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Prevalence of depression and anxiety in the different clinical forms of multiple sclerosis and associations with disability: A systematic review and meta-analysis

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ABSTRACT

Multiple sclerosis (MS) is a chronic neurodegenerative and autoimmune disease. Motor, sensory and cognitive deficits in MS are commonly accompanied by psychiatric disorders. Depression and anxiety affect the quality of life of MS patients, and the treatment is still not well-established. Prevalence rates in MS patients for depression and anxiety vary widely between studies. However, the prevalence of these psychiatric disorders in the subgroups of MS patients and their association with a disability has not been studied yet. Therefore, this systematic review and meta-analysis proposes to estimate the prevalence of depression and anxiety in MS and to perform subgroup analyses (study type, Extended Disability Status Scale/EDSS, duration of MS, region, type of MS) on observational studies. The protocol was registered in PROSPERO (4202125033). A computerized search on PubMed, EMBASE and Scopus for studies on depression and anxiety in MS was performed from 2015 to 2021, and 12 articles were included. Most of the studies in the meta-analysis had a low risk of bias. The prevalence of depression was 27.01% (MS), 15.78% (relapsing-remitting multiple sclerosis/RRMS), and 19.13% (progressive multiple sclerosis/PMS). For anxiety the prevalence was 35.19% (MS), 21.40% (RRMS), and 24.07% (PMS). The prevalence of depression/anxiety for patients with EDSS <3 was 26.69/45.56% and for EDSS >3 was 22.96/26.70%. Using HADS-A (8) the prevalence was 38.5% and for depression was 22.4%. Then, our study brought together current data regarding psychiatric disorders in MS patients, which are comorbidities that affect the quality of life of these patients.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system, characterised by neuroinflammation and demyelination causing damage to the myelin sheath and the axons (Thompson et al., 2018). However, the complete pathophysiology of MS is still unknown, and there are multifactorial hypotheses regarding the onset of this disease (Thompson et al., 2018). The diagnosis of MS is made through clinical examinations using the McDonald criteria in well-established clinical examinations for MS diagnosis (Rovira et al., 2015). Magnetic resonance imaging and analysis of the cerebrospinal fluid can also be performed (Kamińska et al., 2017).

The most common type of MS is relapsing-remitting MS (RRMS), which has an episodic course followed by recurrent phases of symptoms (Marrie et al., 2009). The two progressive MS clinical forms (PMS), primary progressive multiple sclerosis (PPMS) and secondary progressive sclerosis (SPMS), are associated with rapid worsening of symptoms due to neurodegeneration (Jia et al., 2018; Kalincik, 2015; Mathey et al., 2018; Schwenkenbecher et al., 2019). The prevalence of RRMS clinical form is higher in young adult patients, and the sex distribution in women vs. men is 2–3:1 (Kobelt et al., 2017; Robles-Cedeno and Ramio-Torrenta, 2018). In contrast, PMS is mainly found in middle-aged patients and occurs equally in both sexes (1:1) (Jia et al., 2018). Therefore, it is necessary to analyse the clinical scores of the disease to avoid errors in the MS diagnosis (Ibitoye et al., 2016).

The Kurtzke Extended Disability Status Scale (EDSS) classifies MS symptoms according to the degree of disease severity and functional impairment (Lublin et al., 2014). EDSS scores between 0 and 5 indicate

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Abbreviations:

ANTAS	Advanced Neuropsychiatric Tools and Assessment Schedule
BDI	Beck's Depression Inventory
EDSS	Extended Disability Status Scale
EMBASE	Excerpta Medical Database
HADS	Hospital Anxiety and Depression Scale
ICD	International Classification of Diseases
MS	Multiple sclerosis
NOS	Newcastle-Ottawa Scale
PMS	Progressive multiple sclerosis
PRISMA	Protocol report items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
RRMS	Relapsing-remitting multiple sclerosis
SCID	Structured Clinical Interview
SCOPUS,	Sci Verse Scopus
SD	Standard deviations

alterations in sensory detection and mental function, including anxiety and depression symptoms. An EDSS score higher than 6 indicates daily life activity and motor ability dysfunction (Piri Çinar and Güven Yorgun, 2018). These, psychiatric disorders occur even in patients who have not demonstrated motor deficits (Compston and Coles, 2008; Anthony Feinstein et al., 2014; Foley et al., 2013). Psychiatric conditions in MS are associated with changes in cognitive function, such as concentration deficits and memory impairment (Tauil et al., 2018).

Depression and anxiety affect professional and social interactions, and they can be observed throughout the course of the MS disease (Tauil et al., 2018). There are different types of scales to measure depression and anxiety in the clinic practice, such as Hospital Anxiety and Depression Scale (HADS) (Julian, 2011), Beck's Depression Inventory (BDI), Advanced Neuropsychiatric Tools and Assessment Schedule (ANTAS), Structured Clinical Interview (SCID), and International Classification of Diseases (ICD) (Kahraman et al., 2021; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021a; Lorefice et al., 2015). However, the HADS-type scale is the most found in studies, but the other scales can be used to determine depression and anxiety. The HADS-A total score can range from 0 to 21 and the increase of the score indicates worsening of the symptoms. The following guidelines are recommended for interpreting scores: normal or no anxiety (0–7), mild anxiety (8–10), moderate anxiety (11–14) and severe anxiety (12–21) (Julian, 2011).

It has already been shown that patients with MS have a higher prevalence of anxiety and depression than healthy subjects (Patten et al., 2003) or patients with other neurological disorders (Tauil et al., 2018). In a previous systematic review, only PMS patients presented anxiety symptoms (Butler et al., 2016), while a later systematic review and meta-analysis showed the presence of depression (30.5%) and anxiety (22.1%) in MS patients (Boeschoten et al., 2017). Similarly, another systematic review and meta-analysis showed a relatively high prevalence of anxiety (21.9%) and depression (27.3%) in MS patients (Marrie et al., 2015)

However, there is still a lack of updated systematic reviews that describe the prevalence of depressive and anxiety disorders in individuals in MS. Thus, further studies are needed with more recent data to associate these psychiatric disorders with the different forms of MS over the course of the disease. Therefore, this systematic review and meta-analysis discusses the prevalence of depression and anxiety in MS patients. We also performed a subgroup analysis according to the type of study, MS clinical forms, the location where the study was conducted, the HADS scale (8 and 11), the EDSS, and the time since MS diagnosis.

2. Methods

This systematic review followed the protocol report items for systematic reviews and meta-analyses PRISMA 2020 (Shamseer et al., 2015). In addition, the protocol was registered in the international prospective register of systematic reviews (PROSPERO) (registration 4202125033, CRD).

2.1. Research strategy

The search strategy was performed through the scientific databases PubMed, Excerpta Medical Database (Embase) and Sci Verse Scopus (Scopus) to identify studies indexed on these platforms in March 2021. The period of publications used was from 2015 to 2021, with the combination of the keywords *MS, depression* and *anxiety*, based on medical subject headings (MeSH) (Supplement 1). Two independent reviewers searched the articles on the three platforms (D.P and P.R).

The selection of articles was conducted as shown in Fig. 1. First, we removed duplicate articles, reviews and conference abstracts using EndNote X9® software before screening. Afterward, the articles were revised in three steps. In the first and second steps, we excluded studies not focused on MS/depression/anxiety, performed in non-human animals, in pregnant subjects, not articles, case reports, not written in English, performed on children/adolescents, randomised. The title and the abstract were analysed to identify relevant articles. Finally, in the third step, the full text was examined to verify the inclusion criteria, not McDonald, less than 200 patients, not access/answer. The selected studies were reviewed by six researchers (D.P., P.R., F.V, J. F., S. K., G. M.), and in case of disagreement, a seventh researcher was consulted (G. T.). Subsequently, we searched the selected articles' references and other related reviews manually (J.F).

2.2. Exclusion and inclusion criteria

The inclusion criteria were observational articles written in English, which addressed the prevalence of depression and/or anxiety symptoms in patients with MS. Exclusion criteria were studies that MS/depression/anxiety, animal, pregnant, not articles, case report, not English, children/adolescents, randomised, case report, review articles, the MS diagnosis criteria were not Mc Donald, not access/answer prevalence rate of depression and/or anxiety in MS, samples with $<$200 patients. When performing the analysis of subgroups, we merged those from PPMS/SPMS, a general PMS, because not all articles contain these subclassifications.

Two pairs of independent reviewers (D.P., P.R., J.F., F.V.) analysed the exclusion or inclusion of data, and discrepancies were evaluated and resolved by the third investigator (G.T.). We contacted the author of the articles that lacked the prevalence, but only two responded with the necessary data.

2.3. Data extraction

Data extraction was performed using tables and the results were categorised based on the outcomes of interest, i.e. anxiety or depression in MS. Three reviewers (D.P., P.R., F.V.) independently extracted the information from each article and compared the results; any discrepancies were resolved by consensus in meetings with the authors. Thus, we emphasize that the discrepancies may have been caused by the lower number of articles included in our review due to the specified search time (2015–2021). Attempts were made to contact the authors of studies with unclear data.

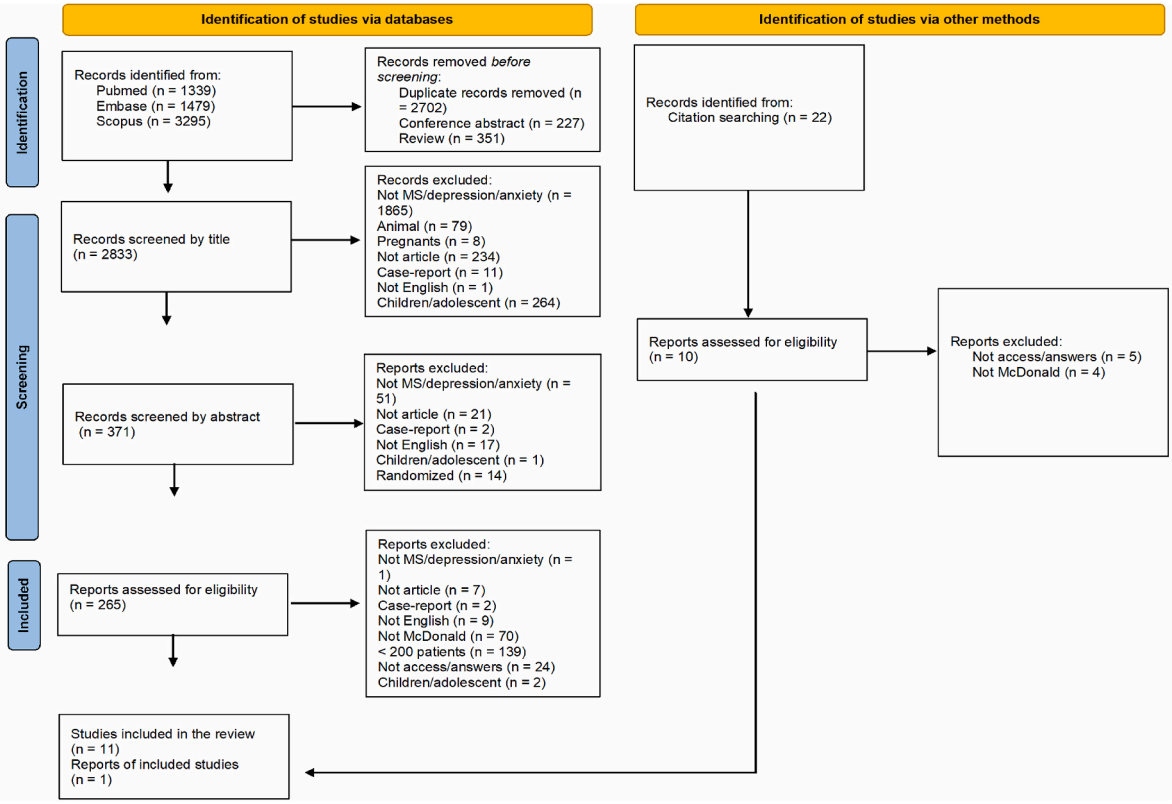

Fig. 1. Flow diagram of studies identification.

2.4. Risk of bias

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the articles and risk of bias (Stang, 2010). For this, each study was evaluated independently (D.P., F.V.) according to eight items categorised into three groups: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome. Each item was classified with a maximum score of one point, except for comparability, which allows for two points. In order to assess the quality scale of the studies, parameters ranging from 0 to 7 were used for cross-sectional studies, and for prospective and retrospective studies measures ranging from 0 to 9 were used (Fiest et al., 2016; Kurtzke, 1983). Articles with NOS scores less than 4 were to be excluded, but we did not exclude any articles (Stang, 2010).

We identify high-quality choices by answering "Yes" to questions in each domain. The more "Yes" answers allocated to a study (up to a maximum of seven or nine), the better the quality. The more Yes responses to a questionnaire, the higher the NOS of the article. At any point, any disagreement between the reviewers was resolved by meeting and discussing with the authors to establish a consensus. The risk of bias includes the number of patients, without clinical form, sex balance in MS, anxiety and depression treatment, and retrospective studies. Also, publication bias was evaluated by the Egger test (Egger et al., 1997), the Begg test (Begg and Mazumdar, 1994), and funnel plots.

2.5. Statistics analysis

Pooling the data was performed with the random-effects model using weighted averages relative to the sample size of the single studies (DerSimonian and Laird, 1986). We considered the risk of bias results, so when a study presented more than two standard deviations (SD) than the total percentage of high bias (41%), we excluded it from the analysis (Rodrigues et al., 2021). The meta-analysis was performed using the total number of MS patients and the percentage of patients with anxiety or depression. Additionally, we performed a subgroup analysis based on the type of study, MS clinical form, location, HADS (8 and 11), EDSS, and the time since MS diagnosis. Heterogeneity was measured by the I^2 index and classified as without heterogeneity (0%), low (<25%), mild (25–50%), moderate (50–75%), and high heterogeneity (>75%) (Higgins et al., 2003). Statistical analysis was performed using RStudio software with two-tailed $p < 0.05$ as the minimum significance level.

3. Results

3.1. Article selection and characteristics

The selection of studies is presented in a flowchart (Fig. 1). The search resulted in 6113 articles from the PubMed, Scopus, and EMBASE databases. In the classification phase, 2702 duplicate articles, 227 conference abstracts, and 351 reviews were excluded. After reviewing the titles and abstracts, 2833 articles were excluded for not meeting the inclusion criteria. Then, 265 articles were analysed in full text to confirm the eligibility of the studies, and 11 studies were included. In addition, 22 articles were identified through a manual search, of which we included one additional article after the full-text analysis.

Finally, we used 12 studies for data extraction and found that 7507 patients had multiple sclerosis (MS). The sex distribution was 5605 female patients and 1902 male patients, and the mean age was 45.6 years. Among the methodologies, six studies were cross-sectional (Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021a; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021b; Marrie et al., 2018b; Viana et al., 2015), five were prospective cohort studies (Fiest et al., 2016; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Whitehouse et al., 2019; Wicks et al., 2016) and one was a retrospective cohort study (Lorefice et al., 2015) (Table 1). It was observed that six studies were carried out in North America, two studies in Oceania and four studies in Europe (Table 1).

Furthermore, 3501 patients used disease-modifying drugs to treat

Table 1
Data extraction from clinical aspects of multiple sclerosis (MS) patients.

Experimental groups, age, and sex distribution	Study type	Country or continent	Clinical aspects	Risk of bias	NOS	Reference
MS patients (N = 949, 48.6 ± 11.4 years, F 714, M 235)	Prospective cohort	Canada, North America.	RRMS: (N = 687), SPMS: (N = 193), PPMS: (N = 60); EDSS (Median (IQR)): (2.5 (3.5)); Age at MS symptom onset: 33.2 ± 10 years; MS duration: 15.4 ± 10.0 years.	No mention of treatment.	9	Fiest et al. (2016)
MS patients (N = 279, 35.7 ± 10.9 years, F 199, M 80)	Cross-sectional	United States, North America.	Treatments: Fingolimod: (N = 91), Interferon beta: (N = 82), Teriflunomide: (N = 52), Glatiramer acetate: (N = 51), Others: (N = 3); RRMS: (N = 265), SPMS: (N = 11), PPMS: (N = 3); EDSS: (1.9 ± 1.7); MS duration: 7.2 ± 7.0 years.	Cross-sectional study.	7	Kahraman et al. (2021)
MS patients (N = 885, 48.2 ± 11.1 years, F 678, M 207)	Cross-sectional	Canada, North America.	Treatments: Interferon beta: (N = 298), Natalizumab: (N = 31), Glatiramer acetate: (N = 133), No therapy: (N = 419), Missing: (N = 4); RRMS: (N = 687), SPMS: (N = 193); EDSS (Median (IQR)): (2.5 (1.5–4.0)); Age at MS symptom onset: 32.6 ± 9.1 years; MS duration: 15.5 ± 10.2 years.	Cross-sectional study.	6	Kovalec (2017)

Experimental groups, age, and sex distribution	Study type	Country or continent	Clinical aspects	Risk of bias	NOS	Reference
MS patients (N = 902, 55.8 ± 11.4 years, F 709, M193)	Cross-sectional	Australia, Oceania.	Treatment: (N = 565); RRMS: (N = 661), PMS: (N = 95), Unknown (N = 146); MS duration:15.4 ± 9.3 years.	Cross-sectional study; No mention of age at MS symptom onset.	7	Lo et al. (2021a)
MS patients (N = 1518, 55.7 ± 11.3 years, F 1204, M 309)	Cross-sectional	Australia, Oceania.	Treatment: (N = 947); PMS: (N = 150), RRMS: (N = 1113), Unknow: (N = 255); Age at MS symptom onset: 36.0 ± 10.8 years. MS duration: 20.5 ± 10.9 years.	Cross-sectional study.	7	Lo et al. (2021b)
MS patients (N = 240, 41.55 ± 10.2 years, F 167, M 73)	Retrospective Cohort	Italy, Europe.	Treatments: Natalizumab (N = 65), Glatiramer acetate (N = 27), Fingolimod (N = 5), Interferon beta (N = 80), No therapy (N = 58), Missing (N = 5); PMS: (N = 45), RRMS: (N = 195); EDSS: (5.8 ± 1.2); MS duration: 12.3 years.	Retrospective study.	9	Lorefice et al. (2015)

Experimental groups, age, and sex distribution	Study type	Country or continent	Clinical aspects	Risk of bias	NOS	Reference
MS patients (N = 253, 31.3 ± 11.3 years, F 206, M 47)	Prospective Cohort	Canada, North America.	RRMS: (N = 183), SPMS: (N = 47), PPMS: (N = 23); EDSS (Median (p25-p75)): 4 (3–6); Age at MS symptom onset: 31.3 ± 11.3 years.	No mention of treatment; No time of MS diagnosis. No mention of the MS duration.	9	Marrie et al. (2018)
MS patients (N = 863, 48.6 ± 11.3 years, F 648, M 215)	Cross-sectional	Canada, North America.	RRMS: (N = 621), PMS + Unknown: (N = 242); EDSS: (3.1 ± 1.9); MS duration: 15.2 ± 10.1 years; Age at MS symptom onset: 31.3 ± 11.3 years.	No mention of treatment.	7	Marrie (2018b)

Experimental groups, age, and sex distribution	Study type	Country or continent	Clinical aspects	Risk of bias	NOS	Reference
MS patients (N = 949, 48.6 ± 11.4 years, F 714, M 235)	Prospective Cohort	Canada, North America.	Treatment: Yes (N = 477), No (N = 470); RRMS: (N = 687), SPMS: (N = 193), PPMS: (N = 60), CIS: (N = 5), Unknown: (N = 4); EDSS (Median (IQR)): (2.5 (1.5–5.0)); MS duration: 15.4 ± 10.2 years; Age at MS symptom onset: 33.2 ± 10 years.	Inclusion of CIS patients.	9	McKay et al. (2016)
MS patients (N = 206, 42.1 ± 10.7 years, F 144, M 62)	Cross-sectional	Portugal, Europe.	Treatments: Interferon: (N = 110), Glatiramer acetate: (N = 37), Other: (N = 39), None: (N = 19); RRMS: (N = 183), SPMS: (N = 6), PPMS: (N = 17); Median EDSS was 1.5 ± 2.0; MS duration: 7 ± 10 years.	Cross-sectional study.	7	Viana et al. (2015)

Experimental groups, age, and sex distribution	Study type	Country or continent	Clinical aspects	Risk of bias	NOS	Reference
MS patients (N = 208, 40.6 ±9.2 years, F 155, M 53)	Prospective Cohort	Switzerland Europe.	RRMS: (N = 183), SPMS: (N = 15), PPMS: (N = 6); Median EDSS was: > 3 (N = 136), 3.0–6.0 (N = 38), >6: (N = 34); MS duration: > 10: (N = 56), <10: (N = 152) years.	No mention of treatment.	8	Wicks et al. (2016)
MS patients (N = 255, 50.6 ±12.9 years, F 208, M 47)	Prospective Cohort	Canada, North America.	RRMS: (N = 184), SPMS: (N = 48), PPMS: (N = 23).	No mention of treatment; No time of MS	8	Whitehouse et al. (2019)

(*continued on next page*)

Table 1 (*continued*)

Experimental groups, age, and sex distribution	Study type	Country or continent	Clinical aspects	Risk of bias	NOS	Reference
				diagnosis; No mention of the MS duration.		

Clinically isolated syndrome (CIS); Expanded Disability Status Scale (EDSS); Female (F); Interquartile range (IQR); Male (M); Multiple sclerosis (MS); Newcastle-Ottawa Scale (NOS); Number of subjects (N); Primary progressive multiple sclerosis (PPMS); Progressive multiple sclerosis (PMS); Relapsing-remitting multiple sclerosis (RRMS); Secondary progressive multiple sclerosis (SPMS).

MS, 42 patients used other types of drugs, and 975 patients had no treatment or these data were absent (Table 1). According to MS subtypes, 5649 patients had RRMS and 1430 patients had PMS and 259 patients had an unknown MS clinical form (Table 1). Regarding MS disability, four articles had an EDSS <3 and five had the EDSS >3, also three did not have an EDSS classification. In addition, eight studies had MS duration >10 years, two studies had <10 years and two did not describe the disease duration. Six studies mentioned the age at the onset of MS symptoms with a mean of 33 years and six did not evaluate this parameter. Furthermore, the quality of articles was 8.7 for prospective and retrospective studies and 6.7 for cross-sectional studies (Table 1).

In the 12 articles that evaluated depression in MS, the diagnosis methods used were self-report (eight studies) (Fiest et al., 2016; Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Whitehouse et al., 2019; Wicks et al., 2016), physician diagnosis (three studies) (Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Lorefice et al., 2015; Marrie et al., 2018b) and a questionnaire (one study) (Viana et al., 2015) (Table 2). The most commonly used scale for depression was HADS-D (eight studies) (Fiest et al., 2016; Kowalec et al., 2017; Marrie et al., 2018b; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016), followed by BDI (one study) (Kahraman et al., 2021), ANTAS (one study) (Lorefice et al., 2015) and ICD-10 (one study) (Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a). One study did not use a depression scale (Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b). For the validation test, nine studies contained this information (Fiest et al., 2016; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie et al., 2018b; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016) and three studies did not (Kahraman et al., 2021; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lorefice et al., 2015) (Table 2).

Eight studies did not differ between types of MS (Fiest et al., 2016; Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie, Zhang, et al., 2018a; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016). Only four studies (Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lorefice et al., 2015; Marrie et al., 2018b; McKay et al., 2016) differentiated the clinical forms of the disease, resulting in 2537 patients with RRMS and 690 patients with PMS that were depressed. Regarding antidepressant treatment, two articles (Lorefice et al., 2015; Marrie et al., 2018b) mentioned depression treatment, and the remaining ten articles did not (Kirsten M. Fiest et al., 2016; Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021a; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021b; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016) (Table 2).

The mean prevalence of depression in the 12 articles was 27.6%. Also, four separate studies evaluated the mean prevalence of depression in MS subtypes, i.e. 17.6% in RRMS and 27.6% in PMS (Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021a; Lorefice et al., 2015; Marrie et al., 2018b; McKay et al., 2016). The mean prevalence of depression using HADS-D (8) was 22.4%, and for HADS-D 11 this was 7.3% (Marrie et al., 2018b; Marrie, Zhang, et al., 2018a; Whitehouse et al., 2019; Wicks et al., 2016). However, eight studies did not separate the HADS types (Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021a; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021b; Lorefice et al., 2015; McKay et al., 2016; Viana et al., 2015) (Table 2).

Regarding the average duration of depression, two studies (Marrie et al., 2018b; McKay et al., 2016) showed that it had occurred over a period longer than 10 years, and the remaining ten studies did not assess this parameter (Fiest et al., 2016; Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021a; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021b; Marrie, Zhang, et al., 2018a; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016). Only one study evaluated the EDSS of depressive MS patients, which was greater than 3 (McKay et al., 2016) (Table 2).

Ten articles evaluated anxiety in MS patients, with the use of self-report (seven studies) (Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Whitehouse et al., 2019; Wicks et al., 2016), physician diagnosis (two studies) (Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie et al., 2018b) and a questionnaire (one study) (Viana et al., 2015) (Table 3). Regarding the anxiety scale used, the most commonly used was HADS-A (eight studies) (Fiest et al., 2016; Kowalec et al., 2017; Marrie et al., 2018a; Marrie et al., 2018a,b; McKay et al., 2016; Viana et al., 2015; Wicks et al., 2016; Whitehouse et al., 2019), followed by ICD-10 (one study) (Lo et al., 2021a), while one study did not use any type of scale (Lo et al., 2021b).

In addition, nine studies used a validation test (Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie et al., 2018b; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016) and one study did not present any validation test (Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b). Regarding the MS clinical forms, seven articles did not differentiate between RRMS and PMS (Fiest et al., 2016; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie, Zhang, et al., 2018a; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016). However, three studies evaluated the differentiation of MS subtypes (Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Marrie et al., 2018b; McKay et al., 2016), with the presence of 2421 RRMS patients and 645 PMS patients with anxiety (Table 3).

The average prevalence in the ten studies that evaluated anxiety was 37.5%. When it came to the different clinical forms, the mean prevalence of anxiety was 23.1% in RRMS and 24.9% in PMS. The mean prevalence of anxiety using HADS-A (8) was 38.5% (three studies) (Marrie et al., 2018b; Marrie, Zhang, et al., 2018a; Wicks et al., 2016); with HADS-A (9) this was 16.9% (one study) (Whitehouse et al., 2019), and for HADS-A (11) this was 17.9% (three studies) (Marrie et al., 2018; Whitehouse et al., 2019; Wicks et al., 2016). Seven studies did not divide the HADS-A subtypes (Fiest et al., 2016; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie, Zhang, et al., 2018a; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016).

Only two studies (Marrie et al., 2018b; McKay et al., 2016) evaluated

Table 2
Data extraction from clinical aspects of depression in multiple sclerosis patients.

MS patients (N)	Diagnostic Assessment	Scale and validation test (VT)	MS type	Treatment	Outcomes	Risk of bias	Reference
(N = 949).	Self-reported.	HADS-D; VT= Yes.	All MS types.	No	I) The prevalence was 29%.	No mention of treatment; No differentiated MS subtypes.	Fiest et al. (2016)
(N = 279).	Self-reported.	BDI; VT= No.	All MS types.	No	I) The prevalence was 19.4%.	No mention of treatment; No differentiated MS subtypes; No mention of the validation test.	Kahraman et al. (2021)
(N = 885).	Self-reported.	HADS-D; VT=Yes.	All MS types.	No	I) The prevalence was 21.1%.	No mention of treatment. No differentiated MS subtypes.	Kovalec (2017)
MS patients (N)	Diagnostic Assessment	Scale and validation test (VT)	MS type	Treatment	Outcomes	Risk of bias	Reference
(N = 902).	Physician diagnosed.	ICD-10; VT= Yes.	All MS types.	No	I) The prevalence was 41.2%.	No mention of treatment; No time of depression diagnosis; No differentiated MS subtypes.	Lo et al. (2021a)
(N = 1518)	Self-reported.	No scale; VT= No.	RRMS (N = 1113); PMS (N = 150).	No	I) The prevalence was 26.9%; II) The prevalence for RRMS was 16.5% and for PMS was 16.4%.	No mention of treatment; No use a scale; No mention of the validation test.	Lo et al. (2021b)
MS patients (N)	Diagnostic Assessment	Scale and validation test (VT)	MS type	Treatment	Outcomes	Risk of bias	Reference
(N = 240)	Physician diagnosed.	ANTAS, SCID; VT= No.	RRMS (N = 195); PMS (N = 45).	28% reported treatment.	I) The prevalence was 31.5%; II) The prevalence for RRMS was 23% and for PMS was 40%.	No time of depression diagnosis; No mention of the validation test.	Lorefice et al. (2015)
(N = 253).	Self-reported.	HADS-D; VT=Yes.	All MS types.	No	I) The prevalence was 17%; II) HADS-D (8) 23.9%; III) HADS-D (11) 8.0%.	No mention of treatment; No time of depression diagnosis; No differentiated MS subtypes.	Marrie (2018a)
MS patients (N)	Diagnostic Assessment	Scale and validation test (VT)	MS type	Treatment	Outcomes	Risk of bias	Reference
(N = 859).	Physician diagnosed.	HADS-D; VT= Yes.	RRMS (N = 621); PMS + Unknow (N = 242).	83.8% reported treatment.	I) The prevalence was 27.5%; II) HADS-D (8+) was 20.5%; III) The prevalence for RRMS was 17.4% and for PMS was 28.1%; IV) The mean depression duration was 15.3 ± 12.3 years; V) The mean age at MS onset for depressed patients was 35.0 ± 9.9 years.	No risk of bias.	Marrie (2018b)
(N = 949).	Self-reported.	HADS-D; VT= Yes.	RRMS (N = 687); PMS (N = 253).	No	I) The prevalence was 39.3%; II) The total HADS-D (Median (p25-p75)): 4 (2–7); III) The prevalence for RRMS was 13.4%, for SPMS was 15% and for PPMS was 11.7%; IV) The mean age at MS onset for depression was 32.2 ± 9.9 years; V) The mean depression duration was 16.1 ± 10.0 years; VI) EDSS for depressed patients was (Median (IQR)): (3.0 ± 2.0–5.0)).	No mention of treatment.	McKay et al. (2016)
MS patients (N)	Diagnostic Assessment	Scale and validation test (VT)	MS type	Treatment	Outcomes	Risk of bias	Reference
(N = 206).	Interview questionnaire.	HADS-D; VT= Yes.	All MS types.	No	I) The prevalence was 25%. II) The total HADS-D was 6%.	No mention of treatment; No time of depression diagnosis; No differentiated MS subtypes.	Viana et al. (2015)
(N = 208).	Self-reported.	HADS-D; VT= Yes.	All MS types.	No	I) The prevalence was 21.4%; II) The HADS-D (8+) was	No mention of treatment; No time of depression diagnosis;	Wicks et al. (2016)

(*continued on next page*)

Table 2 (*continued*)

MS patients (N)	Diagnostic Assessment	Scale and validation test (VT)	MS type	Treatment	Outcomes	Risk of bias	Reference
					25.3%; III) The HADS-D (11+) was 6.1%.	No differentiated MS subtypes.	
MS patients (N)	Diagnostic Assessment	Scale and validation test (VT)	MS type	Treatment	Outcomes	Risk of bias	Reference
(N = 255).	Self-reported.	HADS-D; VT= Yes.	All MS types.	No	I) The prevalence was 32%; II) The HADS-D (8+) was 19.9%; III) The HADS-D (11+) was 7.9%.	No mention of treatment; No time of depression diagnosis; No differentiated MS subtypes.	Whitehouse et al. (2019)

Beck Depression Inventory (BDI); Female (F); Hospital Depression Scale (HADS-D); International Classification of Diseases–10th revision (ICD-10); Interquartile range (IQR); Male (M); Number of subjects (N); Patient Health Questionnaire-2 (PHQ-2); Patient Health Questionnaire-9 (PHQ-9); Structured Clinical Interview (SCID); Validation test (VT).

the mean duration of anxiety, i.e. 14.6 years, while eight studies (Fiest et al., 2016; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie, Zhang, et al., 2018a; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016) did not measure the duration of anxiety. Additionally, the EDSS scores of anxious MS patients were greater than 3 in two studies (Marrie et al., 2018b; McKay et al., 2016), while eight studies (Fiest et al., 2016; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie, Zhang, et al., 2018a; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016) did not assess this disability scale (Table 3).

3.2. Risk of bias

We found a low risk of bias in all articles when we used the NOS scale. When analysing prospective and retrospective studies, we found that in four articles NOS = 9 (Fiest et al., 2016; Lorefice et al., 2015; Marrie, Zhang, et al., 2018a; McKay et al., 2016) and in two articles NOS = 8 (Whitehouse et al., 2019; Wicks et al., 2016). These results indicate low risk, since "YES" answers were prevalent among the studies, with a scale score of 0–9. When using cross-sectional studies, we found five articles with NOS = 7 (Kahraman et al., 2021; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie et al., 2018b; Viana et al., 2015) and one article with NOS = 6 (Kowalec et al., 2017). These results also indicate low risk, using an evaluation scale with scores of 0–7.

Three studies had a low risk of bias (Tables 1–3). We considered low risk studies to have no mention of age at MS symptom onset (Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a), MS duration (Marrie, Zhang, et al., 2018a; Whitehouse et al., 2019), or time of MS diagnosis (Marrie, Zhang, et al., 2018a; Whitehouse et al., 2019). Most of the studies presented an unclear risk of bias, and included no mention of MS treatment (Fiest et al., 2016; Marrie et al., 2018b; Marrie, Zhang, et al., 2018a; Whitehouse et al., 2019; Wicks et al., 2016), treatment for depression (Fiest et al., 2016; Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Viana et al., 2015; Whitehouse et al., 2019) or treatment for anxiety (Fiest et al., 2016; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Viana et al., 2015; Whitehouse et al., 2019; Wicks et al., 2016). Also, the types of studies included five cross-sectional studies (Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Viana et al., 2015) which were considered to have an unclear risk of bias.

Finally, four studies had a high risk of bias due to the inclusion of CIS patients (Lorefice et al., 2015; McKay et al., 2016), being a retrospective study (Lorefice et al., 2015), not using a scale for depression/anxiety (Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b), and not mentioning the validation test for the depression/anxiety measure (Kahraman et al., 2021; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lorefice et al., 2015). Therefore, 25% of studies had a low risk, 83.3% presented an unclear classification, and 33.3% of the studies showed a high risk of bias. Additionally, for the meta-analysis, we excluded Lorefice et al. (75%), as it was more than two standard deviations higher than of the total percentage of high bias (41%).

Funnel plots were used to assess publication bias and plotted as the SD against the mean difference (Fig. 2). Both depression and anxiety prevalence funnel charts revealed asymmetries (Fig. 2A and B). The Egger's and Beggs's test results in the depressive prevalence measure were p = 0.1436 and p = 0.1857, respectively. Similarly, the Egger's and Beggs's test results for the anxiety prevalence evaluation were p = 0.8638 and p = 0.9287. This indicates no evidence of publication bias for both depression and anxiety prevalence.

3.3. Meta-analysis results and quality assessment

The meta-analyses showed that the total prevalence of depression in MS patients was 27.01% (95% CI: 22.80 to 31.68) with high heterogeneity (I^2 = 94%) (Fig. 3A). In prospective studies, the prevalence of depression in MS patients was 27.48% (95% CI: 20.87 to 35.25), with high heterogeneity (I^2 = 94%), whereas in cross-sectional studies it was 26.57% (95% CI: 20.88 to 33.18), with high heterogeneity (I^2 = 95%) (Fig. 3A). The overall prevalence of anxiety in MS patients was 35.19% (95% CI: 24.01 to 48.28), with high heterogeneity (I^2 = 99%) (Fig. 3B). The prevalence of anxiety for MS patients in prospective studies was 30.37% (95% CI: 16.99 to 48.16) with high heterogeneity (I^2 = 98%), while in cross-sectional studies the prevalence of anxiety was 40.29% (95% CI: 22.87 to 60.56), also with high heterogeneity (I^2 = 99%) (Fig. 3B).

The prevalence of depression according to MS subtype was 15.78% in RRMS (95% CI: 13.64 to 18.19), with moderate heterogeneity (I^2 = 56%), while in the PMS subtype it was 19.13% (95% CI: 11.70 to 29.69), with high heterogeneity (I^2 = 87%) (Fig. 4A). The prevalence of anxiety in the RRMS form was 21.40% (95% CI: 10.39 to 39.00), with high heterogeneity (I^2 = 99%). The prevalence of anxiety in the PMS subtype was 24.07% (95% CI: 13.08 to 40.05), with high heterogeneity (I^2 = 99%) (Fig. 4B).

In relation to the location of the study, the prevalence of depression in MS patients in North America was 26.10% (95% CI: 20.90 to 32.07), with high heterogeneity (I^2 = 94%) (Fig. 5A). The prevalence of depression in Oceania was 33.66% (95% CI: 21.21 to 48.89), with high heterogeneity (I^2 = 98%) (Fig. 5A). The MS prevalence of depression in

Table 3
Data extraction from clinical aspects of anxiety in multiple sclerosis patients.

MS patients (N)	Diagnostic Assessment	Scale and validation test (VT)	MS type	Treatment	Outcome	Risk of bias	Reference
(N = 949)	Self-reported.	HADS-A; VT= Yes.	All MS types.	No	I) The prevalence was 11.5%.	No mention of treatment; No differentiated MS subtypes; No time of anxiety diagnosis.	Fiest et al. (2016)
(N = 885)	Self-reported.	HADS-A; VT= Yes.	All MS types.	No	I) The prevalence was 40.3%.	No mention of treatment; No differentiated MS subtypes. No time of anxiety diagnosis.	Kovalec (2017)
(N = 902)	Physician diagnosed.	ICD-10; VT= Yes.	All MS types.	No	I) The prevalence was 38.1%.	No mention of treatment; No differentiated MS subtypes; No time of anxiety diagnosis.	Lo et al. (2021a)
(N = 1518)	Self-reported.	No anxiety scale; VT= No.	RRMS (N = 1113); PMS (N = 150).	No	I) The prevalence was 15.9%; II) The prevalence for RRMS was 17.2%, and for PMS was 18.7%.	No mention of treatment; No differentiated MS subtypes; No time of anxiety diagnosis; No use scale; No mention of the validation test.	Lo et al. (2021b)
(N = 253)	Self-reported.	HADS-A; VT= Yes.	All MS types.	No	I) The prevalence was 19%; II) HADS-A (8): N = 86, (34.1%); III) HADS-A (11): N = 40, (15.9%).	No mention of treatment; No differentiated MS subtypes; No time of anxiety diagnosis.	Marrie et al., 2018a
(N = 863)	Physician diagnosed.	HADS-A VT= Yes.	RRMS (N = 621); PMS + Unknow (N = 242).	73.2% reported treatment.	I) The prevalence was 68.9%; II) The HADS-A (8) was 39%; III) The prevalence for RRMS was 39% and PMS was 38%. IV) The mean age at MS onset for anxiety was 33.3 ± 9.0 years; V) The mean anxiety duration was 14.3 ± 9.7 years; VI) EDSS for anxiety patients was 3.1 ± 1.9.	No risk of bias.	Marrie (2018b)
(N = 949)	Self-reported.	HADS-A; VT= Yes.	RRMS (N = 687); PMS (N = 253).	No	I) The prevalence was 39.3%; II) The median HADS-A (Median (p25-p75)): 6 (3–9); III) The prevalence for RRMS was 13.2%, and for SPMS and PPMS was 18%; IV) The mean age at MS onset for anxiety patients was 33.5 ± 10.6; V) The mean anxiety duration was 14.9 ± 9.9 years; VI) EDSS for anxiety patients was (Median (p25-p75)): 3.0 (2.0–6.0).	No mention of treatment.	McKay et al. (2016)
(N = 206)	Questionnaire.	HADS-A; VT= Yes.	All MS types.	No	I) The prevalence was 43.6%; II) The median HADS-A was 7.	No mention of treatment; No differentiated MS subtypes; No time of anxiety diagnosis.	Viana et al. (2015)
(N = 208)	Self-reported.	HADS-A; VT= Yes.	All MS types	No	I) The prevalence was 54.8%; II) HADS-A (8+) was 42.5%; III) HADS-A (11+) was 22.1%.	No mention of treatment; No differentiated MS subtypes; No time of anxiety diagnosis.	Wicks et al. (2016)
(N = 255)	Self-reported.	HADS-A; VT= Yes.	All MS types.	No	I) The prevalence was 44%; II) The HADS-A (9+) was 16.9%; III) The HADS-A (11+) was 15.8%.	No mention of treatment. No differentiated MS subtypes; No time of anxiety diagnosis.	Whitehouse et al. (2019)

Female (F); Generalized anxiety disorder, (DSMIV); Generalized Anxiety Disorder-7 (GAD-7); Hospital Anxiety Scale (HADS-A); Interquartile range (IQR); Male (M); Number of subjects (N); Overall Anxiety and Severity Impairment Scale (OASIS); Validation test (VT).

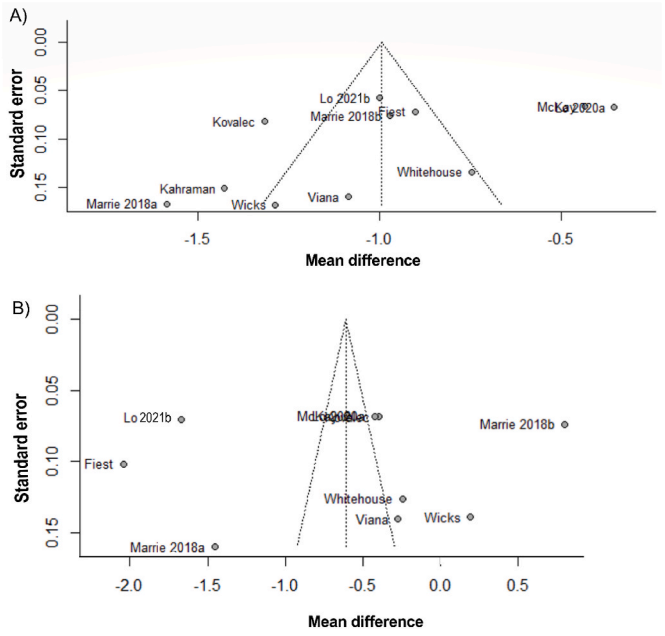

Fig. 2. Funnel plot of depression and anxiety in multiple sclerosis patients. **A)** Prevalence of depression in MS patients; **B)** Prevalence of anxiety in MS patients.

Europe was 23.48% (95% CI: 19.64 to 27.81), without heterogeneity (I^2 = 0%) (Fig. 5A). The prevalence of anxiety in North America was 34.23% (95% CI: 19.55 to 52.72), with high heterogeneity (I^2 = 99%) (Fig. 5B). In Oceania, the prevalence of anxiety was 26.02% (95% CI: 9.41 to 54.35), with high heterogeneity (I^2 = 99%) (Fig. 5B). Finally, the prevalence of anxiety in Europe was 49% (95% CI: 37.82 to 60.28), with high heterogeneity (I^2 = 82%) (Fig. 5B).

Additionally, when the highlighter was performed in HADS-D > 8, the prevalence was 21.79% (95% CI: 19.58 to 24.18), with low heterogeneity (I^2 = 15%). However, with HADS-D > 11, we found a prevalence of 7.44% (95% CI: 5.73 to 9.61), without heterogeneity (I^2 = 0%) (Fig. 6A). In the same way, when HADS-A > 8 was used for the analysis, the prevalence of anxiety was 39.21% (95% CI: 33.89 to 44.81), with moderate heterogeneity (I^2 = 69%), but for HADS-A > 11, we found a prevalence of anxiety in MS patients of 17.73% (95% CI: 14.05 to 22.12), with moderate heterogeneity (I^2 = 51%) (Fig. 6B).

Moreover, the prevalence of depression in MS patients that had EDSS <3 was 26.69% (95% CI: 18.96 to 36.17), with high heterogeneity (I^2 = 97%) (Fig. 7A). With EDSS >3, the prevalence was 22.96% (95% CI: 18.44 to 28.20), with high heterogeneity (I^2 = 76%) (Fig. 7A). The prevalence of anxiety in MS patients with EDSS <3 was 26.70% (95% CI: 13.36 to 46.25), with high heterogeneity (I^2 = 99%), but in MS patients with EDSS >3, the prevalence of anxiety was 45.56% (95% CI 24.74 to 68.06), with high heterogeneity (I^2 = 98%) (Fig. 7B).

Finally, we observed that the prevalence of depression in MS patients that were diagnosed >10 years ago was 29.21% (95% CI: 23.93 to 35.08), with high heterogeneity (I^2 = 96%). The prevalence of depression in MS patients that were diagnosed <10 years ago was 22.09% (95% CI: 16.87 to 28.37), with moderate heterogeneity (I^2 = 58%) (Fig. 8).

4. Discussion

MS leads to physical, motor, and cognitive disability, which generates psychiatric symptoms, such as depression and anxiety (Anthony Feinstein et al., 2014). In addition, MS patients may be predisposed to these comorbidities due to changes in brain structure or in immunological and inflammatory pathways (Feinstein et al., 2004; Feinstein, 2011; Anthony Feinstein et al., 2014; Gold and Irwin, 2006; Schiffer et al., 2005). There have been some systematic reviews and meta-analyses evaluating depression and/or anxiety in MS patients (Boeschoten et al., 2017; Butler et al., 2016; Marrie et al., 2015). However, there is still a lack of updated studies regarding this subject, and the prevalence of anxiety and/or depression in MS subtypes (RRMS and PMS) has not been evaluated yet. Thus, our study sought to assess the prevalence of these disorders in MS patients. In addition, we intended to obtain recent data related to the different clinical forms of MS, EDSS, HADS (>8 and >11) and the time since MS diagnosis.

Among the 12 studies, it was observed that 7507 patients had MS; females were more affected than males, and the mean age was 45.6 years. The incidence of MS was higher in females compared to males mainly in the RRMS clinical form (Zeydan and Kantarci, 2020). The methodologies included cross-sectional (Kahraman et al., 2021; Kowalec et al., 2017; Lo, Taylor, Winzenberg, Palmer, Blizzard and van der Mei, 2021b; Lo, Taylor, Winzenberg, Palmer, Blizzard, Ahmad, et al., 2021a; Marrie et al., 2018b; Viana et al., 2015), prospective cohort studies (Fiest et al., 2016; Marrie, Zhang, et al., 2018a; McKay et al., 2016; Whitehouse et al., 2019; Wicks et al., 2016) and a retrospective cohort study (Lorefice et al., 2015). Prospective studies are the gold standard for observational studies, while cross-sectional studies are also called prevalence studies (Thiese, 2014). The retrospective study was withdrawn due to the high risk of bias. Therefore, the methodological difference may be responsible for the bias in the meta-analysis. Since the difference was within the confidence interval, we used both cross-sectional and prospective cohort studies in our assessments. However, in other reviews on this subject (Boeschoten et al., 2017; Butler et al., 2016; Marrie et al., 2015) the types of studies were not reported. Thus, in future studies, the methodology of the study should be described, as this could help to improve the obtained data.

There are two other systematic reviews and meta-analyses, published before 2017, on the prevalence of depression and anxiety in MS patients. One study showed that the prevalence of depression was 23.7% and that of anxiety was 21.9% (Marrie et al., 2015). Another study observed a prevalence of depression of 30.5% and anxiety of 22.1% (Boeschoten et al., 2017). We found that depression affects 27.01% (95% CI: 22.8 to 31.68) and anxiety affects 35.19% (95% CI: 24.01 to 48.28) of the population with MS. Thus, we found a different prevalence of depression/anxiety symptoms compared to the published systematic reviews and meta-analyses, but our results were within the confidence interval for depression. However, our data related to the prevalence of anxiety was higher than those previously observed. Thus, we emphasize that perhaps the discrepancies could be caused by the lower number of articles included in our review due to the specified search time (2015–2021). We use this search time due to McDonald established diagnostic criteria that occurred in 2010. The earlier use of less accurate Schumacher and Poser (Poser et al., 1983; Schumacher et al., 1965) diagnostic criteria could generate inconsistencies in MS diagnosis. In addition, the criteria for the diagnosis of MS was updated in 2017 (Thompson et al., 2018). Therefore, with the inclusion of data from 2015, we included only patients diagnosed by McDonald diagnosis criteria, demonstrating the reliability of prevalence rates related to symptoms of depression and anxiety in MS.

The inclusion criteria of our study were stricter, including only studies with a sample number >200, which also makes our study different from those already published. Also, the time of data collection was 2015–2021, which differs from other reviews, but our results are similar to the previously published studies because the confidence interval of 95% included the results of the two earlier reviews. We

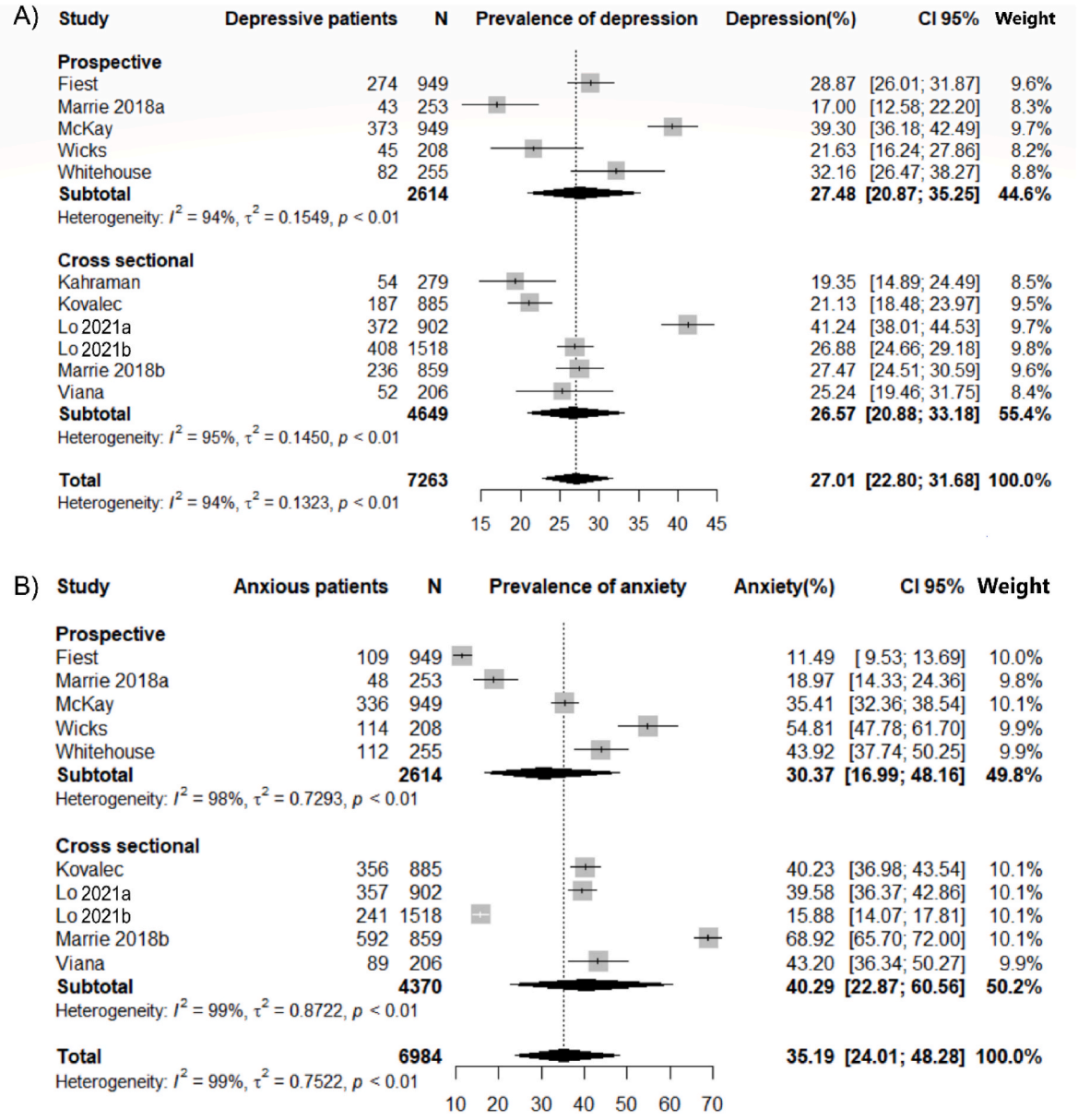

Fig. 3. Meta-analysis of study types for depression and anxiety in MS expressed as forest plots. **A)** Prevalence of depression comparing cross-sectional versus prospective studies; **B)** Prevalence of anxiety comparing cross-sectional versus prospective studies. The forest graphs presented the number of depressive and anxious patients in MS and the total number of patients with MS.

followed the inclusion criteria which included samples >200 patients as previously described by a systematic review using MS patients and depression/anxiety data (Boeschoten et al., 2017). However, we found a smaller number of studies, because we performed the extraction in a different period from the reviews already published.

Furthermore, we evaluated the differences between the MS clinical forms, and to the best of our knowledge, this is the first report on the prevalence of depression/anxiety in RRMS and PMS. We showed that anxiety is more prevalent in the different clinical forms of MS (21.40% RRMS; 24.07% PMS) compared to depression (15.78% RRMS; 19.13% PMS). Also, these prevalence values were lower than those described for MS patients (depression in 27.01% and anxiety in 35.19%). We performed data extraction from the 12 articles, but not all of them brought the measures of depression and anxiety simultaneously. Therefore, these discrepancies could have been caused because it was not possible to include all 12 articles in the subgroup meta-analysis (MS clinical types), as shown in Fig. 4 in relation to psychiatric disorders in patients.

The studies selected for our data extraction, not all brought separately the types of progressive multiple sclerosis (primary/secondary). Then, when performing the subgroup analysis, we merged the data into general PMS, because not all articles contain these subclassifications. So, we found a small number of studies that differentiated the subtypes of MS and few patients with the clinical form of PMS in general. Therefore, this shows how important it is for clinical studies to provide complete data on the prevalence of depression and anxiety for RRMS and PMS.

Many factors can contribute to the symptoms of depression and anxiety in the course of MS, as PMS and RRMS have different clinical and treatments (Thompson et al., 2018). The prevalence of depression and anxiety could be different in PMS and RRMS patients. However, we could not detect a significant result, although PMS patients tended to have a higher prevalence of depression and anxiety than RRMS patients. This would be expected because the PMS clinical form of MS is more difficult to treat compared to RRMS (Correale et al., 2017). Thus, this could impact the development of depression and anxiety. Patients with PMS usually have visual and motor deficits, as well as fatigue and central

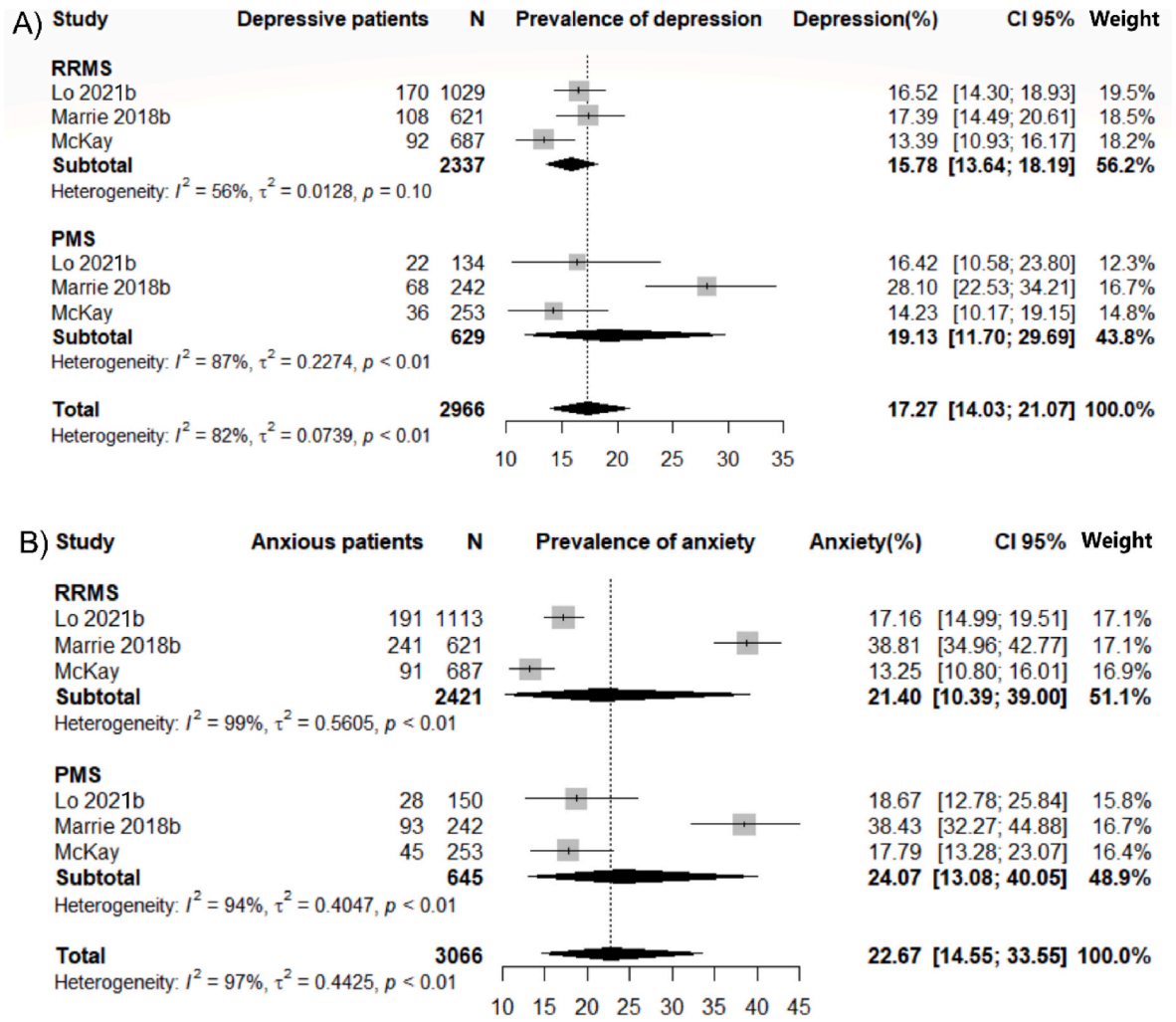

Fig. 4. Meta-analysis of depression and anxiety in MS subtypes expressed as forest plots. **A)** prevalence of depression in RRMS versus PMS; **B)** prevalence of anxiety in RRMS versus PMS. The forest graphs presented the number of depressive and anxious patients in the different clinical forms of MS (RRMS/PMS) and the total number of MS patients.

neuropathic pain (Yousuf et al., 2019). However, these symptoms can also be seen in the flare-up phase of RRMS, with the exacerbation of symptoms such as blurred vision, dizziness, tingling, fatigue, and pain, which can last for about a week (Kalincik, 2015). In PMS, the symptoms are more severe and abrupt compared to RRMS (Thompson et al., 2018).

Furthermore, a minority of studies differentiated MS subtypes in depression and anxiety, which resulted in 2537 and 2421 patients with RRMS and 690 and 645 may with PMS, respectively. RRMS is the most common MS clinical form, which possibly explain the larger number of patients (Doshi and Chataway, 2016; Zeydan and Kantarci, 2020). Also, the RRMS patients presented milder symptoms compared to PMS, being more difficult for patients' involvement in clinical research (Nathoo and Mackie, 2017).

When performing the analysis of subgroups of regions used for the prevalence of depression and anxiety as shown in Fig. 5, it was not possible to use the 12 articles, as not all studies brought the region. Being observed for depression in Oceania (2 studies), Europe (2), and North America (7), and anxiety in Oceania (2), Europe (2), and North America (6). Regarding confidence intervals, the prevalence of depression in Oceania (33.6%) is higher and is outside the confidence intervals of North America (21.90–32.07%) and Europe (19.64–27.81%). In a systematic review from 2017, it was evidenced that in the analysis of subgroups related to regions of Oceania with 3 studies, there was a higher prevalence of depression (42.5%) compared to the other regions of North America (30.9%) and Europe (37.9%) (Boeschoten et al., 2017). Furthermore, the prevalence of anxiety in Europe (49%) is higher and within the confidence interval of other continents. This result was similar to that described before, where a higher prevalence of anxiety was found for Europe (37.9%) compared to North America (24.4%), but these values are also within the confidence interval of other continents (Boeschoten et al., 2017).

Although most of the studies used diagnosis by self-report, and the HADS-D/HADS-A scale for depression/anxiety diagnosis, the studies also had a validation test. Self-report scales can be useful for the evaluation of depression/anxiety in MS (Butler et al., 2016), but this may have contributed to the high heterogeneity observed in the meta-analysis. However, most of the included studies presented validation tests for self-reports. Therefore, the validation test can be considered a parameter that strengthens the self-reported diagnosis (Pereira et al., 2021).

Additionally, the different cut-off scores for the HADS-D/HADS-A assessment may also be responsible for the high heterogeneity of the meta-analysis. The HADS was developed to help to identify anxiety and depression in people with a physical illness (Wu et al., 2021; Zigmond and Snaith, 1983). A cut-off value of >8 is used to identify possible anxiety/depression, while a value of >11 indicates probable anxiety/depression (Brennan et al., 2010; Mitchell et al., 2010; Wu et al., 2021). Thus, these cut-off values have been used as standards in research

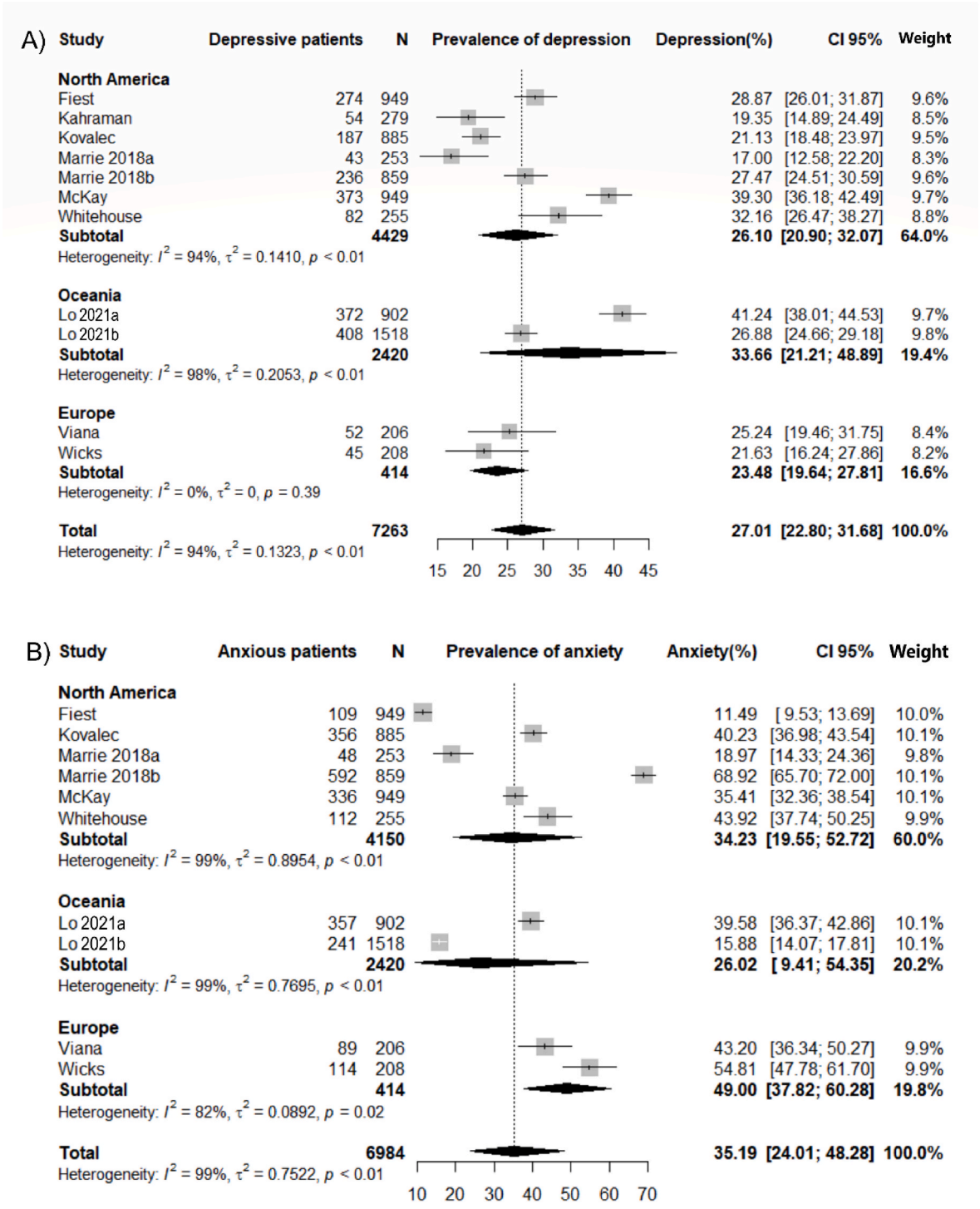

Fig. 5. Meta-analysis of depression and anxiety in MS different regions expressed as forest plots. **A)** prevalence of depression in MS patients in North America, Oceania and Europe; **B)** prevalence of anxiety in MS patients in North America, Oceania and Europe. The forest graphs presented the number of depressive and anxious patients in the different regions and the total number of MS patients.

and clinical practice (Brennan et al., 2010; Mitchell et al., 2010; Wu et al., 2021). Corroborating our results, a systematic review and meta-analysis showed that the prevalence of general HADS for anxiety in MS patients was 27.2% (Marrie et al., 2015). Also, we observed a higher prevalence for both HADS-D and HADS-A > 8 than HADS-D/HADS-A > 11. Similarly, another systematic review and meta-analysis also observed a higher prevalence of HADS-D/HADS-A > 7 in MS patients than HADS-D/HADS-A > 10 (Boeschoten et al., 2017). In our research, we were only able to perform the meta-analysis of the subgroups using the HADS, as the other scales (BDI, ANTAS, SCID) only have one study selected, thus the studies were not sufficient to carry out the meta-analysis. Consequently, it was not possible to perform subgroup analysis, related to the other scales mentioned. Furthermore, in the reviews already published on depression and anxiety in MS (Boeschoten et al., 2017; Butler et al., 2016; Nathoo and Mackie, 2017), we found that the most used scale was HADS. Then, we assumed that the use of HADS in our meta-analyses would not be a limitation since this scale is one of the most used in previous reports (Boeschoten et al., 2017; Butler

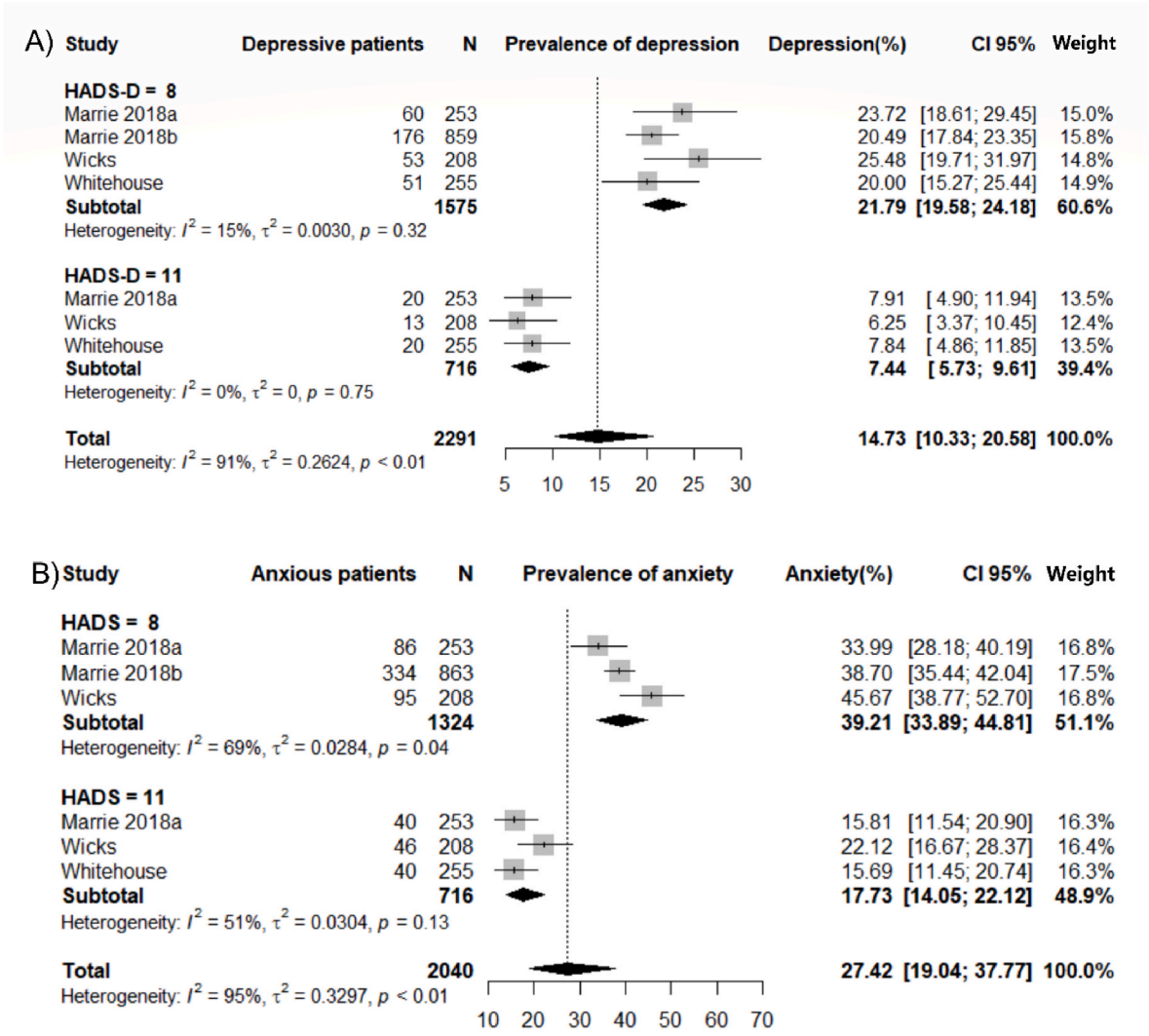

Fig. 6. Meta-analysis of HADS in depression and anxiety in MS patients expressed as forest plots. **A)** prevalence of HADS-D in MS patients; **B)** prevalence of HADS-A in MS patients. The forest plots presented the number of HADS-D and HADS-A patients compared to the total number of MS patients.

et al., 2016; Nathoo and Mackie, 2017).

There are no studies that provide our findings related to disability values and these psychiatric disorders. We observed that the prevalence of depression/anxiety in patients with EDSS <3 was 26.69%/26.70% and EDSS >3 was 22.96%/45.56%. Also, it would be relevant to see if treatments for depression and anxiety could be used or have better efficacy in different subgroups of patients depending on their disability seen by the EDSS. Therefore, there is still a need for more clinical studies to evaluate if the disability could alter the induction of depression and anxiety. Besides, there is still a lack of studies related to HADS-A/HADS-D and the disability score (EDSS), as well as the diagnosis of depression and anxiety.

Another important aspect is related to patient treatment, since antidepressant drugs have a large number of adverse effects (Cordeau and Courtois, 2014; Correale et al., 2017; Lew-Starowicz and Rola, 2014). However, only two articles mentioned the use of antidepressants for the treatment of depression (Lorefice et al., 2015; Marrie et al., 2018b), and only one study reported the use of treatment for anxiety in patients with MS (Marrie et al., 2018b). One of the main issues regarding patient treatment is the worsening of MS deficits in the course of the disease (Nathoo and Mackie, 2017). Moreover, there is still no standard treatment or systematic reviews that have not been found for depression and anxiety in MS patients. It is necessary to do this type of study, because depression and anxiety are important comorbidities in MS, and as current patients have a longer life expectancy than before, and adequate treatment for these psychiatric diseases in MS patients is urgently necessary.

In addition, a strong point of this systematic review and meta-analysis is the analysis of publication bias, which was not observed. The subgroup analysis is also a strength and important to report in our study. Despite this, our meta-analysis should be viewed with some limitations, as the strength of the results depends on the parameters of the articles. First, it was observed that some articles did not provide all the data needed to analyse the subgroups related to the HADS scale, EDSS, disease duration, and the different clinical forms, which limited our analyses. Thus, we were unable to include the 12 articles in all analyses due to this lack of data. Also, the missing data related to the treatment of psychiatric disorders made it impossible to carry out the meta-analysis regarding treatment.

EDSS is recorded by the neurologist in charge on the day of recruitment and on follow-up visits, which includes the history of relapses and patient treatment. It is a disability status that ranges from normal (0.0–3.0), to moderate (3.5–5.5) to maximum impairment (6.0–9.0) (Kurtzke, 1983; Fiest et al., 2016). Most articles did not report the EDSS value for depression and anxiety patients separately. It is also a limitation because the EDSS score can be interpreted in different ways by health professionals. Therefore, our results indicate a higher prevalence rate of anxiety in MS patients compared to depression. As well, we

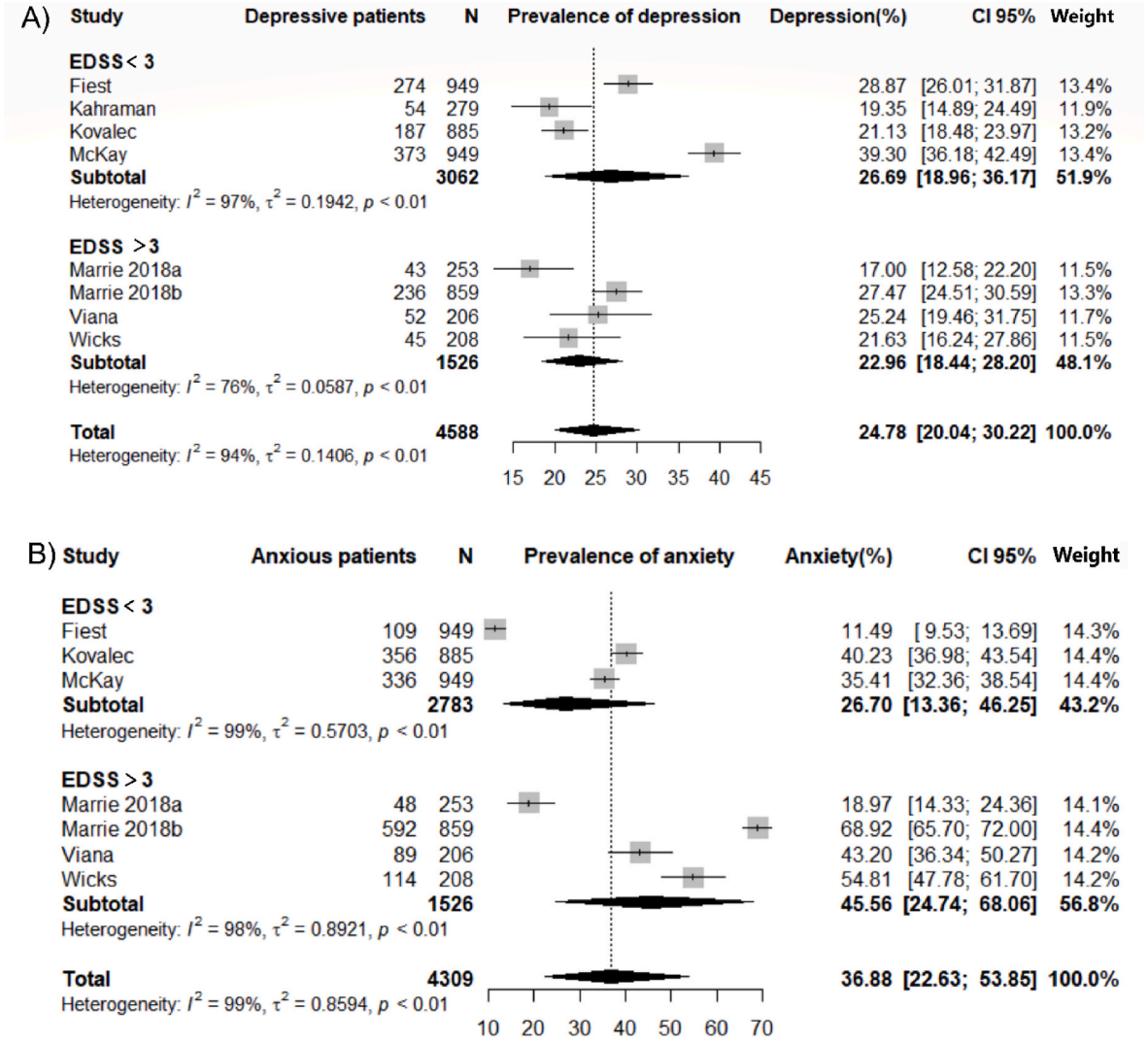

Fig. 7. Meta-analysis of EDSS in depression and anxiety in MS patients expressed as forest plots. **A)** prevalence of EDSS the depression in MS patients; **B)** prevalence of EDSS the anxiety in MS patients. The forest plots presented the number of EDSS depression and anxiety patients compared to the total number of MS patients.

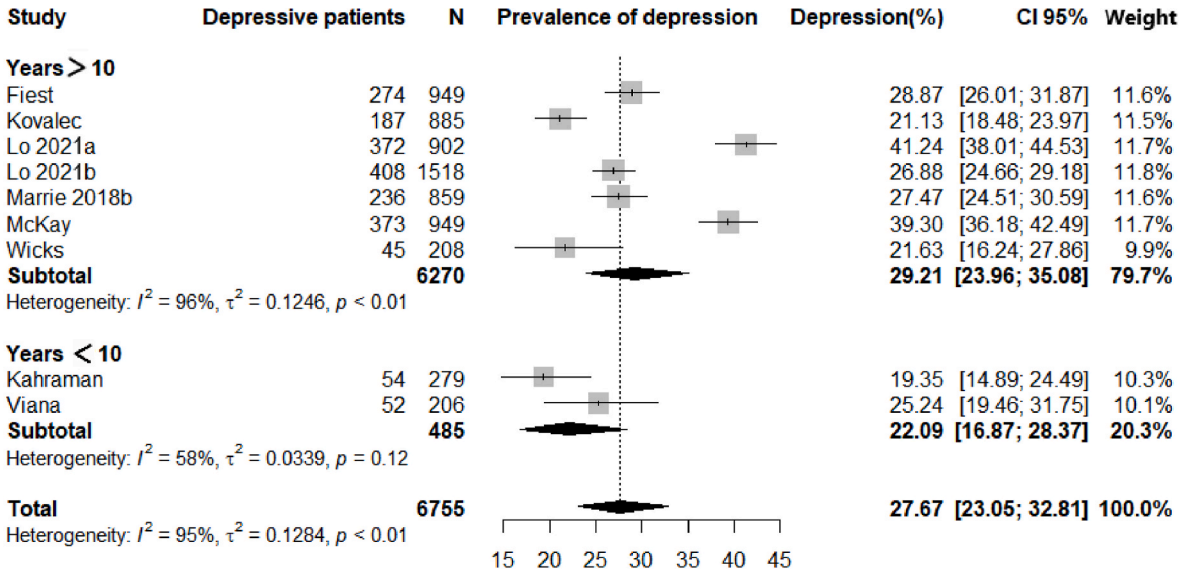

Fig. 8. Meta-analysis of the duration of MS in depression expressed as forest plots. **A)** prevalence of depression in time >10 years; **B)** prevalence of depression in time <10 years. The forest plots presented the number of depressed patients in MS and the total number of patients with MS.

provide innovative results from the subgroup analysis related to prevalence in terms of the time since diagnosis of the disease, EDSS, as well as types of MS associated with depression and anxiety. We recommend that in future studies a standard scale be used to assess the symptoms of anxiety and depression in patients with MS, in order to assist in the treatment of the disease. Another important factor is that the drugs used to treat depression and anxiety in MS should be listed. This study is very important for the literature, as updated data are lacking, and because it is very important to know how these psychiatric disorders affect the quality of life of patients affected by MS.

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Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare that no competing interests exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100484.

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