et al., 2021; Chiaravalloti et al., 2021; Costabile et al., 2021; Garjani et al., 2021; Motolese et al., 2020; Shaygannejad et al., 2021a; Stojanov et al., 2020; Zanghi et al., 2020). However, the level or severity of concurrent quarantine or lockdown measures was not clearly described.

Nine studies (47.4%) reported the prevalence of mental health outcomes during the COVID-19 pandemic as determined by psychometric scales (Alschuler et al., 2021; Altunan et al., 2021; Bonavita et al., 2021; Capuano et al., 2021; Garjani et al., 2021; Naser Moghadasi, 2020; Ramezani et al., 2021; Talaat et al., 2020; Zanghi et al., 2020). However, only two studies (10.5%) reported a prospective comparison before and during the pandemic (Capuano et al., 2021; Garjani et al., 2021). All 15 cross-sectional studies reported the severity of mental health symptoms during the COVID-19 pandemic. Of these, eight (53.3%) sampled a control population to compare with PwMS (Bonavita et al., 2021; Costabile et al., 2021; Dilek et al., 2021; Garjani et al., 2021; Motolese et al., 2020; Shaygannejad et al., 2021a; Stojanov et al., 2020; Talaat et al., 2020). Two cross-sectional studies examined the mental health status of parents and caregivers of PwMS as well as PwMS (Dilek et al., 2021; Talaat et al., 2020). All six longitudinal studies reported the severity of mental health symptoms among PwMS prior to or early in the COVID-19 pandemic along with follow-up measures in a lockdown period (Andreu-Caravaca et al., 2021; Capuano et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Garjani et al., 2021; Stojanov et al., 2020). However, none of the longitudinal studies recruited a control group for prospective comparison.

Most studies did not limit their study population by MS phenotype. However, one study only included participants with primary or secondary progressive MS (Chiaravalloti et al., 2021). Most of the studies ($n = 14$) used online surveys for data collection. Four studies excluded participants with comorbid psychiatric conditions (Altunan et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Stojanov et al., 2020), nine studies did not mention pre-existing psychiatric comorbidities prior to the onset of the COVID-19 outbreak (Alschuler et al., 2021; Andreu-Caravaca et al., 2021; Bonavita et al., 2021; Broche-Perez et al., 2021; Capuano et al., 2021; Dilek et al., 2021; Naser Moghadasi, 2020; Shaygannejad et al., 2021b; Talaat et al., 2020), and the remaining six articles reported baseline psychiatric comorbidity status (Costabile et al., 2021; Garjani et al., 2021; Motolese et al., 2020; Ramezani et al., 2021; Shaygannejad et al., 2021a; Zanghi et al., 2020).

3.2. Risk of bias assessment

Tables 3 and 4 provide the details of quality assessment, including rationale. Among the longitudinal studies ($n = 6$), two items (comparability domain and selection of the non-exposed cohort sub-domain) were not applicable and were not considered in the overall score. Thus, the maximum achievable number of stars for longitudinal studies was 6. The domain that was best addressed by all longitudinal studies was "outcome" and all the six studies were rated full points in this domain. Conversely, the selection domain was poorly addressed by five of the six studies in this group, due to the use of convenience sampling methods and the study cohort not being representative of PwMS in the community. A total of four studies had ≥ 5 points (Chiaravalloti et al., 2021; Demir et al., 2020; Garjani et al., 2021; Stojanov et al., 2020), indicating satisfactory quality.

All cross-sectional studies ($n = 15$) had a possible risk of selection bias. All but one study in this group had a high risk of bias related to the representativeness of the sample as their sampling was not random. The sample size was justified and satisfactory (including sample size calculation) in only four (26.7%) cross-sectional studies. Seven (46.7%) studies had a satisfactory recruitment rate or summarized the characteristics of non-respondents. All cross-sectional studies utilized a validated psychometric tool to measure mental health outcomes and clearly described their statistical analyses. In total, only four studies in this

Table 3
Results of the critical appraisal of the included longitudinal studies [#].

Citation	Selection										Comparability	Outcome									Overall rating
	Representativeness of the exposed cohort			Selection of the non-exposed cohort	Ascertainment of exposure			Demonstration that outcome of interest was not present at start of study			Based on design and analysis	Assessment of outcome			Was follow up long enough for outcomes to occur			Adequacy of follow up cohorts			
	Acceptable criteria	Reasoning	Point	Not applicable	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	Not applicable	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	
Andreu-Caravaca et al. 2021	Truly/ somewhat representative of the average PwMS in the community	Convenience sample		NA	Enrolment and surveys conducted during pandemic or lockdown	Measurements were conducted during the state of alarm in the country	*	Demonstration that outcome of interest was not present at start of study	Psychiatric comorbidities not reported		NA	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	*	Adequate follow up period for outcome of interest	Yes	*	Complete follow up or subjects lost to follow-up unlikely to introduce bias	Complete follow up	*	4
Capuano et al. 2021	Truly/ somewhat representative of the average PwMS in the community	Convenience sample		NA	Enrolment and surveys conducted during pandemic or lockdown/ structured interview	Structured phone call interview	*	Demonstration that outcome of interest was not present at start of study	Psychiatric comorbidities not reported		NA	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	*	Adequate follow up period for outcome of interest	Yes	*	Complete follow up or subjects lost to follow-up unlikely to introduce bias	Subjects' loss to follow up unlikely to introduce bias	*	4
Chiaravalloti et al. 2021	Truly/ somewhat representative of the average PwMS in the community	Convenience sample		NA	Enrolment and surveys conducted during pandemic or lockdown/ structured interview	Structured phone call interview	*	Demonstration that outcome of interest was not present at start of study	Exclusion criteria	*	NA	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	*	Adequate follow up period for outcome of interest	Yes	*	Complete follow up or subjects lost to follow-up unlikely to introduce bias	Subjects' loss to follow up unlikely to introduce bias	*	5
Demir et al. 2020	Truly/ somewhat representative of the average PwMS in the community	Convenience sample		NA	Enrolment and surveys conducted during pandemic or lockdown/ structured interview	Data were collected when the pandemic had its peak effects and strict restrictions were being imposed by the government	*	Demonstration that outcome of interest was not present at start of study	Exclusion criteria	*	NA	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	*	Adequate follow up period for outcome of interest	Yes	*	Complete follow up or subjects lost to follow-up unlikely to introduce bias	Subjects' loss to follow up unlikely to introduce bias	*	5
Garjani et al. 2021	Truly/ somewhat representative of the average PwMS in the community	somewhat representative of the average PwMS in the community	*	NA	Enrolment and surveys conducted during pandemic or lockdown/ structured interview	This study covers the first lockdown.	*	Demonstration that outcome of interest was not present at start of study	Baseline status was clearly reported	*	NA	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	*	Adequate follow up period for outcome of interest	Yes	*	Complete follow up or subjects lost to follow-up unlikely to introduce bias	Subjects' loss to follow up unlikely to introduce bias	*	6
Stojanov et al. 2020	Truly/ somewhat representative of the average PwMS in the community	Convenience sample		NA	Enrolment and surveys conducted during pandemic or lockdown/ structured interview	Data were collected during the state of emergency and police lockdown	*	Demonstration that outcome of interest was not present at start of study	Exclusion criteria	*	NA	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	*	Adequate follow up period for outcome of interest	Yes	*	Complete follow up or subjects lost to follow-up unlikely to introduce bias	Subjects' loss to follow up unlikely to introduce bias	*	5

#This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to provide quality assessment of the included longitudinal studies). A study could be awarded a maximum of one star for each numbered item within the "Selection" and "Outcome" domains. The final score for each study was calculated as the total number of awarded stars. The higher total number stars indicate better research quality (Wells et al.) Two items (comparability domain and selection of the non-exposed cohort sub-domain) were not applicable and were not considered in the overall score. The maximum achievable number of stars for longitudinal studies was 6.

Table 4
Results of the critical appraisal of the included cross-sectional studies [#].

Citation (first author)	Selection												Comparability			Outcome						Overall rating
	Representativeness of the sample			Sample size			Non-respondents			Ascertainment of exposure			Based on design and analysis			Assessment of outcome			Statistical test			
	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	Acceptable criteria	Reasoning	Point	
Alschuler et al., 2021 (Alschuler et al., 2021)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample		Justified and satisfactory(including sample size calculation)	Justified and calculated	*	Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	Satisfactory recruitment rate	*	Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the period of the most restrictive public health measures	*	Results adjusted for relevant predictors/risk factors/confounders	Results were adjusted for some relevant risk factors	*	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	7
Altunan et al., 2021 (Altunan et al., 2021)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample		Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	Unsatisfactory recruitment rate		Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the COVID-19 pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	4
Bonavita et al., 2020 (Bonavita et al., 2020)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample		Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	Satisfactory recruitment rate	*	Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the COVID-19 pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	5
Broche-Pérez et al., 2021 (Broche-Pérez et al., 2021)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample		Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	Satisfactory recruitment rate	*	Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the COVID-19 pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	5
Costabile et al., 2020 (Costabile et al., 2020)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample		Justified and satisfactory(including sample size calculation)	Justified and calculated	*	Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	Satisfactory recruitment rate	*	Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the national lockdown period	*	Results adjusted for relevant predictors/risk factors/confounders	Results adjusted for relevant predictors	*	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	7
Dilek et al., 2021 (Dilek et al., 2021)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample		Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	Satisfactory recruitment rate	*	Enrolment and surveys conducted during pandemic or lockdown	The recruitment process took place before the end of the lockdown.	*	Results adjusted for relevant predictors/risk factors/confounders	Case and controls were age and sex matched	**	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	7
Garjani et al., 2021 (Garjani et al., 2021)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	somewhat representative of the average PwMS in the community	*	Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	Satisfactory recruitment rate	*	Enrolment and surveys conducted during pandemic or lockdown	This study covers the first lockdown.	*	Results adjusted for relevant predictors/risk factors/confounders	Confounding factors were controlled for	**	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	8
Motolese et al., 2020 (Motolese et al., 2020)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample		Justified and satisfactory(including sample size calculation)	Justified and calculated	*	Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	No information provided		Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	5
Naser-Moghadasi et al., 2020 (Naser Moghadasi, 2020)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-	Convenience sample		Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling	No information provided		Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	4

Table 4 (*continued*)

	random sampling)					frame recorded															
Ramezani et al. 2021 (*Ramezani et al., 2021*)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample	Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	No information provided		Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	4
Shaygannejad et al., 2021 (*Shaygannejad et al., 2021b*)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample	Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	No information provided		Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	4
Shaygannejad et al., 2021 (**Shaygannejad et al., 2021a**)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Snowball sampling technique was used	Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	Satisfactory recruitment rate	*	Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	5
Stojanov et al. 2020 (*Stojanov et al., 2020*)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Selected group of participants	Justified and satisfactory(including sample size calculation)	Not justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	No information provided		Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the state of emergency and police lockdown	*	Results adjusted for relevant predictors/risk factors/confounders	Sex and age-matched healthy controls (HC) were included in this study	**	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	6
Talaat et al., 2020 (*Talaat et al., 2020*)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample	Justified and satisfactory(including sample size calculation)	Justified and calculated	*	Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	No information provided		Enrolment and surveys conducted during pandemic or lockdown	Data were collected during the pandemic	*	Results adjusted for relevant predictors/risk factors/confounders	No information provided		Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	5
Zanghi et al., 2020 (*Zanghi et al., 2020*)	Truly/ somewhat representative of the average PwMS in the community (i.e., random sampling or non-random sampling)	Convenience sample	Justified and satisfactory(including sample size calculation)	No justified		Proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded	No information provided		Enrolment and surveys conducted during pandemic or lockdown	Data were collected after the ease of lockdown	*	Results adjusted for relevant predictors/risk factors/confounders	Results adjusted for relevant predictors	*	Independent blind/unblinded assessment using objective validated methods	Validated tools were used	**	Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and p value	The statistical analyses were clearly described, and analyses were consistent with a priori plan	*	5

#This scale has been adapted from the modified Newcastle-Ottawa Quality Assessment Scale for cross-sectional studies to provide quality assessment of the included studies. A study could be awarded a maximum of one star for each numbered item except for "ascertainment of exposure", "comparability" and "assessment of the outcome" in which a maximum of two stars can be awarded. The final score for each study was calculated as the total number of awarded stars. The higher total number stars indicate better research quality. The maximum number of stars for cross-sectional studies is 10 (Herzog et al., 2013).

group were rated $\geq$ 7 out of 10 (Alschuler et al., 2021; Costabile et al., 2021; Dilek et al., 2021; Garjani et al., 2021), indicating satisfactory quality.

A wide range of assessment tools were used in the included studies. Detailed descriptions of the HRQOL and psychometric scales used are presented in the Supplementary Table 2.

3.3. Anxiety

Anxiety was the primary outcome variable in 16 (84.2%) of the included studies (Alschuler et al., 2021; Andreu-Caravaca et al., 2021; Broche-Perez et al., 2021; Capuano et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Dilek et al., 2021; Garjani et al., 2021; Motolese et al., 2020; Naser Moghadasi, 2020; Ramezani et al., 2021; Shaygannejad et al., 2021a, 2021b; Stojanov et al., 2020; Talaat et al., 2020; Zanghi et al., 2020). Measurement scales used to assess anxiety included the Depression Anxiety Stress Scales-21 (DASS-21) ($n = 4$) (Shaygannejad et al., 2021a, 2021b; Talaat et al., 2020; Zanghi et al., 2020); the State-Trait Anxiety Inventory (STAI) ($n = 3$) (Andreu-Caravaca et al., 2021; Capuano et al., 2021; Dilek et al., 2021); the Hospital Anxiety and Depression Scale (HADS) ($n = 3$) (Chiaravalloti et al., 2021; Garjani et al., 2021; Ramezani et al., 2021); the Generalized Anxiety Disorder-7(GAD-7) ($n = 3$) (Broche-Perez et al., 2021; Garjani et al., 2021; Motolese et al., 2020); the Beck Anxiety Inventory (BAI) ($n = 2$) (Demir et al., 2020; Naser Moghadasi, 2020); the Hamilton scales for anxiety (HAM-A) ($n = 1$) (Stojanov et al., 2020); and the PROMIS Short Form v1.0 – Anxiety 6a ($n = 1$) (Alschuler et al., 2021). One study used two scales to assess anxiety in their participants (Garjani et al., 2021).

Four studies reported the prevalence of clinically significant anxiety,

which ranged from 16% (Capuano et al., 2021) to 31% (Alschuler et al., 2021; Ramezani et al., 2021) during the COVID-19 pandemic. Additionally, three studies reported severe to extremely severe anxiety in 13.9% (Zanghi et al., 2020), 37.4% (Talaat et al., 2020) and 45.4% (Naser Moghadasi, 2020) of their sample populations. A Turkish study of pediatric MS ($n = 30$) found that 100% of the sample reported clinically meaningful anxiety during lockdown (Dilek et al., 2021). It is noteworthy that two studies only reported the average severity of anxiety symptoms in their samples rather than the frequency of different severity groups or categories (Broche-Perez et al., 2021; Shaygannejad et al., 2021b).

Anxiety was measured prospectively in six studies (Andreu-Caravaca et al., 2021; Capuano et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Garjani et al., 2021; Stojanov et al., 2020). Two studies found a significant increase in anxiety. A Serbian study reported increased levels of anxiety during a COVID-19 lockdown compared to the pre-pandemic period (HAM-A: 18.9 ± 5.1 vs. 15.8 ± 4.7; $p < 0.05$) (Stojanov et al., 2020). Similarly, a Spanish study found a significant increase in state anxiety (i.e., anxiety about an event) (STAI: 22.1 ± 11.8 vs. 17.40 ± 12.8; $p = 0.01$) but not in trait anxiety (i.e., anxiety level as a personal characteristic) (STAI: 21.8 ± 9.8 vs. 20.6 ± 11.1; $p = 0.19$) among PwMS after ease of the lockdown compared with the pre-lockdown period (Andreu-Caravaca et al., 2021). Conversely, the remaining four studies found no significant difference (Capuano et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Garjani et al., 2021). A large longitudinal study in the UK ($n = 2226$) did not show a significant increase in the severity of anxiety symptoms (HADS-A(IQR): 6 (3–10) vs. 6 (3–10); $p = 0.87$) or the proportion of sample with a clinically significant anxiety (470 (21.1%) vs. 463 (20.8%); $p = 0.72$) during

the outbreak compared to the year before (Garjani et al., 2021).

Two studies found that PwMS had significantly higher levels of anxiety during lockdown compared to controls: one in Egypt (12.7 ± 10.0 vs. 9.3 ± 6.7; $p < 0.001$) (Talaat et al., 2020) and one in Serbia (18.9 ± 5.1 vs. 10.2 ± 4.3; $p < 0.01$) (Stojanov et al., 2020). However, studies in Iran (Shaygannejad et al., 2021a) and Italy (Motolese et al., 2020) did not find a difference between PwMS and controls. Similarly, results from a large cross-sectional study ($n = 1714$ PwMS/269 controls) in the UK did not report significant differences in median symptom severity (GAD-7(IQR): 4(1–8) vs. 4 (1–7); $p = 0.81$) or frequency of participants with anxiety (19.5% vs. 16.7%; $p = 0.29$) between PwMS and controls (Garjani et al., 2021). Among a pediatric MS sample in Turkey, the average state anxiety level was significantly higher than among age-and sex-matched controls. However, trait anxiety was not significantly different between groups (Dilek et al., 2021).

3.4. Depression

Fourteen studies (73.7%) examined depression among PwMS (Alschuler et al., 2021; Bonavita et al., 2021; Broche-Perez et al., 2021; Capuano et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Garjani et al., 2021; Motolese et al., 2020; Ramezani et al., 2021; Shaygannejad et al., 2021a, 2021b; Stojanov et al., 2020; Talaat et al., 2020; Zanghi et al., 2020). They used a variety of scales, including the Beck Depression Inventory-II (BDI-II) ($n = 5$) (Broche-Perez et al., 2021; Capuano et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Motolese et al., 2020); the Depression Anxiety Stress Scales-21 (DASS-21) ($n = 4$) (Shaygannejad et al., 2021a, 2021b; Talaat et al., 2020; Zanghi et al., 2020); and the Hospital Anxiety and Depression Scale (HADS) ($n = 3$) (Chiaravalloti et al., 2021; Garjani et al., 2021; Ramezani et al., 2021); the Hamilton scales for Depression (HAM-D) ($n = 1$) (Stojanov et al., 2020); the PROMIS Short Form v1.0 – Depression 6a ($n = 1$) (Alschuler et al., 2021); the Patient Health Questionnaire −2 (PHQ-2) ($n = 1$) (Bonavita et al., 2021); and Patient Health Questionnaire −9 (PHQ-9) ($n = 1$) (Garjani et al., 2021). Two studies used two different scales to assess depression in their participants (Chiaravalloti et al., 2021; Garjani et al., 2021).

Four studies reported the proportion of PwMS with clinically significant depressive symptoms, which ranged from 12 to 39% during the COVID-19 pandemic (Alschuler et al., 2021; Capuano et al., 2021; Garjani et al., 2021; Ramezani et al., 2021). Similarly, studies from Egypt (Talaat et al., 2020) and Italy (Zanghi et al., 2020) reported severe to extremely severe depression in 39.1% and 3.5% of PwMS sampled, respectively.

Depression was assessed longitudinally in five studies (Capuano et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Garjani et al., 2021; Stojanov et al., 2020). Two studies found a significant increase in depression scores during the pandemic. A multicentre study among progressive MS cases in North America and Europe found significantly higher depression scores (HADS: 6.7 ± 4.6 vs. 5.8 ± 3.7; $p = 0.03$) during lockdown compared to baseline. Interestingly, this result was mainly driven by the substantial increase in cases from Belgium (HADS: 6.7 ± 6.1; $p < 001$) whilst the remaining five countries (Denmark, Canada, the United Kingdom, Italy and the USA) reported minor changes (Chiaravalloti et al., 2021). A Turkish study also showed a significant increase in depression scores during a pandemic peak compared to the early stages of the outbreak (BDI: 16.4 ± 9.5 vs. 12.6 ± 8.2; $p < 0.001$) (Demir et al., 2020). Conversely, four studies found no significant difference in a least one depression-related outcome measure (Capuano et al., 2021; Chiaravalloti et al., 2021; Garjani et al., 2021; Stojanov et al., 2020). A large longitudinal study in the UK ($n = 2226$) showed that the median depressive symptom severity among PwMS had not significantly changed during the outbreak and lockdown compared to the year before (HADS(IQR): 7 (3–10) vs. 6 (3–10); $p = 0.23$). Similarly, the proportion of participants with clinically significant depression did not change during the follow-up compared with the year before

(475 (21.3%) vs. 470 (21.1%) $p = 0.81$) (Garjani et al., 2021). Three longitudinal studies did not demonstrate a significant change in depression scores (Capuano et al., 2021; Stojanov et al., 2020) and/or the frequency of clinical depression before and during pandemic (Capuano et al., 2021; Chiaravalloti et al., 2021).

In four of the five studies in which it was assessed, PwMS showed significantly higher levels of depression than healthy controls during the pandemic or lockdown period (Motolese et al., 2020; Stojanov et al., 2020; Talaat et al., 2020). For example, studies from Italy ($n = 612$PwMS/674controls, 43.1 vs. 23.1%; $p < 0.001$) and the UK ($n = 1751$PwMS/269controls, 32.7 vs. 23.8%; $p = 0.003$) reported a significantly higher proportion of depression among PwMS compared to controls (Bonavita et al., 2021; Garjani et al., 2021). Conversely, one study reported a non-significant difference (Shaygannejad et al., 2021a).

3.5. Health-related quality of life (psychological wellbeing)

Seven studies (36.8%) reported the impact of the COVID-19 pandemic on HRQOL among PwMS (Alschuler et al., 2021; Altunan et al., 2021; Capuano et al., 2021; Chiaravalloti et al., 2021; Costabile et al., 2021; Demir et al., 2020; Stojanov et al., 2020). Three studies used the Multiple Sclerosis Quality of Life-54 instrument (MSQoL-54) (Capuano et al., 2021; Demir et al., 2020; Stojanov et al., 2020), two used the Quality of Life in Neurological Disorders (Neuro-QoL)(Alschuler et al., 2021; Costabile et al., 2021), one used SF-12 (Altunan et al., 2021), and one used a multi-attribute utility instrument to assess health state utilities (EuroQol's EQ-5D) and the Multiple Sclerosis Impact Scale (MSIS-29) (Chiaravalloti et al., 2021).

Two cross-sectional studies reported HRQOL among PwMS (Alschuler et al., 2021; Altunan et al., 2021). In an online survey in the USA, 4.5% of respondents were below the clinical cut-off for positive affect and wellbeing, which are proxies of emotional health and distress (Alschuler et al., 2021). A Turkish study reported the average score of the mental health component of HRQOL (SF-12: 43.2 ± 10.4) among a sample of PwMS without any comparator (Altunan et al., 2021).

Three longitudinal studies used the MSQoL-54 to evaluate HRQOL before or during the early months of COVID-19 pandemic and then again during a lockdown period (Capuano et al., 2021; Demir et al., 2020; Stojanov et al., 2020). All studies reported a decline in the average mental health subscale score later in the pandemic compared to pre- or early in the pandemic. However, the reduction was only statistically significant (60.5 ± 10.7 vs. 64.4 ± 9.9; $p < 0.001$) in one study (Demir et al., 2020). Similarly, Chiaravalloti et al. (2021) did not find any difference in the subscales of the MSIS-29 subscale scores or EQ5D dimensions, during lockdown compared to pre-pandemic.

Two studies compared the HRQOL of PwMS with a control group (Costabile et al., 2021; Stojanov et al., 2020); both found that PwMS had a lower HRQOL. A Serbian study found that PwMS had considerably lower mental health super-dimension scores than healthy controls (47.1 ± 18.4 vs. 77.2 ± 19.7; $p < 0.01$) (Stojanov et al., 2020). Similarly, an Italian study reported significantly higher scores (i.e., worse QoL) in multiple domains of the NeuroQoL instrument, including depression (15.5 ± 7.0 vs. 13.9 ± 5.8; $p = 0.005$), emotional dyscontrol (17.9 ± 7.0 vs. 16.5 ± 6.3; $p = 0.01$) and sleep disturbances (16.7 ± 6.0 vs. 15.4 ± 5.5; $p = 0.02$), among PwMS compared with a control group of family members or friends not living with MS. The latter study accounted for pre-existing psychiatric conditions and comorbidities in their analysis (Costabile et al., 2021).

3.6. Stress

Eight studies (42.1%) assessed stress among PwMS during the COVID-19 pandemic. All eight reported the frequency of stress-related symptoms. Four studies assessed stress among PwMS during the COVID-19 pandemic using the DASS-21 (Shaygannejad et al., 2021a, 2021b; Talaat et al., 2020; Zanghi et al., 2020). Severe to extremely

severe stress levels were reported in 16% and 34% of cases in Italy (Zanghi et al., 2020) and Egypt (Talaat et al., 2020), respectively. Similarly, studies from Turkey (Altunan et al., 2021) and Italy (Bonavita et al., 2021) utilized the Perceived Stress Scale (PSS) to measure stress severity in PwMS and reported high levels of stress among 11.2% (Altunan et al., 2021) and 58.0% (Bonavita et al., 2021) of their samples, respectively.

Post-Traumatic Stress Disorder (PTSD) was assessed by two studies using the Short Screening Scale for DSM-IV (SSS DSM-IV) (Zanghi et al., 2020) and the Impact of Event Scale–Revised (IES-R) (Garjani et al., 2021). Zanghi and colleagues reported PTSD-like symptoms among 31.8% of 432 relapsing-remitting MS cases in Italy (Zanghi et al., 2020). Similarly, in a large cross-sectional study in the UK ($n = 1714$), 23.5% of PwMS was found to have symptoms of PTSD during the pandemic (Garjani et al., 2021).

None of the included studies longitudinally assessed stress or PTSD symptoms before and during the COVID-19 outbreak.

Four studies compared stress in PwMS to healthy controls (Bonavita et al., 2021; Garjani et al., 2021; Shaygannejad et al., 2021a; Talaat et al., 2020). Studies in Iran (Shaygannejad et al., 2021a) and Egypt (Talaat et al., 2020) found that stress was significantly higher among PwMS compared to healthy controls (Iran: 13.1 ± 9.9 vs. 9.6 ± 8.4; $p = 0.02$; Egypt: 21.0 ± 12.7 vs. 10.7 ± 8.4; $p < 0.001$) during the pandemic. Similarly, an Italian cross-sectional study reported that a significantly higher number of PwMS had high levels of perceived stress compared to controls (58% vs. 39.8%; $p < 0.001$) (Bonavita et al., 2021). In contrast, a large study in the UK ($n = 1696$ PwMS/306 control) found no difference between PwMS and controls in the prevalence of PTSD symptoms during the outbreak (OR: 1.13, 95%CI: 0.84–1.52). Further, this study found that the median PTSD symptom severity was significantly lower in PwMS than controls (IES-R:16(6–32) vs. 20(10–33); $p = 0.01$) (Garjani et al., 2021).

3.7. Sleep quality

Three studies (15.8%) assessed sleep quality (Demir et al., 2020; Motolese et al., 2020; Zanghi et al., 2020). One study used the Insomnia Severity Index (ISI) to measure sleep quality in participants with RRMS. This study reported that 28.7% of cases had subthreshold insomnia and 29.6% had moderately severe or severe clinical insomnia (Zanghi et al., 2020).

Sleep quality was longitudinally evaluated in one study. Demir and colleagues used the Pittsburgh Sleep Quality Index (PSQI); they found a significantly higher PSQI score (8.8 ± 1.5 vs. 8.3 ± 1.4; $p < 0.001$), indicating more acute sleep disturbances, during lockdown compared with the pre-lockdown period among PwMS (Demir et al., 2020).

Similarly, only one of the included studies compared sleep quality between PwMS and health controls. In this Italian study, PwMS showed significantly more disturbed sleep than healthy controls (6.9 ± 3.7 vs. 4.7 ± 2.7; $p = 0.001$) (Motolese et al., 2020).

4. Discussion

To our knowledge, this is the first systematic review to synthesize evidence on the impact of the COVID-19 pandemic on the mental health of PwMS. We identified 19 studies that met our inclusion criteria. Studies reported a variety of mental health-related outcomes including anxiety, depression, HRQOL, stress and sleep quality, and used a variety of tools to measure these outcomes. Due to the observed heterogeneity in measurement scales and in reporting, we decided to focus this review on data synthesis. The available evidence, which was mainly derived from the early stages of the pandemic, indicates that anxiety, depression and stress have been prevalent among PwMS during the COVID-19 pandemic. Further, there is convincing evidence that PwMS experienced more severe symptoms of depression and stress compared to healthy and more limited evidence that PwMS have worse HRQOL

compared to controls during the pandemic. However, these results may reflect the status quo, rather than the impact of the COVID-19 epidemic. Longitudinal studies among PwMS demonstrate that anxiety, depression and the mental health dimensions of HRQOL were generally not significantly affected during the pandemic and/or lockdown compared with the period before the COVID-19 outbreak.

Anxiety and depression are prevalent coexisting medical conditions among PwMS (Butler et al., 2016; Siegert and Abernethy, 2005) and the prevalence of anxiety and depression are substantially higher in PwMS than in the general population (Marrie et al., 2015, 2017). A recent meta-analysis reported that the overall prevalence of anxiety and depression in the general population during the COVID-19 pandemic was 23.4% (95%CI: 19.9–27.3%) and 23.9% (95% CI: 18.4–30.3%), respectively (Zhao et al., 2021). In our review, with the different scales used by the included studies, the prevalence estimates for anxiety among PwMS during the COVID-19 pandemic ranged from 16 to 31%, which does not seem higher than the meta-analysis estimate of 22.1% (95% CI:15.2%–31.0%) of studies conducted prior to the pandemic (Boeschoten et al., 2017). For depression, the prevalence estimates of our included studies ranged from 12 to 39%, while the meta-analysis estimate of studies prior to the pandemic was 30.5% (95%CI:26.3%–35.1%) (Boeschoten et al., 2017). However, three other studies included in this review that only assessed different severity levels of anxiety and depression (i.e., mild to extremely severe) found higher frequencies of severe to extremely severe anxiety and depression than those mentioned above (14–45% of PwMS) (Naser Moghadasi, 2020; Talaat et al., 2020; Zanghi et al., 2020). These findings align with a 2021 meta-analysis ($n = 15$) of general population samples which demonstrated that people with pre-existing psychiatric comorbidities have significantly higher anxiety and depressive symptoms during a pandemic compared to controls (Neelam et al., 2021). Cumulatively, given the high baseline prevalence of psychiatric comorbidities in PwMS, these findings highlight the need for tailored mental health services in people PwMS during a pandemic.

According to the quality and risk of bias assessments, few of the included studies were sufficiently sized and were representative samples that are required for conclusive evidence. Given these limitations, it is difficult to determine the impact of the COVID-19 pandemic on the mental health of PwMS. However, based on the six longitudinal studies that were included, the prevalence of mental health disorders among PwMS was not affected by the COVID-19 outbreak. Although a few studies reported a significant increase in the severity of anxiety and depression symptoms and a negative impact on HRQOL (Andreu-Caravaca et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Stojanov et al., 2020), the majority of longitudinal studies (including the largest study) did not show a significant difference in the severity of mental health symptoms during the peak of the pandemic and/or lockdown compared to a pre-pandemic period (Capuano et al., 2021; Chiaravalloti et al., 2021; Demir et al., 2020; Garjani et al., 2021; Stojanov et al., 2020). These findings suggest that PwMS may not experience MS symptomatology and psychosocial difficulties differently during the COVID-19 pandemic compared to the pre-pandemic period. This may be because through the existence of a chronic illness, PwMS may have developed psychological self-protection behaviours that allowed an increased resilience during the outbreak and lockdown, compared to the general population (Capuano et al., 2021; Reguera-Garcia et al., 2020). It is also possible that PwMS may have already reduced their activities and involvement in society to some degree in the pre-pandemic period, due to MS-related symptoms. Therefore, their behavior and activity may be less influenced by pandemic-related restrictions (Chiaravalloti et al., 2021; Reguera-Garcia et al., 2020).

We found convincing evidence, supported by a study with a large sample size (> 1000) and high-quality study design, that PwMS experienced more severe depressive and stress symptoms during the COVID-19 pandemic than controls. We also found some evidence that the mental health domains of HRQOL were also significantly worse among

PwMS compared to controls during the pandemic (Costabile et al., 2021; Talaat et al., 2020). However, the evidence for anxiety symptoms was contradictory, with three studies finding significantly more severe symptoms among PwMS (Dilek et al., 2021; Stojanov et al., 2020; Talaat et al., 2020) and three studies reporting no difference between PwMS and controls (Garjani et al., 2021; Motolese et al., 2020; Shaygannejad et al., 2021a). Again, the observed differences between PwMS and the general population during the COVID-19 pandemic may be the result of MS-related factors (e.g., the overall higher prevalence of depression among PwMS) rather than the pandemic (Garjani et al., 2021; Motolese et al., 2020; Stojanov et al., 2020). It is also noteworthy that most of the included studies were conducted during the early phases of pandemic when uncertainty was high, and no vaccinations had been introduced. It is unclear what the long-term impact of the pandemic would be on vulnerable populations, and long-term prospective studies among PwMS are warranted.

The impact of the COVID-19 pandemic has been challenging to study effectively, largely due to the sudden onset of the outbreak globally and the ongoing rapid changes in circumstances of countries and regions. It did not allow researchers to carefully plan their studies. As a result, in this early phase of the pandemic, many convenience samples were used. In addition, due to the regional or national quarantine and lockdown, many studies used an online survey methodology, which will have resulted in a more selected group of participants. However, quantifying the effect of the pandemic is an important goal that should not be abandoned due to logistical issues. Further detailed retrospective and prospective studies are needed to determine whether mental distress occurs among PwMS as a direct result of pandemic-related restrictions because of higher baseline prevalence of physical and psychiatric comorbidities.

Due to the high prevalence of psychiatric comorbidities among PwMS, we would suggest that future studies include individuals with mental health comorbidities to ensure that the data is generalisable and captures the effect of restrictions on those most likely to be impacted. An ideal study design would be collecting data prospectively throughout the pandemic utilizing a blended method measuring mental health status both qualitatively and quantitatively. We recommend that future research in periods of crisis consider an appropriate sampling method to achieve representativeness and attempt to include suitable comparators. To gain deeper insights into the factors that are associated with the impact of COVID-19, it will be important to collect COVID-related variables at the personal level and population level. Person-related variables include history of COVID-19 contraction, vaccination status, and covid-related changes in health-care utilization, formal and informal care, financial status and income, and lifestyle behaviours (e.g., physical activity, smoking). Population-related variables include country/region, states of lockdown, COVID-19 incidence rates, and vaccination rates. To provide useful recommendations, it is important to understand the heterogeneity between countries and sub-groups. Ongoing initiatives, such as COVID-19 and MS global data sharing initiative, will be a valuable asset for future research, providing robust data from various data registries collected during the COVID-19 pandemic (Peeters et al., 2020).

5. Limitations

The major limitation of this systematic review was that there may be unpublished research that we have overlooked. Because the COVID-19 pandemic is a rapidly evolving issue and has only been in existence for approximately 2 years, future studies which have the benefit of a longer timeframe and more studies to review will enhance the interpretations made here. It is noteworthy that, due to the rapid process of conducting this review, only one reviewer performed the screening and identification of records in this study.

6. Conclusion

The evidence gathered as of June 2021 suggests that anxiety, depression and stress have been relatively common among PwMS during the COVID-19 pandemic. Also, based on satisfactory evidence from cross-sectional studies, PwMS experienced more severe symptoms of depression and stress compared to general populations. However, evidence from longitudinal studies comparing the severity of mental health symptoms during the pandemic and/or lockdown with a pre- or early pandemic period, have demonstrated that the anxiety, depression and mental health dimensions of HRQOL among PwMS were generally not significantly affected by the pandemic. Due to the limited number of studies and heterogeneity in methodology, the true impact of the COVID-19 pandemic on the mental health of PwMS remains unclear. Improving methodological consistency and study design, where possible, is essential to effectively collect the data needed to inform robust and effective policies for PwMS during regional, national, and international health crises.

CRediT authorship contribution statement

Amin Zarghami: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Mohammad A. Hussain:** Conceptualization, Methodology, Writing – review & editing. **Julie A. Campbell:** Methodology, Writing – review & editing. **Chigozie Ezegbe:** Data curation, Writing – review & editing. **Ingrid van der Mei:** Supervision, Writing – review & editing. **Bruce V. Taylor:** Supervision, Writing – review & editing. **Suzi B. Claflin:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103562.

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