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The effect of exercise on mental health and health-related quality of life in individuals with multiple sclerosis: A Systematic review and meta-analysis

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ABSTRACT

Background: A large body of evidence has tested the effect of exercise interventions on mental health and health-related quality of life (HRQoL) in individuals with multiple sclerosis (PwMS).
Objective: To determine the effect of exercise interventions on mental health and HRQoL in PwMS.
Methods: We searched four databases up to April 2023, and included randomized controlled trials that: 1) involved PwMS ≥18 years old; 2) delivered an exercise intervention; 3) measured subjective well-being, psychological well-being, social well-being, or HRQoL as outcomes. We reported standardized differences in means (d) with a 95 % confidence interval (CI), for continuous outcomes and an incidence rate ratio (IRR) with a 95 % CI for dichotomous outcomes.
Results: Forty-nine studies (n = 2,057 participants) were included. Exercise improved overall well-being (d = 0.78; 95 % CI 0.483, 1.077; moderate certainty evidence), subjective well-being (d = 0.666; 95 % CI 0.405, 0.928; moderate certainty evidence), social well-being (d = 1.046; 95 % CI 0.569, 1.523; low certainty evidence), and HRQoL (d = 0.568; 95 % CI 0.396, 0.74; moderate certainty evidence).
Conclusion: Exercise interventions can improve well-being and HRQoL in PwMS. Future studies should focus on PwMS ≥ 65 years or with higher level of impairments.

1. Introduction

Nearly 20 % and 30 % of individuals with MS report symptoms of depression and anxiety, respectively (Chwastiak and Ehde, 2007; Pham et al., 2018). Poor mental health is associated with presenteeism and absenteeism (van Egmond et al., 2022), thus representing a barrier to employment, with up to 43 % of people with MS (PwMS) that stop working within 3 years of diagnosis and up to 70 % within 10 years (Multiple Sclerosis International Federation, 2016). On the other hand, the loss of employment, along with fatigue and poor mental health, has a negative impact on health-related quality of life (HRQoL) (Berrigan et al., 2016; Marck et al., 2020; Wu et al., 2007). People living with disabilities face barriers to accessing healthcare and display higher rates of health-compromising behaviours which, combined with a lower exposure to disease prevention and health promotion services compared with people without disabilities (World Health Organization and World Bank, 2011), can further compromise mental health and HRQoL.

Mental health can be defined as the absence of clinical mental health disorders combined with high levels of well-being (Keyes, 2006). Well-being is a multidimensional concept, which can be conceptualized as subjective well-being (individuals' assessments of their emotions and affects, happiness, satisfaction with life and domains of life), psychological well-being (purpose in life, personal growth, self-efficacy, and self-acceptance), and social well-being (individuals' perceptions of the quality of their relationships with other people, their neighbourhoods, and their communities) (Diener et al., 1999; Keyes, 2006). Mental health influences health-related quality of life (HRQoL), which can be described as the individual's perception of physical and mental health

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over time (Centers for Disease Control and Prevention). According to Dijkers (1977), HRQoL refers to those components of QoL that are directly and indirectly affected by health, disease, disorder, and injury (e.g., signs, symptoms, treatment side effects, physical, cognitive, emotional and social functioning).

In the recent years, disability has moved from being considered a medical condition to be treated to be recognized as part of human life (World Health Organization and World Bank, 2011), as such it can be rich, fulfilling, and gifted (Goodley et al., 2014). Therefore, there is a need for effective, accessible, safe, sustainable strategies to increase mental health and HRQoL in this population. Exercise has been proposed as a strategy to accomplish this goal. A large body of evidence shows that exercise increases positive affective states and it is negatively associated with anger, confusion, tension, and fatigue in the general population (Biddle et al., 2021; Reed and Buck, 2009; Reed and Ones, 2006). Furthermore, physical activity (PA) seems to play a preventative role against the development of depressive symptoms: individuals with a more sedentary lifestyle were more likely to develop depressive symptoms (Farmer et al., 1988; McDowell et al., 2018; Paffenbarger et al., 1994), while increases in PA may reduce risk for depression (Jerstad et al., 2010). Similarly, meta-analyses showed that regular exercise leads to a better HRQoL in the general population (Gillison et al., 2009) as well as in persons with physical disabilities, such as spinal cord injury (Martin Ginis et al., 2010; Ponzano et al., review) and MS (Alphonsus et al., 2019; Motl and Gosney, 2008). Motl & Gosney (2008) included 13 studies, and detected positive effects of exercise on HRQoL. Alphonsus et al. (2019) included 18 studies, and detected small to moderate effects on the mental, physical, and social domains of HRQoL. In the most recent years, growing research has tested the effects of exercise on mental health and HRQoL in people with physical disabilities; furthermore, many studies assessed aspects of mental health with specific measures of well-being, beyond mental functioning domains of HRQoL questionnaires and measures of anxiety and depression. Hence, a systematic synthesis of the literature was needed to provide a scientific ground to the recommendation of PA and exercise to improve well-being and HRQoL among PwMS. Therefore, the aim of the present systematic review and meta-analysis was to determine the effects of exercise on mental health and HRQoL in PwMS.

2. Method

This systematic review is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Page et al., 2021). The protocol was informed by the Cochrane Handbook for Systematic Review of Interventions and registered via the International Prospective Register of Systematic Reviews (PROSPERO) at https://www.crd.york.ac.uk/prospero/ (registration number CRD42022298361, last updated on December 6, 2022). The protocol was co-developed by a working group consisting of researchers in the fields of physical disabilities, knowledge translation, and exercise science, a clinical psychologist with expertise in treating patients with MS, a physiatrist specialized in the treatment of individuals with MS, and two graduate students.

2.1. Data sources and searches

The literature searches were conducted in December 2021 and updated in April 2023. We searched the following databases: MEDLINE; Cochrane CENTRAL (clinical trials); CINAHL (allied health journal content); PsycINFO. The search strategy was developed using Medical Subject Headings (MeSH terms) and keywords related to the management of MS and the effects of the interventions. No restrictions by language were applied for the literature search.

2.2. Study selection

2.2.1. Study design

Only randomized (RCT) and quasi-randomized controlled trials (quasi-RCT) were eligible for inclusion. Non-RCT, pre-post design studies, cohort studies, case-control studies, review articles, observational studies, cross-sectional studies, letters to editors, and commentaries were excluded.

2.2.2. Population

We included studies on men and women aged 18 years or older diagnosed with any forms of MS (clinically isolated syndrome, relapsing remitting, primary progressive, or secondary progressive) living in the community. We excluded studies on individuals younger than 18 years and studies which included both individuals with MS and people with other neurological disorders.

2.2.3. Intervention

We included any exercise or PA interventions, operationalized as participation in sport (both competitive and non-competitive) and other activities to improve or maintain one or more components of health-related (e.g., aerobic fitness, muscular strength and endurance, body composition and flexibility) or skill-related (e.g., balance, coordination, speed, etc.) fitness (Caspersen et al., 1985). Physical therapy and rehabilitation interventions were deemed eligible if at least one component was performed actively and independently by the participants, to distinguish active exercise from passive mobilization performed by a physical therapist.

2.2.4. Comparator

We included in the meta-analysis studies that had at least one comparator group that received no intervention. In case the control group was offered a non-exercise intervention (e.g., dietary supplementation), the study was included only if the same intervention (dose, frequency, intensity, type, time, etc.) was administered to the intervention group as well. Studies with an active or attention control group were considered for inclusion in the meta-analysis if the attention control was not hypothesized to have an effect on the outcomes of interest (e.g., information on services available to individuals with MS).

2.2.5. Outcomes

Primary outcomes were:

1) Aspects of mental health, conceptualized based on Diener et al. (1999) and Keyes (2006) as:
    a) subjective well-being (individuals' assessments of their emotions and affects, happiness, satisfaction with life and domains of life, anxiety, and depression);
    b) psychological well-being (purpose in life, personal growth, and self-acceptance);
    c) social well-being (individuals' perceptions of the quality of their relationships with other people, their neighbourhoods, and their communities).
2) Health-related quality of life, (HRQoL), defined by Dijkers (1977) as "*components of quality of life that centre upon or are directly and indirectly affected by health, disease, disorder, and injury*".

Secondary outcomes were serious adverse events (SAEs), defined as any untoward medical occurrence that, at any dose, results in death, a threat to life, inpatient hospitalization, or prolongation of existing hospitalization, or in persistent or significant disability/incapacity (Health Canada, 2018), and non-serious adverse events (non-SAEs), defined as any reaction related to the intervention such as musculoskeletal injuries (e.g., sprains, strains, joint pain, overuse injuries) that do not require immediate medical attention. We also reported on retention, operationalized as the number of participants that completed both baseline and post-intervention assessment, and adherence, operationalized as any information about the number of sessions attended by the participants (e.g., percentage of sessions attended).

2.3. Data extraction and quality assessment

Pairs of reviewers (LB, LB, SA, MP) independently assessed the titles and abstracts to confirm their eligibility. All the discrepancies between reviewers were resolved by discussion. Full texts published in English, or Italian were retrieved, and each full text was screened by two authors (LB, LB, SA, MP). All the conflicts between reviewers were resolved by discussion or, when an agreement was not reached, by a third author. Data extraction was completed independently by two authors (LB, LB, SA, MP). We extracted the following information from each study: descriptive information about the study (title, authors, publication date and status, country, study design); population and participants characteristics according to Cochrane PROGRESS Plus;(O'Neill et al., 2014) number of recruited participants, dropout rates and reasons, adherence rates and adverse events; intervention (frequency, intensity, type, duration and setting of the delivered intervention, qualification of the person delivering the intervention, if the programs were supervised/unsupervised or in group/alone and information about progression); type of comparator (if any); outcomes described above. In case of missing information, the corresponding authors of the individual studies will be contacted a maximum of two times. All the discrepancies between reviewers were resolved by discussion. In case some information was missing, the authors of the original studies were contacted a maximum of two times. Two authors (FM and MP) categorized the outcome measures from the included studies into the three dimensions of well-being (i.e., subjective, psychological, and social), according to Diener et al. (1999) and Keyes (2006). Pairs of reviewers (LB, LB, FM, MP) independently assessed risk of bias using the Revised Cochrane Risk-of-bias Tool for Randomized Trials (RoB 2) (Higgins et al., 2022); disagreements were resolved by consensus or consultation with a third reviewer. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Schünemann et al., 2022) was used to assess the certainty of the evidence (Fig. 6).

2.4. Data synthesis and analysis

Data were extracted using Covidence (https://www.covidence.org/home; Covidence, Melbourne, Australia) and then imported to Comprehensive Meta-Analysis (v.4; Biostat Inc., Englewood, NJ, USA; Borenstein et al., 2022) for statistical analysis. We performed random-effects meta-analyses of between-group comparisons of pre-post change scores. We reported standardized differences in means (d) with a 95 % confidence interval (CI) for continuous outcomes, and interpreted it as small (0.2), medium (0.5), or large (0.8) (Cohen, 1988). Meta-analyses based on between-group comparisons of changes from baseline are recommended over comparisons of post-intervention values, as they remove any between-person variability from the analysis (Deeks et al., 2023). However, most of the studies did not report pre-post change scores nor did they adjust the analyses for baseline values, and pooling post-intervention values with change scores is not recommended when the estimate of the effect is a standardized mean difference (Deeks et al., 2023). Therefore, we calculated pre-post change scores (Borenstein et al., 2022) from the studies that reported unadjusted post-intervention values, and we pooled them in the meta-analyses by imputing a $r_{xy} = 0.5$ correlation coefficient between pre- and post-intervention assessments (Borenstein, 2009; Kelley et al., 2022). We reported analyses with correlations coefficients between pre- and post-intervention assessments as $r_{xy} = 0.1$, and $r_{xy} = 0.9$ in sensitivity analyses (supplementary material S3, Fig. 11–18) (Borenstein, 2009; Kelley et al., 2022). We assessed heterogeneity between trials by using I^2, Tau^2, and Q, and reported a 95 % prediction interval (PI) when $Tau^2 > 0$. We calculated an incidence rate ratio (IRR) with a 95 % CI for SAEs, and presented non-SAEs in a narrative synthesis, as less than three studies had at least one non-SAEs in both groups, and thus it was not possible to calculate an IRR. We assessed publication bias by visual inspection of funnel plots (Egger et al., 1997).

Regarding mental health outcomes, we performed a main meta-analysis combining all the well-being outcomes. For the studies that assessed more than one dimension of well-being, the software calculated within-study averages of the between-group differences in well-being outcomes that were then pooled in the meta-analysis (Borenstein et al., 2022). We performed sensitivity analyses to explore the effects of exercise on the different dimensions of well-being measured by more than two studies (i.e., subjective well-being, and social well-being). With regard to overall well-being and HRQoL, we performed sensitivity analyses by intervention type, to explore the effects of aerobic training and combined aerobic and progressive resistance training on such outcomes, since a network meta-analysis showed that combined training, aerobic and resistance training were the most effective interventions to improve muscular fitness in PwMS (Reina-Gutiérrez et al., 2023).

3. Results

3.1. Characteristics of included studies

We screened 8491 deduplicated abstracts and 280 full-text, and 49 studies from 48 RCTs ($n = 2057$ participants, 77 % females, mean age < 65 years in every study) were included (Fig. 1). Thirty-three studies (Ahmadi et al., 2010; Andreu-Caravaca et al., 2022; Bahmani et al., 2022; Carter et al., 2014, 2013; Correale et al., 2021; Dalgas et al., 2010; Escudero-Uribe et al., 2017; Feys et al., 2016; Grubic Kezele et al., 2021; Hebert et al., 2018; Heine et al., 2017; Kargarfard et al., 2012; Kooshiar et al., 2015; Langeskov-Christensen et al., 2021a, 2021b; Mokhtarzade et al., 2017, 2021; Najafi et al., 2023; Negahban et al., 2013; Oken et al., 2004; Ozdogar et al., 2020; Ozkul et al., 2020; Petajan et al., 1996; Prosperini et al., 2013; Razazian et al., 2016; Romberg et al., 2005; Schulz et al., 2004; Straudi et al., 2014, 2022; Sutherland et al., 2001; Tarakci et al., 2013; Yazgan et al., 2020) from 32 RCTs were performed in people with a mean EDSS < 5.5, one study (Incheol Jeong et al., 2021) in people with EDSS between 5.5 and 7.5, one study (McAuley et al., 2015) in people with a mean EDSS ≤ 6.5, one study (Thomas et al., 2017) in people with a mean EDSS < 6, one study (Cakit et al., 2010) in people with a mean EDSS ≤ 6, one study (Heinrich et al., 2021) in participants with a mean EDSS ≤ 5.5, one study (Correale et al., 2021) in people with a mean EDSS < 4, one study (Paul et al., 2014) in people with a mean EDSS > 5.5, one study (Learmonth et al., 2012) in participants with a mean EDSS ≥ 5, two studies in participants with a median EDSS < 6 (Gunn et al., 2021) and < 5 (Tollár et al., 2020), respectively, one study (Louie et al., 2021) in participants with a median EDSS < 6 (intervention group) and < 4 (control group). Five studies had an inclusion criterion based on ambulation abilities: Buttolph et al. (2021) included people able to walk 50 feet without assistance, Dodd et al. (2011) participants with an Ambulation Index (Hauser et al., 1983) score of 2, 3 or 4, Fleming et al. (2021) participants with a patient-determined disease steps score < 3, Hebert et al. (2011) people able to walk 100 m with or without a single-sided aid, and Toomey & Coote (2017) included non-ambulatory individuals. Most studies delivered interventions that combined more than one type of exercise, with an average intervention duration of 3.5 ± 2.0 months, for 3.0 ± 1.5 days per week (supplementary material S1, Table 1). Twelve studies (Ahmadi et al., 2010; Bahmani et al., 2022; Feys et al., 2016; Hebert et al., 2011; Heine et al., 2017; Heinrich et al., 2021; Langeskov-Christensen et al., 2021a, 2021b; Mokhtarzade et al., 2017; Oken et al., 2004; Petajan et al., 1996; Schulz et al., 2004) delivered an aerobic intervention; six studies (Escudero-Uribe et al., 2017; Hebert et al., 2018; Prosperini et al., 2013; Thomas et al., 2017; Tollár et al., 2020; Yazgan et al., 2020) a balance exercise intervention; five studies (Cakit et al., 2010; Carter et al., 2014, 2013; Learmonth et al., 2012; Paul et al., 2014) an aerobic,

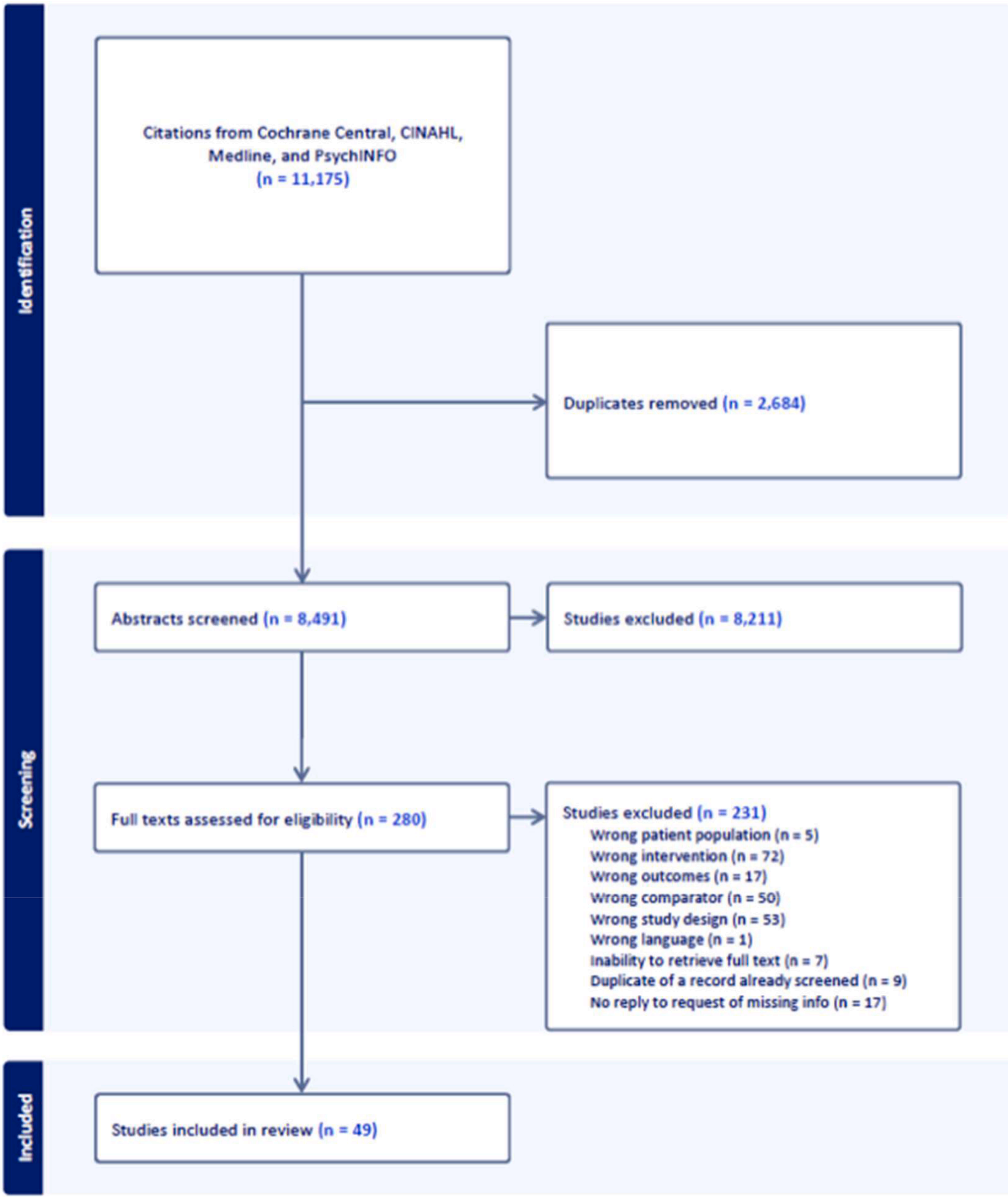


Fig. 1. PRISMA flowchart.

resistance training, and balance multicomponent intervention; four studies (Kargarfard et al., 2012; Kooshiar et al., 2015; Razazian et al., 2016; Sutherland et al., 2001) an aquatic exercise intervention; three studies a resistance training intervention, (Andreu-Caravaca et al., 2022; Dalgas et al., 2010; Dodd et al., 2011) and an aerobic and resistance training combined intervention; (Correale et al., 2021; Mokhtarzade et al., 2021; Romberg et al., 2005) two studies Pilates, (Fleming et al., 2021; Najafi et al., 2023) and multicomponent interventions including gait training, flexibility and resistance training (Straudi et al., 2014, 2022), and balance, resistance training, and flexibility (McAuley et al., 2015); one study delivered a multimodal individualized home exercise program(Toomey and Coote, 2017), a telerehabilitation exercise program (Incheol Jeong et al., 2021), qigong (Buttolph et al., 2021), and other multicomponent interventions including: gait training, balance, and functional training (Gunn et al., 2021), aerobic, resistance training, balance, and flexibility (Negahban et al., 2013), balance, resistance training, and functional training (Louie et al., 2021), resistance training, breathing, and coordination (Grubic Kezele et al., 2021), balance and arm and core stability exercises (Ozdogar et al., 2020), and aerobic and Pilates (Ozkul et al., 2020). Eight studies (Ahmadi et al., 2010; Bahmani et al., 2022; Kargarfard et al., 2012; Kooshiar et al., 2015; Mokhtarzade et al., 2017, 2021; Negahban et al., 2013; Razazian et al., 2016) were performed in Iran; seven studies (Buttolph et al., 2021; Hebert et al., 2011, 2018; Incheol Jeong et al., 2021; McAuley et al., 2015; Oken et al., 2004; Petajan et al., 1996) in USA; six studies (Carter et al., 2014, 2013; Gunn et al., 2021; Learmonth et al., 2012; Paul et al., 2014; Thomas et al., 2017) in UK; five studies (Cakit et al., 2010; Ozdogar et al., 2020; Ozkul et al., 2020; Tarakci et al., 2013; Yazgan et al., 2020) in Turkey; four studies (Correale et al., 2021; Prosperini et al., 2013; Straudi et al., 2014, 2022) in Italy; three studies in Australia (Dodd et al., 2011; Louie et al., 2021; Sutherland et al., 2001), and Denmark (Dalgas et al., 2010; Langeskov-Christensen et al., 2021a, 2021b); two studies in Germany (Heinrich et al., 2021; Schulz et al., 2004), Ireland (Fleming et al., 2021; Toomey and Coote, 2017), and Spain (Andreu-Caravaca et al., 2022; Escudero-Uribe et al., 2017); one study in Belgium (Feys et al., 2016), Croatia (Grubic Kezele et al., 2021), Finland (Romberg et al., 2005), Hungary (Tollár et al., 2020), Iran and Malaysia (Najafi et al., 2023), and The Netherlands (Heine et al., 2017). Thirty-three studies (Ahmadi et al., 2010; Buttolph et al., 2021; Carter et al., 2013; Dalgas et al., 2010; Dodd et al., 2011; Feys et al., 2016; Grubic Kezele et al., 2021; Gunn et al., 2021; Hebert et al., 2011, 2018; Heine et al., 2017; Heinrich et al., 2021; Langeskov-Christensen et al., 2021a, 2021b; Learmonth et al., 2012; Louie et al., 2021; McAuley et al., 2015; Mokhtarzade et al., 2017, 2021; Najafi et al., 2023; Negahban et al., 2013; Oken et al., 2004; Ozdogar et al., 2020; Paul et al., 2014; Petajan et al., 1996; Romberg et al., 2005; Schulz et al., 2004; Straudi et al., 2014, 2022; Sutherland et al., 2001; Thomas et al., 2017; Toomey and Coote, 2017; Yazgan et al., 2020) received funding from non-profit organizations, eight studies (Andreu-Caravaca et al., 2022; Bahmani et al., 2022; Fleming et al., 2021; Ozkul et al., 2020; Prosperini et al., 2013; Razazian et al., 2016; Tarakci et al., 2013; Tollár et al., 2020) declared they received no funding, and seven studies (Cakit et al., 2010; Carter et al., 2014; Correale et al., 2021; Escudero-Uribe et al., 2017; Incheol Jeong et al., 2021; Kargarfard et al., 2012; Kooshiar et al., 2015) did not report funding information.

3.2. Effects of exercise on psychosocial outcomes

3.2.1. Overall well-being

Exercise improved overall well-being ($d = 0.780$; 95 % CI 0.483, 1.077; 95 % PI −0.876, 2.436; 1410 participants, 34 studies from 33 RCTs; $I^2 = 86$ %, $Tau^2 = 0.6538$, $Q = 232.131$; moderate certainty evidence; Fig. 2). Ten studies (Ahmadi et al., 2010; Bahmani et al., 2022; Hebert et al., 2011; Heine et al., 2017; Heinrich et al., 2021; Langeskov-Christensen et al., 2021a, 2021b; Oken et al., 2004; Petajan et al., 1996; Schulz et al., 2004) delivered an aerobic intervention, four studies (Escudero-Uribe et al., 2017; Hebert et al., 2018; Thomas et al., 2017; Tollár et al., 2020) a balance intervention, four studies (Kargarfard et al., 2012; Kooshiar et al., 2015; Razazian et al., 2016; Sutherland et al., 2001) an aquatic exercise intervention, two studies (Fleming et al., 2021; Najafi et al., 2023) Pilates, one study a telerehabilitation exercise program (Incheol Jeong et al., 2021), resistance training (Andreu-Caravaca et al., 2022), and qigong (Buttolph et al., 2021), while eleven studies delivered multicomponent exercise interventions: aerobic, resistance, and balance training (Cakit et al., 2010; Carter et al., 2014, 2013; Learmonth et al., 2012; Paul et al., 2014), aerobic and resistance training (Correale et al., 2021; Mokhtarzade et al., 2021; Romberg et al., 2005), balance, resistance training, and flexibility (McAuley et al., 2015), balance and arm and core stability exercises (Ozdogar et al., 2020), aerobic and Pilates (Ozkul et al., 2020). Sensitivity analyses by intervention type showed positive effects of both aerobic ($d = 0.778$; 95 % CI 0.213, 1.343; 332 participants, 10 studies; $I^2 = 87$ %, $Tau^2 = 0.67$, $Q = 70.797$; supplementary material S2, Fig.7) and combined aerobic and progressive resistance training ($d = 0.338$; 95 % CI 0.130, 0.547; 378 participants, 7 studies; $I^2 = 0$ %, $Tau^2 = 0.00$, $Q = 5.649$; supplementary material S2, Fig. 9).

3.2.2. Subjective well-being

Exercise improved subjective well-being ($d = 0.666$; 95 % CI 0.405, 0.928; 95 % PI −0.577, 1.910; 1081 participants, 28 RCTs; $I^2 = 76$ %, $Tau^2 = 0.348$, $Q = 111.867$; moderate certainty evidence; Fig. 3A). Eight studies (Ahmadi et al., 2010; Bahmani et al., 2022; Hebert et al., 2011; Heinrich et al., 2021; Langeskov-Christensen et al., 2021a; Oken et al., 2004; Petajan et al., 1996; Schulz et al., 2004) delivered an aerobic intervention, three studies an aquatic exercise intervention (Kargarfard et al., 2012; Razazian et al., 2016; Sutherland et al., 2001) and a balance

Study name	Outcome	Statistics for each study						
		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ahmadi 2010	Combined	0.264	0.449	0.202	-0.617	1.144	0.587	.557
Andreu-Caravaca 2022	Psychological well-being	0.000	0.373	0.139	-0.730	0.730	0.000	.000
Bahmani 2022	Combined	6.807	1.284	1.649	4.291	9.324	5.301	.000
Buttolph 2021	Subjective well-being	-0.041	0.516	0.267	-1.053	0.972	-0.078	.937
Cakit 2010	Combined	0.311	0.433	0.188	-0.538	1.161	0.718	.473
Carter 2014	Combined	0.388	0.184	0.034	0.027	0.749	2.106	.035
Correale 2021	Subjective well-being	0.654	0.438	0.192	-0.205	1.512	1.493	.135
Escudero-Uribe 2017	Combined	0.564	0.363	0.132	-0.148	1.277	1.552	.121
Fleming 2021	Combined	0.660	0.230	0.053	0.210	1.111	2.872	.004
Hebert 2011	Subjective well-being	0.081	0.392	0.154	-0.688	0.850	0.207	.836
Hebert 2018	Social well-being	4.383	0.423	0.179	3.553	5.212	10.359	.000
Heine 2017	Social well-being	1.910	0.256	0.065	1.408	2.411	7.462	.000
Heinrich 2021	Subjective well-being	0.219	0.278	0.077	-0.327	0.764	0.785	.432
Jeong 2021	Combined	0.195	0.312	0.098	-0.418	0.807	0.623	.533
Kargarfard 2012	Combined	3.533	0.566	0.320	2.424	4.642	6.243	.000
Kooshiar 2015	Social well-being	1.655	0.381	0.145	0.908	2.401	4.342	.000
Langeskov-Christensen 2021a	Subjective well-being	0.153	0.216	0.047	-0.271	0.576	0.707	.480
Langeskov-Christensen 2021b	Social well-being	0.059	0.216	0.047	-0.364	0.481	0.271	.786
Learmonth 2012	Subjective well-being	0.312	0.367	0.135	-0.408	1.032	0.850	.395
McAuley 2015	Subjective well-being	0.528	0.300	0.090	-0.060	1.117	1.759	.079
Mokhtarzade 2021	Subjective well-being	0.894	0.324	0.105	0.260	1.529	2.763	.006
Najafi 2023	Subjective well-being	1.406	0.408	0.166	0.607	2.205	3.448	.001
Oken 2004	Combined	0.228	0.343	0.117	-0.444	0.899	0.664	.507
Ozdogar 2020	Subjective well-being	0.217	0.331	0.109	-0.431	0.866	0.657	.511
Ozkul 2020	Combined	0.836	0.358	0.128	0.134	1.537	2.334	.020
Paul 2014	Subjective well-being	0.100	0.365	0.133	-0.616	0.816	0.273	.785
Petajan 1996	Combined	1.379	0.336	0.113	0.720	2.037	4.102	.000
Razazian 2016	Subjective well-being	2.234	0.425	0.180	1.401	3.066	5.259	.000
Romberg 2005	Combined	0.073	0.205	0.042	-0.329	0.475	0.355	.722
Schulz 2004	Combined	0.656	0.392	0.154	-0.113	1.425	1.673	.094
Straudi 2022	Social well-being	-0.143	0.334	0.111	-0.797	0.511	-0.428	.668
Sutherland 2001	Combined	0.728	0.441	0.195	-0.137	1.593	1.649	.099
Thomas 2017	Combined	0.313	0.367	0.135	-0.407	1.033	0.851	.395
Tollár 2020	Subjective well-being	-0.083	0.394	0.155	-0.854	0.689	-0.210	.833
Pooled		0.780	0.152	0.023	0.483	1.077	5.145	.000
Prediction Interval		0.780			-0.876	2.436		

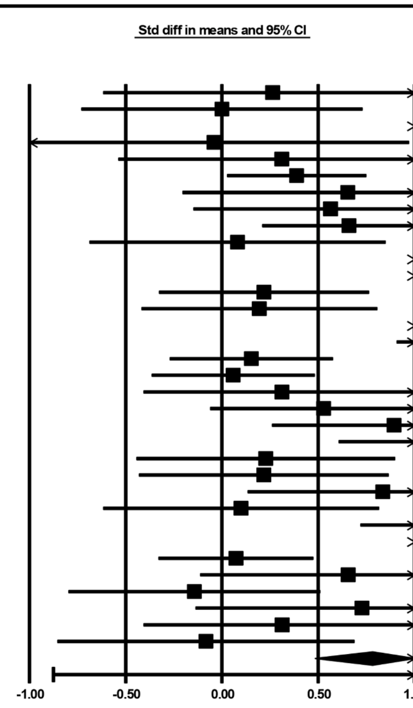
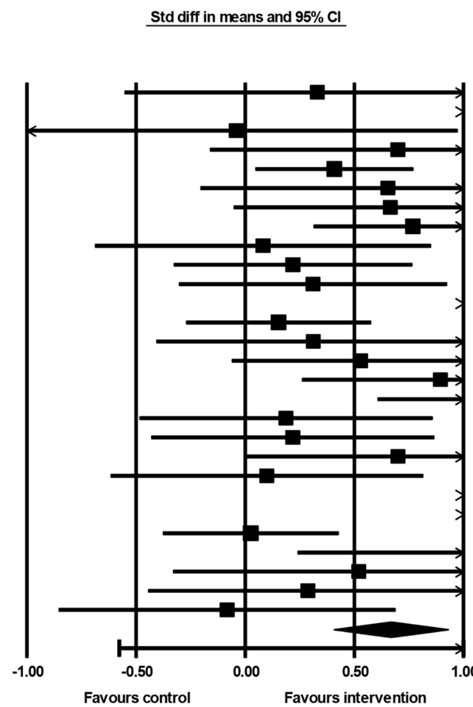


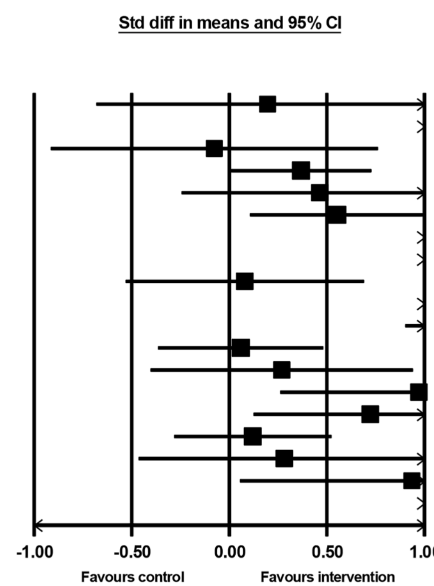
Fig. 2. Forest plot of the effects of exercise on overall well-being.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ahmadi 2010	0.330	0.450	0.203	-0.552	1.213	0.734	.463
Bahmani 2022	9.687	1.637	2.681	6.478	12.896	5.917	.000
Buttolph 2021	-0.041	0.516	0.267	-1.053	0.972	-0.078	.937
Cakit 2010	0.699	0.440	0.193	-0.162	1.561	1.591	.112
Carter 2014	0.409	0.184	0.034	0.047	0.770	2.215	.027
Correale 2021	0.654	0.438	0.192	-0.205	1.512	1.493	.135
Escudero-Uribe 2017	0.665	0.366	0.134	-0.052	1.382	1.817	.069
Fleming 2021	0.768	0.232	0.054	0.313	1.222	3.312	.001
Hebert 2011	0.081	0.392	0.154	-0.688	0.850	0.207	.836
Heinrich 2021	0.219	0.278	0.077	-0.327	0.764	0.785	.432
Jeong 2021	0.310	0.313	0.098	-0.304	0.924	0.990	.322
Kargarfard 2012	3.435	0.687	0.472	2.089	4.782	5.001	.000
Langeskov-Christensen 2021a	0.153	0.216	0.047	-0.271	0.576	0.707	.480
Learmonth 2012	0.312	0.367	0.135	-0.408	1.032	0.850	.395
McAuley 2015	0.528	0.300	0.090	-0.060	1.117	1.759	.079
Mokhtarzade 2021	0.894	0.324	0.105	0.260	1.529	2.763	.006
Najafi 2023	1.406	0.408	0.166	0.607	2.205	3.448	.001
Oken 2004	0.186	0.342	0.117	-0.484	0.857	0.545	.586
Ozdogar 2020	0.217	0.331	0.109	-0.431	0.866	0.657	.511
Ozkul 2020	0.700	0.353	0.125	0.007	1.392	1.980	.048
Paul 2014	0.100	0.365	0.133	-0.616	0.816	0.273	.785
Petajan 1996	2.034	0.364	0.133	1.320	2.748	5.586	.000
Razazian 2016	2.234	0.425	0.180	1.401	3.066	5.259	.000
Romberg 2005	0.025	0.205	0.042	-0.377	0.428	0.123	.902
Schulz 2004	1.030	0.403	0.163	0.240	1.820	2.555	.011
Sutherland 2001	0.520	0.434	0.188	-0.330	1.370	1.199	.231
Thomas 2017	0.287	0.374	0.140	-0.445	1.019	0.768	.442
Tollár 2020	-0.083	0.394	0.155	-0.854	0.689	-0.210	.833
Pooled	0.666	0.133	0.018	0.405	0.928	5.004	.000
Prediction Interval	0.666			-0.577	1.910		



A

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ahmadi 2010	0.197	0.448	0.201	-0.682	1.076	0.439	.660
Bahmani 2022	3.928	0.786	0.617	2.388	5.467	5.000	.000
Cakit 2010	-0.077	0.427	0.183	-0.914	0.761	-0.179	.858
Carter 2014	0.368	0.184	0.034	0.007	0.728	1.997	.046
Escudero-Uribe 2017	0.464	0.361	0.130	-0.244	1.171	1.285	.199
Fleming 2021	0.553	0.228	0.052	0.106	1.000	2.426	.015
Hebert 2018	4.383	0.423	0.179	3.553	5.212	10.359	.000
Heine 2017	1.910	0.256	0.065	1.408	2.411	7.462	.000
Jeong 2021	0.079	0.312	0.097	-0.531	0.690	0.254	.799
Kargarfard 2012	3.652	0.577	0.333	2.520	4.784	6.325	.000
Kooshiar 2015	1.648	0.381	0.145	0.902	2.394	4.329	.000
Langeskov-Christensen 2021b	0.059	0.216	0.047	-0.364	0.481	0.271	.786
Oken 2004	0.269	0.343	0.118	-0.404	0.941	0.783	.433
Ozkul 2020	0.972	0.363	0.132	0.261	1.683	2.680	.007
Petajan 1996	0.723	0.305	0.093	0.124	1.322	2.367	.018
Romberg 2005	0.121	0.205	0.042	-0.282	0.523	0.587	.557
Schulz 2004	0.282	0.381	0.145	-0.465	1.028	0.740	.459
Sutherland 2001	0.936	0.449	0.202	0.055	1.816	2.083	.037
Pooled	1.046	0.243	0.059	0.569	1.523	4.300	.000
Prediction Interval	1.046			-1.054	3.145		



B

Fig. 3. Forest plot of the effects of exercise on subjective well-being (A) and social well-being (B).

exercise intervention (Escudero-Uribe et al., 2017; Thomas et al., 2017; Tollár et al., 2020), two studies (Fleming et al., 2021; Najafi et al., 2023) Pilates, one study qigong (Buttolph et al., 2021) and a telerehabilitation exercise program (Incheol Jeong et al., 2021), while ten studies delivered multicomponent exercise interventions: aerobic, resistance training, and balance (Cakit et al., 2010; Carter et al., 2014; Learmonth et al., 2012; Paul et al., 2014), aerobic and resistance training (Correale et al., 2021; Mokhtarzade et al., 2021; Romberg et al., 2005), aerobic and Pilates (Ozkul et al., 2020), balance and arm and core stability exercises (Ozdogar et al., 2020), and resistance training, flexibility, and balance (McAuley et al., 2015).

3.2.3. *Psychological well-being*

Only two studies measured psychological well-being. Andreu-Caravaca et al. (2022) observed a statistically significant group x time interaction for general physical self-perception (p = .030) after a 10-week fast-velocity concentric resistance training. Thomas et al. (2017) did not observe statistically significant differences in the MS Self-efficacy Scale and the Spinal Cord Injury Self-Efficacy Scale after a home-based balance intervention with Nintendo Wii.

3.2.4. *Social well-being*

Exercise improved social well-being (d = 1.046; 95 % CI 0.569, 1.523; 95 %PI −1.054, 3.145; 863 participants, 18 RCTs; $I^2 = 91$ %, $Tau^2 = 0.96$, Q = 180.386; low certainty evidence; Fig. 3B). Seven studies

(Ahmadi et al., 2010; Bahmani et al., 2022; Heine et al., 2017; Langeskov-Christensen et al., 2021a; Oken et al., 2004; Petajan et al., 1996; Schulz et al., 2004) delivered an aerobic intervention, three studies (Kargarfard et al., 2012; Kooshiar et al., 2015; Sutherland et al., 2001) an aquatic exercise intervention, two studies an aerobic, resistance training, and balance multimodal intervention (Cakit et al., 2010; Carter et al., 2014), and a balance exercise intervention (Escudero-Uribe et al., 2017; Hebert et al., 2018), one study an aerobic and resistance training combined intervention (Romberg et al., 2005), Pilates (Fleming et al., 2021), an aerobic and Pilates combined intervention (Ozkul et al., 2020), and a telerehabilitation exercise program (Incheol Jeong et al., 2021).

3.2.5. Health-related quality of life

Exercise improved HRQoL ($d = 0.568$; 95 % CI 0.396, 0.740; 95 % PI −0.292, 1.428; 1580 participants, 39 studies; $I^2 = 62$ %, Tau$^2 = 0.415$, $Q = 100.400$; low certainty evidence; Fig. 4). Nine studies (Ahmadi et al., 2010; Bahmani et al., 2022; Feys et al., 2016; Heinrich et al., 2021; Langeskov-Christensen et al., 2021b; Mokhtarzade et al., 2017; Oken et al., 2004; Petajan et al., 1996; Schulz et al., 2004) delivered an aerobic intervention, six studies (Escudero-Uribe et al., 2017; Hebert et al., 2018; Prosperini et al., 2013; Thomas et al., 2017; Tollár et al., 2020; Yazgan et al., 2020) a balance exercise intervention, four studies (Kargarfard et al., 2012; Kooshiar et al., 2015; Razazian et al., 2016; Sutherland et al., 2001) an aquatic exercise intervention, two studies (Dalgas et al., 2010; Dodd et al., 2011) a resistance training intervention, one study a multicomponent individualized home exercise program (Toomey and Coote, 2017), a telerehabilitation exercise program (Incheol Jeong et al., 2021), qigong (Buttolph et al., 2021), and Pilates (Najafi et al., 2023), while 13 studies delivered multicomponent interventions: aerobic, resistance training, and balance (Cakit et al., 2010; Carter et al., 2014, 2013; Learmonth et al., 2012; Paul et al., 2014), aerobic and resistance training (Correale et al., 2021; Romberg et al., 2005), resistance training, flexibility, and balance (McAuley et al., 2015; Tarakci et al., 2013), balance, resistance training, and functional training (Louie et al., 2021), gait, balance, and functional training (Gunn et al., 2021), balance and arm and core stability exercises (Ozdogar et al., 2020), and aerobic and Pilates (Ozkul et al., 2020). Sensitivity analyses showed that aerobic training improved HRQoL ($d = 1.389$; 95 % CI 0.696, 2.083; 325 participants, 9 studies; $I^2 = 88$ %, Tau$^2 = 0.941$, $Q = 67.500$; supplementary material S2, Fig. 8), while the effects of combined aerobic and resistance training program are uncertain ($d = 0.529$; 95 % CI −0.176, 1.234; 343 participants, 7 studies; $I^2 = 89$ %, Tau$^2 = 0.78$, $Q = 52.231$; supplementary material S2, Fig.10).

3.3. Adverse events

3.3.1. Serious adverse events

Fifteen studies (Andreu-Caravaca et al., 2022; Bahmani et al., 2022; Carter et al., 2014, 2013; Dodd et al., 2011; Escudero-Uribe et al., 2017; Fleming et al., 2021; Grubic Kezele et al., 2021; Hebert et al., 2011; Kargarfard et al., 2012; McAuley et al., 2015; Ozkul et al., 2020; Tarakci et al., 2013; Thomas et al., 2017; Tollár et al., 2020) stated that no SAEs were recorded. Seven studies (Cakit et al., 2010; Gunn et al., 2021; Hebert et al., 2018; Langeskov-Christensen et al., 2021a, 2021b; Louie et al., 2021; Petajan et al., 1996) from six RCTs reported SAEs in both the intervention and control group; therefore, six RCTs could be pooled in the meta-analysis. The effects of exercise on the total number of SAEs are uncertain (IRR = 0.957, 95 % CI 0.470, 1.948, 329 participants, 6 studies, $I^2 = 0$ %, Tau$^2 = 0.000$, $Q = 4.528$; low certainty evidence;

Study name	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ahmadi 2010	0.506	0.454	0.206	-0.385	1.396	1.113	.266
Bahmani 2022	5.190	0.959	0.920	3.310	7.070	5.411	.000
Buttolph 2021	-0.323	0.520	0.270	-1.341	0.695	-0.621	.534
Cakit 2010	0.112	0.428	0.183	-0.726	0.950	0.263	.793
Carter 2014	0.927	0.192	0.037	0.551	1.304	4.827	.000
Correale 2021	0.319	0.430	0.185	-0.523	1.161	0.742	.458
Dalgas 2010	0.568	0.367	0.134	-0.150	1.287	1.550	.121
Dodd 2011	0.361	0.231	0.054	-0.092	0.815	1.561	.118
Escudero-Uribe 2017	0.385	0.360	0.129	-0.320	1.090	1.070	.284
Feys 2016	0.857	0.322	0.104	0.225	1.489	2.657	.008
Gunn 2021	0.256	0.287	0.082	-0.307	0.818	0.891	.373
Hebert 2018	0.392	0.232	0.054	-0.062	0.846	1.692	.091
Heinrich 2021	0.220	0.278	0.078	-0.326	0.766	0.790	.430
Jeong 2021	0.462	0.315	0.099	-0.155	1.080	1.467	.142
Kargarfard 2012	3.479	0.692	0.479	2.123	4.836	5.026	.000
Kooshiar 2015	1.729	0.385	0.149	0.973	2.484	4.485	.000
Langeskov-Christensed 2021b	0.043	0.216	0.047	-0.380	0.466	0.200	.841
Learmonth 2012	0.072	0.365	0.133	-0.644	0.788	0.197	.844
Louie 2021	0.625	0.498	0.248	-0.350	1.601	1.257	.209
McAuley 2015	0.366	0.298	0.089	-0.217	0.949	1.229	.219
Mokhtarzade 2017	0.837	0.331	0.110	0.188	1.487	2.528	.011
Najafi 2023	1.141	0.394	0.155	0.369	1.912	2.897	.004
Negahban 2013	0.724	0.421	0.178	-0.102	1.550	1.719	.086
Oken 2004	0.083	0.342	0.117	-0.586	0.753	0.244	.807
Ozdogar 2020	1.033	0.351	0.123	0.345	1.721	2.942	.003
Ozkul 2020	1.395	0.382	0.146	0.645	2.144	3.647	.000
Paul 2014	0.110	0.365	0.134	-0.606	0.827	0.302	.763
Petejan 1996	1.115	0.318	0.101	0.492	1.738	3.506	.000
Prosperini 2013	0.574	0.340	0.116	-0.093	1.241	1.687	.092
Romberg 2005	0.046	0.206	0.043	-0.358	0.450	0.224	.823
Schulz 2004	0.697	0.390	0.152	-0.068	1.462	1.786	.074
Straudi 2014	0.526	0.415	0.172	-0.288	1.340	1.267	.205
Straudi 2022	0.274	0.335	0.112	-0.383	0.930	0.817	.414
Sutherland 2001	0.362	0.430	0.185	-0.481	1.204	0.842	.400
Tarakci 2013	0.246	0.202	0.041	-0.150	0.641	1.216	.224
Thomas 2017	0.181	0.372	0.139	-0.549	0.911	0.486	.627
Tollár 2020	0.131	0.394	0.155	-0.641	0.903	0.333	.739
Toomey 2017	0.343	0.285	0.081	-0.216	0.901	1.203	.229
Yazgan 2020	1.118	0.416	0.173	0.303	1.934	2.688	.007
Pooled	0.568	0.088	0.008	0.396	0.740	6.476	.000
Prediction Interval	0.568			-0.292	1.428		

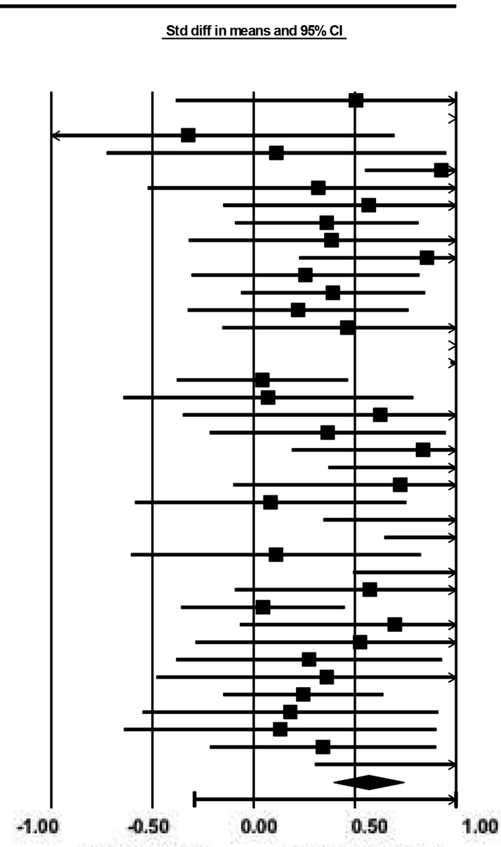


Fig. 4. Forest plot of the effects of exercise on HRQoL.

supplementary material S4, Fig. 19). All the SAEs reported by Cakit et al. (2010), Hebert et al. (2018), and Petajan et al. (1996) were MS relapses, and the authors did not specify whether they were related to the intervention, while Gunn et al. (2021), Langeskov-Christensen et al. (2021a, 2021b), and Louie et al. (2021) stated that all the SAEs were not attributable to the intervention. Twenty-six other RCTs reported on SAEs. Heine et al. (2017) observed an odd ratio of reporting a relapse corrected for disease severity of 0.277 (95 % CI 0.097, 0.787; $p = .016$) in favor of aerobic training. Mokhtarzade et al. (2017) reported one relapse in the intervention group, Mokhtarzade et al. (2021) two relapses in the control group, and Straudi et al. (2022) reported one relapse in each group. Heinrich et al. (2021) reported two non-intervention-related SAEs in the intervention group (a participant sustained a lower leg fracture and one other developed pyelonephritis). Prosperini et al. (2013) stated that 70 % of the participants reported at least one adverse event, five of which, deemed moderate and mild, attributable to the intervention, while a 54-year-old female with an EDSS score of 5.0 assigned to the control group experienced a motor relapse. Four studies reported on adverse events across groups. Feys et al. (2016) reported a relapse-related hospitalization, Oken et al. (2004) reported six adverse events (three surgeries, two MS exacerbations, one low back pain related to a car accident) unrelated to the intervention, Paul et al. (2014) an elbow fracture, an hospital admission due to infection, and breast cancer diagnosis unrelated to intervention, and Yazgan et al. (2020) reported one exacerbation among 42 participants.

3.3.2. Non-serious adverse events

Eight studies (Buttolph et al., 2021; Dodd et al., 2011; Feys et al., 2016; Hebert et al., 2011; Heinrich et al., 2021; Langeskov-Christensen et al., 2021; Mokhtarzade et al., 2021; Thomas et al., 2017) reported some non-SAEs. Buttolph et al. (2021) stated that two participants reported back pain, and one participant developed spasticity. Dodd et al. (2011) stated that 25 of 36 participants in the intervention group reported muscle soreness that was resolved in a few days. Feys et al. (2016) reported that two participants sustained strain injuries of the ankle and one calf muscle strain, while one other participant experienced hip and groin pain. Hebert et al. (2011) reported that one participant sustained an ankle sprain, that did not require medical care and did not interfere with participation in the study, while Heinrich et al. (2021) stated than one patient reported neck and shoulder pain. Langeskov-Christensen et al. (2021a) and Langeskov-Christensen et al. (2021b) reported one participant with back pain and a case of a bladder dysfunction in the control group. Mokhtarzade et al. (2021) stated that some contusions were reported at the beginning of the exercise program, especially the first week, while Thomas et al. (2017) reported 11 non-SAEs, which included five falls or near falls, pain in leg, pain in back, aggravation of existing scar tissue, discomfort in hand, exacerbation of a pre-existing knee injury, and toe contusion on balance board.

3.4. Retention and adherence

The average (± SD) retention rates were 88.21 % ± 11.00 % for the intervention groups and 88.79 % ± 16.86 % for the control groups. Twenty-three studies (Buttolph et al., 2021; Cakit et al., 2010; Carter et al., 2014, 2013; Correale et al., 2021; Dalgas et al., 2010; Dodd et al., 2011; Escudero-Uribe et al., 2017; Feys et al., 2016; Grubic Kezele et al., 2021; Hebert et al., 2018; Heine et al., 2017; Heinrich et al., 2021; Langeskov-Christensen et al., 2021a, 2021b; Learmonth et al., 2012; Louie et al., 2021; Mokhtarzade et al., 2021; Oken et al., 2004; Ozkul et al., 2020; Petajan et al., 1996; Prosperini et al., 2013; Straudi et al., 2022; Sutherland et al., 2001; Tollár et al., 2020) from 22 RCTs reported on adherence. The average adherence was 85.48 % ± 11.95 %; the adherence to supervised interventions was 89.80 % ± 8.84 % ($n = 11$), 90.75 % ± 3.95 % to unsupervised interventions ($n = 3$), and 83.60 % ± 8.52 % to interventions that combined a supervised and an unsupervised component ($n = 5$). Buttolph et al. (2021) reported that 100 % of the participants at least 50 % of the classes, and 50 % at least 70 % of the classes. Heinrich et al. (2021) reported that participants attended 67 ± 26.4 training sessions. Oken et al. (2004) reported an adherence of 65 % to the weekly classes and of 45 % to the home exercise program. Straudi et al. (2022) reported an adherence of 62 % to a home-based task-oriented circuit training program following a 2-week supervised program.

3.5. Risk of bias

Forty-two of the 49 included studies presented some concerns for at least one domain. The risk of bias summary across studies is reported in Fig. 5, and the risk of bias for each domain for the individual studies is presented in the supplementary material (supplementary material S4, Fig. 20). The visual inspection of funnel plot did not show evidence of publication bias (supplementary material S4, Fig. 21–24).

4. Discussion

Exercise can improve overall well-being, in particular subjective well-being and social well-being, and health-related quality of life in PwMS. The effects on psychological well-being and on the rate of adverse events are uncertain; however, 15 studies reported that no SAEs occurred during the interventions. The results of our sensitivity analyses support the use of aerobic training as a strategy for improving mental health and HRQoL in PwMS, and combined aerobic and resistance training programs showed positive effects on mental health. We detected moderate certainty evidence that exercise improve overall well-being, subjective well-being and HRQoL, and the low certainty evidence with regard to social well-being and SAEs suggest authors adopt more rigorous methodologies to minimize the potential for bias. Finally, more studies in PwMS with ≥ 65 years of age and/or with a higher level of impairments are needed before making final inferences on the effectiveness and safety of exercise in such subgroups.

We reported medium-to-large effects sizes on the effect of exercise to improve overall well-being, subjective well-being, and HRQoL, and a large effect size with regard to social well-being. Our results are in line with previous meta-analyses on the effects of exercise on QoL in PwMS (Alphonsus et al., 2019; Motl and Gosney, 2008), and with a systematic review that showed improvements of depressive symptoms after exercise interventions in PwMS diagnosed with depression (Kyriakatis et al., 2022). We decided to investigate the effects of exercise on mental health in PwMS without restricting our analysis to those diagnosed with depression, as mood disorders are often undiagnosed, especially in primary care (Cepoiu et al., 2008; Mitchell et al., 2009). Moreover, in accordance with Diener's definition of subjective well-being, which encompasses emotions, affects, happiness, and satisfaction with life, we expanded our analysis beyond depression and anxiety, and included any validated outcome measures that assessed constructs of subjective well-being in line with Diener's theorization. Furthermore, PwMS can experience limitations and restrictions in terms of interpersonal relationships, community life, and recreation and leisure activities(Coenen et al., 2011); therefore, we assessed the effect of exercise on constructs of social well-being, to assess the potential of exercise at improving social participation and interactions in PwMS. Only two studies reported on psychological well-being, and the results were conflicting. A meta-analysis in people with spinal cord injury (Ponzano et al., review) showed a medium effect size on the effect of exercise on psychological well-being; therefore, more studies in PwMS should explore the impact that exercise may have on psychological well-being, as constructs such as self-esteem and self-efficacy are related to HRQoL (Barbalat et al., 2022; Peters et al., 2019; Yazdi-Ravandi et al., 2013); hence, improvements in psychological well-being may lead to better HRQoL. Many definitions of HRQoL have been proposed over the years, and no consensus upon a comprehensive definition has been reached. Exercise and physical activity studies have often conceptualized HRQoL

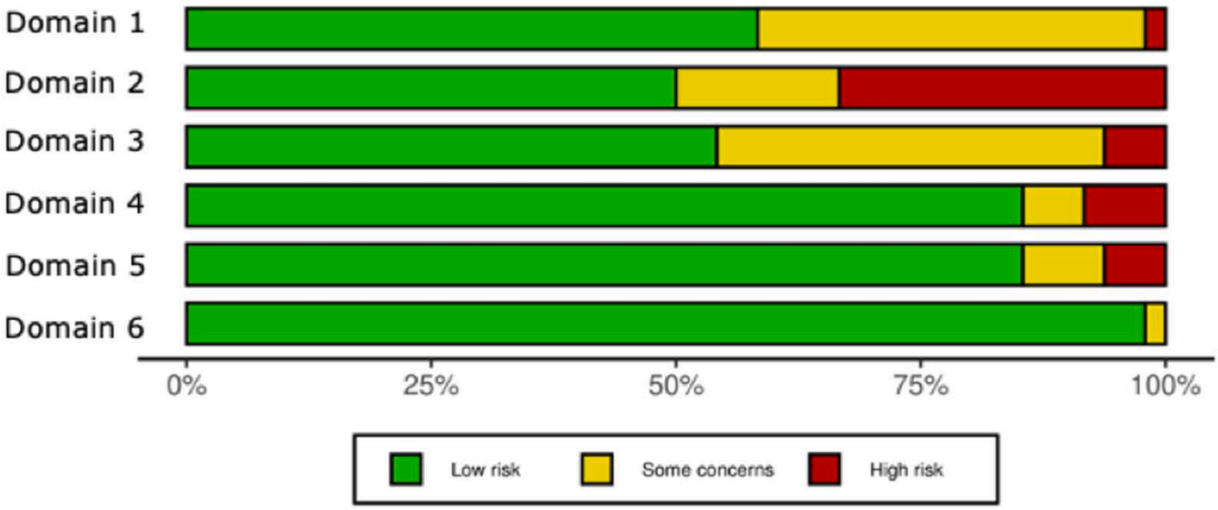


Fig. 5. Review author's judgement about each risk of bias domain presented as percentage across the included studies. NOTE. D1= bias arising from randomization process; D2= deviations from the intended interventions (effect of assignment to intervention); D3= deviations from the intended interventions (effect of adhering to intervention); D4= missing outcome data; D5= measurement of the outcome; D6= selection of reported results.

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With control	With exercise	Relative effect (95% CI)	Risk with control	Risk difference with exercise
Overall well-being											
1410 (34 RCTs)	serious[a]	not serious[b]	not serious	not serious	none	⊕⊕⊕◯ Moderate	701	709	-	-	d **0.78 SD higher** (0.483 higher to 1.077 higher)
Subjective well-being											
1081 (28 RCTs)	serious[a]	not serious[c]	not serious	not serious	none	⊕⊕⊕◯ Moderate	541	540	-	-	d **0.666 SD higher** (0.405 higher to 0.928 higher)
Psychological well-being											
29 (2 RCTs)	serious[d]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	Andreu-Caravaca et al observed a statistically significant group x time interaction in general physical self-perception after a 10-week resistance training. Thomas et al did not observe statistically significant differences in the MS Self-efficacy Scale after a balance intervention with Nintendo Wii.				
Social well-being											
816 (16 RCTs)	serious[a]	serious[f]	not serious	not serious	none	⊕⊕◯◯ Low	409	407	-	-	d **1.046 SD higher** (0.569 higher to 1.523 higher)
Health-related quality of life											
1490 (39 RCTs)	serious[a]	not serious[c]	not serious	not serious	none	⊕⊕⊕◯ Moderate	740	750	-	-	d **0.568 SD higher** (0.396 higher to 0.74 higher)
Serious adverse events											
329 (6 RCTs)	serious[g]	not serious	not serious	serious[h]	none	⊕⊕◯◯ Low	17/164 (10.4%)	15/165 (9.1%)	**IRR 0.957** (0.470 to 1.948)	104 per 1,000	**4 fewer per 1,000** (from 55 fewer to 98 more)
Non-serious adverse events											
374 (8 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	Eight studies reported some non-SAEs, including pain or muscle soreness (n = 6 studies), strains and sprains (n = 2 studies), contusions (n = 2 studies).				

Fig. 6. GRADE summary of findings table. CI: Confidence interval; d: Standardized difference in means; IRR: incidence rate ratio. Explanations. A. The majority of the studies presented some concerns or were at high risk of bias for at least one domain. B. Outcomes measures of subjective well-being, psychological well-being, and social well-being were pooled into a meta-analysis to determine the effect of exercise on overall well-being, and that explain the heterogeneity. Moreover, the substantial heterogeneity does not reduce the confidence in the recommendation of exercise to improve well-being. C. Heterogeneity is explained by different outcome measures and duration of interventions. D. One study (Andreu-Caravaca et al., 2022) presents some concerns for randomization process and deviation from intended interventions (effect of adhering to intervention). E. We could not perform a meta-analysis; results are presented as a narrative synthesis. F. Substantial heterogeneity ($I^2 = 91$ %) that could not be explained by heterogeneity in interventions or outcome measures. G. All of the studies presented some concerns or were rated at high risk of bias for at least one domain. H. CI crosses the no-difference line.

as physical, subjective, and social HRQoL (Courneya and Friedenreich, 1999; Gillison et al., 2009; Rejeski et al., 1996). In the present work, we used the Dijkers' (1977) definition of HRQoL to guide the decision on the outcome measures to extract and pool in the meta-analyses, as we were interested in determining the effects of exercise on those component of quality of life that are commonly negatively impacted by the symptoms of MS. In summary, the results of the present study endorse the role of exercise for improving aspects of mental health and HRQoL in PwMS.

Our meta-analysis showed uncertainty in the effects of exercise on SAEs. Fifteen studies stated that no SAEs occurred, and most of the SAEs were relapses or deemed not related to the intervention by the authors of the studies. Studies in animal models and preliminary evidence in humans show a potential disease-modifying effect of exercise in PwMS (Dalgas and Stenager, 2012), but more larger scale studies are needed to validate this hypothesis. While we cannot substantiate such theory due to the low number of studies that we could include in the meta-analysis, we can assert that exercise can be a safe tool to promote mental health and HRQoL in PwMS. We observed similar retention rates between intervention and control groups, in line with findings from a meta-analysis of exercise interventions in people with multimorbidity (Harris et al., 2021). The overall adherence to interventions was high and comparable between supervised and unsupervised interventions. A meta-analysis of high-intensity interval training (HIIT) and moderate intensity continuous training (MICT) observed a greater adherence to supervised programs compared to unsupervised interventions (Santos et al., press). This difference can be explained by the very small number of studies that reported on the adherence to unsupervised interventions and by the different types of interventions of the studies in our review.

The high number of included studies is a major strength of the present work. We were able to provide a compelling synthesis of the evidence on the benefits of exercise on overall well-being and HRQoL, as well as on constructs of well-being that can be of importance to people with physical disabilities (i.e., subjective well-being and social well-being). Furthermore, many studies reported on SAEs and non-SAEs, thus allowing us to make inferences on the safety of exercise in addition to its effectiveness. We also acknowledge some limitations to our work. First, we could not perform a meta-analysis to determine the effect of exercise on psychological well-being due to the lower number of studies, hence the effect of exercise on psychological well-being in PwMS is still to be determined. Furthermore, the mean age was < 65 years in every study, and the majority of the studies were performed in adults with a mild-to-moderate level of disability; therefore, caution is recommended when generalizing the findings of this review to older adults or people with a more severe disability. Finally, we observed low certainty evidence with regard to social well-being and SAEs, mainly because of risk of bias and heterogeneity. Most of the studies did not provide adequate details on their randomization process, did not perform intention-to-treat analysis (ITT), or did not report on adherence. Performing ITT is relevant at a health-policy level, as it results in an effect size that is not affected by unmeasured prognostic factors, and thus provides insights on the implementation of the intervention in a specific population, while measuring and reporting on adherence provides information on the efficacy or effectiveness of the intervention if implemented as intended (Higgins et al., 2022).

Our work provides some important implications for both clinical practice and research. Exercise can be an effective and safe tool to improve mental health and HRQoL in PwMS. Exercise programs including an aerobic component, alone or combined with resistance training, should be implemented in the MS population, and individuals living with MS should be referred to a physiotherapist or to an exercise physiologist to receive a tailored exercise program. Future research should investigate whether the effect of exercise on psychosocial outcomes is different in people with relapsing-remitting MS compared to those with progressive forms of MS. Indeed, recent evidence suggest a possible synergistic effect of aerobic exercise on motor, cognitive and psychosocial domains in the course of relapsing-remitting MS (Feinstein et al., 2023). However, it remains unclear whether clinically meaningful improvements can be achieved in those with progressive MS. The studies included in the present review were performed in lower-middle-, upper-middle-, and high-income countries, and the most studies were conducted in a lower-middle-income country (Iran, $n = 8$). Such a diversity allows the generalizability of our findings to PwMS of different race, income, and socioeconomic status, thus supporting the implementation of exercise for improving mental health and HRQoL in a wide array of MS populations. Future research studies should target individuals 65 years or older and people with higher levels of impairments, as well as focus on exploring the effects of exercise on psychological well-being. We recommend authors adopt rigorous methodologies, for example perform both ITT and per-protocol analysis, utilize proper techniques to generate and conceal the allocation sequence, and monitor and report adherence.

5. Conclusion

Exercise can be an effective and safe strategy to improve subjective well-being, social well-being, and HRQoL in PwMS. Exercise interventions, especially aerobic or combined aerobic and resistance training, should be implemented in clinical practice to promote mental health and HRQoL in PwMS. Future research should determine the effects of exercise on psychological well-being and target individuals ≥ 65 years or with higher levels of impairments, as well as investigate whether the effects of exercise on mental health and HRQoL are different between people with relapsing-remitting MS and those with progressive forms of MS.

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CRediT authorship contribution statement

Luca Beratto: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Formal analysis, Data curation, Conceptualization. **Lara Bressy:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – review & editing. **Samuel Agostino:** Writing – review & editing, Software, Formal analysis, Data curation. **Francesca Malandrone:** Writing – review & editing, Visualization, Validation, Investigation, Formal analysis, Data curation. **Giampaolo Brichetto:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Conceptualization. **Matteo Ponzano:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Luca Beratto, Lara Bressy, Samuel Agostino, Francesca Malandrone, Giampaolo Brichetto, and Matteo Ponzano declare they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105473.

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