Multiple Sclerosis and Related Disorders 56 (2021) 103292

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

The prevalence of Myocardial Infarction among Multiple Sclerosis Patients: a Systematic Review and Meta-analysis

Mohammad Javad Tavallaei [a], Amir Hossein Tavallaei [b], Narges Ebrahimi [c], Hamed Ghoshouni [d], Alireza Afshari-Safavi [e], Shervin Badihian [f], Vahid Shaygannejad [c,g], Omid Mirmosayyeb [c,g,*]

[a] School of medicine, Iran university of medical sciences, Tehran, Iran
[b] School of medicine, Tehran University of medical sciences, Tehran, Iran
[c] Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[d] School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[e] Department of Biostatistics and Epidemiology, Faculty of Health, North Khorasan University of Medical Sciences, Bojnurd, Iran
[f] Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[g] Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran

ARTICLE INFO

Keywords:
Myocardial Infarction
Multiple Sclerosis
systematic review
meta-analysis
prevalence

ABSTRACT

Background: People with multiple sclerosis (PwMS) are suggested to have a higher death rate compared to the overall population. Increased risk and incidence of cardiovascular diseases is a possible contributing factor here, as these patients are suggested to be more prone to early death due to myocardial infarction (MI).
Aim: This systematic review aims to describe the prevalence of MI among PwMS in comparison to the non-MS population.
Method: We thoroughly searched for publications reporting the prevalence of MI among PwMS in PubMed, Scopus, Embase, and Web of Science. We excluded studies focusing on the following conditions: ischemic heart disease only, autopsy of PwMS, MS patients with a previous history of cardiovascular diseases, and MS diagnosed after MI. Moreover, we excluded reviews, editorials, and commentaries. We used the random effect model to calculate the pooled prevalence.
Results: We included nineteen studies, comprising 44 to 66616 participants. The overall prevalence of MI was 1.7% among PwMS. The pooled odds ratio estimate for MI was 1.41 in PwMS compared to the MS-free population.
Conclusions: Results of this systematic review confirms the increased risk of MI among PwMS. Consequently, cardiovascular diseases should be considered in the management of these patients.

LIST OF ABBREVIATIONS

MI	Myocardial Infarction
MS	Multiple Sclerosis
IHD	Ischemic Heart Disease
CVD	cardiovascular disease
95% CI	95% Confidence interval;

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune disease that affects over 2.8 million individuals globally (Walton et al., 2020). People with multiple sclerosis (PwMS) are at greater risk of early death in comparison to the general population (Capkun et al., 2015, Kaufman et al., 2014, Kingwell et al., 2013). Moreover, they tend to have more comorbidities, including infection-related hospitalizations (Christiansen et al., 2010), cardiovascular diseases (CVD) (Christiansen et al., 2010, Jadidi et al., 2013), and other autoimmune disorders (Christiansen, 2012, Berkovich et al., 2011). The autoimmune etiology of MS may have a role in developing some concomitant conditions such as type 1 diabetes and inflammatory bowel disease (Berkovich et al., 2011).

In the general population, cardiovascular disorders, such as ischemic heart disease (IHD), are the primary cause of mortality. IHD is caused by

* Corresponding Author.
E-mail address: omid.mirmosayyeb@gmail.com (O. Mirmosayyeb).

https://doi.org/10.1016/j.msard.2021.103292
Received 9 September 2021; Received in revised form 20 September 2021; Accepted 27 September 2021
Available online 30 September 2021
2211-0348/© 2021 Elsevier B.V. All rights reserved.

a mismatch between coronary artery blood flow and myocardial oxygen demand, which is generally caused by atherosclerosis in the coronary arteries. It refers to a collection of conditions that include stable and unstable angina, acute myocardial infarction (AMI), and sudden cardiac death (Marrie et al., 2019). Age, male sex, hypertension, hyperlipidemia, diabetes, IHD family history, and smoking are the major attributable risks for IHD (Nilsson et al., 2006).

On the other hand, MS may increase the chance of AMI incident (Christiansen et al., 2010, Jadidi et al., 2013). In addition, PwMS had a greater mortality rate compared to a matched non-MS population, when admitted to an intensive care unit because of CVDs (Marrie et al., 2014). While MS-related complications remain the primary cause of death in this group, CVDs are the second or third cause based on different studies (Marrie et al., 2015, Brønnum-Hansen et al., 2004). Despite the higher incidence of CVDs and associated mortality among PwMS, it might be neglected in the setting of MS as the "main" problem in these cases. To further investigate the prevalence of MI among MS cases, we conducted this systematic review and meta-analysis.

2. Method

This review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015)

2.1. Literature search strategy

The academic literature search was conducted on March 1, 2021, on four electronic databases (PubMed, Embase, Scopus, and Web of Science). The search strategy was adapted as follows: (comorbidities OR "Myocardial Infarction"[Mesh]) AND "Multiple Sclerosis"[Mesh] (all searches and references can be found in the appendix). We also screened references from the selected papers and other relevant citations for potential additional studies. We included unpublished data, data posted in data storage sites, conference papers, and thesis, if eligible.

2.2. Eligibility criteria

We considered studies investigating the prevalence of MI among PwMS. There were no language limitations.

Citations were excluded if they met any of the following: lack of relevance to the subject; lack of these factors: (1. adequating sample size, 2. appropriate statistical analysis, 3. describing subjects, 4. measuring in a standard way, 5. response rate, 6. sample frame, 7. study participants, 8. sufficient coverage, and 9. valid methods), just reporting IHD; autopsy studies on died MS patients; MS patients with the previous history of cardiovascular diseases; not original research (e.g., reviews, editorials, and letters); case reports and case series.

2.3. Study selection and data extraction

We used Mendeley to identify and merge the duplicate records. Two reviewers (NE and HG) separately screened titles and abstracts to identify studies eligible for inclusion. During the screening, disagreements were settled by consensus or submitted to a third reviewer (OM). one reviewer (MJT) hand-searched and reviewed the reference lists of the included papers for additional references. Studies were assessed for eligibility by reviewing title and abstract, and when there was not sufficient data in the title/abstract, the full text was reviewed.

Two reviewers (NE and HG) carried out separate extraction of data from included citations, including the first author's name, location of study (Region & Continent), type of study, MS patients characteristics (total number, gender, age, MS duration, MS onset), MI information (total number, gender, age), control group information (total number, gender, age, MI incidence), and outcome (hospitalization, death). A third reviewer (OM) was on hand to help resolve any disagreements between the two primary reviewers.

2.4. Assessment of risk of bias

Two reviewers, independently, assessed the quality of the studies using the Joanna Briggs Institute (JBI) checklist for prevalence studies (Ma et al., 2020).

2.5. Statistical analysis

Meta-analysis of the prevalence of MI among PwMS was done using Stata version 14 (StataCorp. 2015. College Station, TX). The Cochran's Q test and inconsistency index (I^2) were used to check heterogeneity. Pooled prevalence was estimated by random effect model (if I^2>50%) or fixed-effect model (if I^2<50%) according to the heterogeneity level. We also performed subgroup analysis by stratifying of study type (cross-sectional/case-control/cohort), continent (Europe/Australia/North America) and sex (female/male). Potential publication bias was visually investigated by funnel plot (logit transformed prevalence) along with Egger's regression and Begg's tests. The trim and fill method was applied when publication bias was observed. The level of statistical significance for all tests was considered to be less than 0.05.

3. Results

3.1. Search result

An aggregate of 2752 records were identified, including 1128 duplicate records, and the remaining 1624 were screened. We excluded 1202 citations by screening the titles. Furthermore, the remaining 403 records were excluded either after full-text review or because the full text were not retrievable. At the end, 19 citations (Capkun et al., 2015, Christiansen et al., 2010, Marrie et al., 2019, Allen et al., 2008, Benjaminsen et al., 2019, Cabreira et al., 2020, Capkun et al., 2014, Castelo-Branco et al., 2020, Chou et al., 2020, Giallafos et al., 2016, Goodman et al., 2014, Jick et al., 2018, Kresa-Reahl et al., 2017, Lindegard, 1985, Lo et al., Lo et al., Murtonen et al., 2018, Persson et al., 2020, Ragonese et al., 2017) were included in this systematic review and meta-analysis. Studies were published from 1985 till 2021 More details on excluded studies are available in the study flowchart in Figure 1.

3.2. Study Characteristics: Design and Participants

The included studies comprised 5 cross-sectional studies (Benjaminsen et al., 2019, Giallafos et al., 2016, Lo et al., Lo et al., Murtonen et al., 2018), 2 case-control studies (Allen et al., 2008, Persson et al., 2020), and 12 cohort studies (Capkun et al., 2015, Christiansen et al., 2010, Marrie et al., 2019, Cabreira et al., 2020, Capkun et al., 2014, Castelo-Branco et al., 2020, Chou et al., 2020, Goodman et al., 2014, Jick et al., 2018, Kresa-Reahl et al., 2017, Lindegard, 1985, Murtonen et al., 2018, Ragonese et al., 2017) (Table 1). The sample size varied from 44 (Cabreira et al., 2020) to 66616 (Kresa-Reahl et al., 2017) participants among these citations. The percentage of female participants was slightly higher (51%) compared to male participants (figure S4). Regarding the study location, 48% of studies were conducted in Europe, 11% in Australia, and 41% in North America (figure S3).

Heterogeneity and variety were apparent among studies, so nine prespecified factors were checked in each study; adequat sample size, appropriate statistical analysis, describing subjects, measuring in a standard way, response rate, sample frame, study participants, sufficient coverage, and valid methods. Of 19 included studies, 7 had reported all the eight factors (Capkun et al., 2015, Christiansen et al., 2010, Allen et al., 2008, Castelo-Branco et al., 2020, Chou et al., 2020, Murtonen et al., 2018, Persson et al., 2020) and the reaming studies have missingness in some of these factors (figure S6).

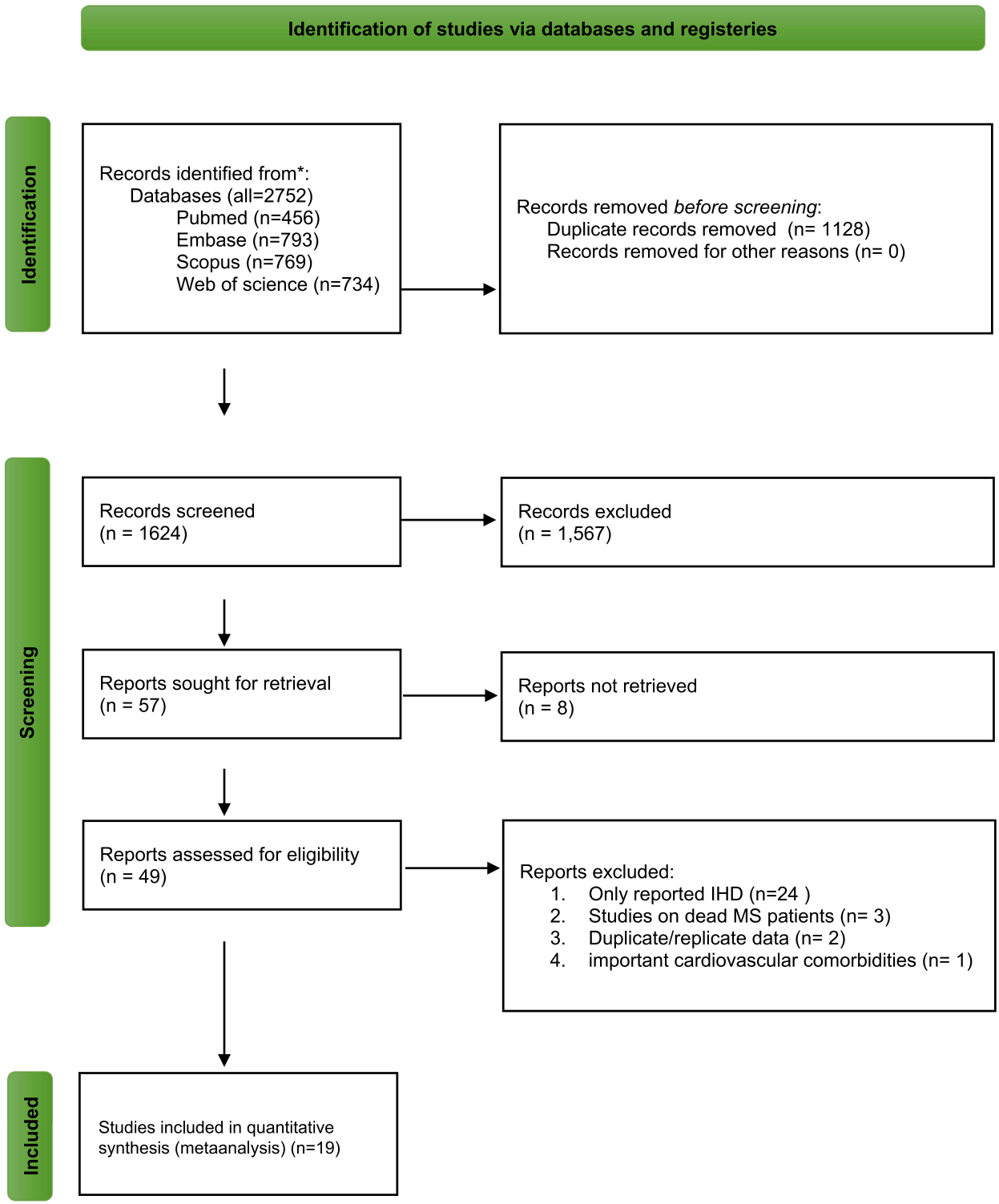

Fig. 1. PRISMA flow-chart

3.3. Assessment of risk of bias

We used the Joanna Briggs Institute (JBI) critical evaluation checklist to assess the quality of included citations. The JBI checklist is the most widely used method for assessing the quality of descriptive studies reporting prevalence data. It assesses the studies based on how many "YES" responses they receive to the checklist questions. The number of "YES" answers an article can earn ranges between 0 to 9 (Ma et al., 2020). Using this checklist, none of the included studies earned less than 4 "YES" answers, four studies earned between 4 to 6 "YES" answers, and nine studies earned more than 6 "YES" answers (Figure S7, Figure S8).

3.4. Assessment of publication bias

The funnel plot (Fig. 2), Egger's test (Bias=-0.980; P=0.713), and Begg's test (p=0.398) showed no evidence of publication bias in the included studies.

Table 1
Baseline characteristics of studies included in systematic review & meta-analysis.**Author (year)**

	Country of study	Study design	MS sample size	Percentage of male MS	MS age	Total MI occurrence	Other notes
(Lo, 2021a)	Australia	Cross-sectional	902	21.39% (193)	Mean 55.8 (±11.4)	17	MS duration Mean = 15.4 (±9.3)
(Lo, 2021b)	Australia	Cross-sectional	1518	20.35% (309)	Mean 55.7 (±11.2)	30	MS duration Mean = 20.5 (±10.9) MS onset Mean= 36 (±10.8)
(Castelo-Branco et al., 2020)	Sweden	cohort	6602	31.50% (2080)	Mean 40.9	35	
(Chou et al., 2020)	United Kingdom	cohort	2503	NR	NR	32	
(Ragonese et al., 2017)	Italy	cohort	264	40.15% (106)	NR	1	MS duration Mean = 11.3 ((Walton et al., 2020– 38) MS onset Mean= 48 (±10.3)
(Cabreira et al., 2020)	Portugal	Cohort	44	40.90% (Benjaminsen et al., 2019)	Median 47 (Chou et al., 2020)	8	MS duration Median = 13 (Jadidi et al., 2013) Hospitalized due to MI = 6
(Cabreira et al., 2020)	Portugal	Cohort	62	33.87% (Castelo-Branco et al., 2020)	Median 47.5 (Allen et al., 2008)	3	MS duration Median = 9.5 (Nilsson et al., 2006)
(Persson et al., 2020)	United States	Case-Control	6406	29.01% (1859)	Median 38 ((Jadidi et al., 2013– 85)	56	male occurrence MI = 18
(Persson et al., 2020)	United Kingdom	Case-Control	5726	28.11% (1610)	Median 41 ((Walton et al., 2020– 87)	19	male occurrence MI = 4
(Marrie et al., 2019)	Canada	cohort	14565	26.93% (3923)	Mean 44.1 (±12.7)	281	male occurrence MI = 151 MI occurrence mean age in MS patients = 63 (±11.1) Hospitalized due to MI = 281
(Benjaminsen et al., 2019)	Norwegian	Cross-sectional	637	NR	NR	11	
(Jick et al., 2018)	United Kingdom	Case-Control	5726	NR	NR	19	
(Murtonen et al., 2018)	Finland	Cross-sectional	1074	29.32% (315)	NR	18	Death du to MI= 1
(Kresa-Reahl et al., 2017)	United States	cohort	66616	23.75% (15826)	Mean 45.6 (±10.4)	490	male occurrence MI = 202
(Giallafos et al., 2016)	Greece	Cross-Sectional	183	46.99% (86)	NR	11	
(Capkun et al., 2015)	United States	Cohort	15684	23.53% (3692)	Mean 46 (±11.7)	639	
(Capkun et al., 2014)	United States	Cohort	49231	23.79% (11716)	Mean 47 (±10.3)	711	
(Goodman et al., 2014)	United States	Cohort	3010	NR	NR	30	
(Christiansen et al., 2010)	Danish	Cohort	13963	35.90% (5013)	Median 44.9	329	
(Allen et al., 2008)	United States	Case-Control	9949	27.19% (2706)	Mean 56.6	142	Hospitalized due to MI = 142 Death due to MI= 17
(Lindegard, 1985)	Sweden	Cohort	351	53.56% (188)	NR	26	male occurrence mi = 19

NR, Not Reported; MS, Multiple Sclerosis; MI, Myocardial Infarction;

3.5. Aggregated findings

The overall prevalence of MI was 1.7% (95% CI: 1.2%-2.3%; I^2=98.2%) with a range of from 0.3% (Persson et al., 2020) to 18.2% (Cabreira et al., 2020) among PwMS (*Figure S9)*. The forest plot of the prevalence estimates is reported in Figures 1, 3 and 4. The pooled prevalence of MI was 2.1% (95% CI: 1.4%-2.8%; I^2=58.4%), 0.8% (95% CI: 0.3%-1.6%; I^2=not reported) and 1.9% (95% CI: 1.2%-2.7%; I^2=98.8%) for cross-sectional, case-control and cohort studies, respectively (figure 2). The overall prevalence estimate of MI was 2.1% (95% CI: 1.1%-3.3%; I^2=96.5%) in Europe, 1.9% (95% CI: 1.4%-2.5%; I^2=not reported) in Australia, and 1.5% (95% CI: 0.9%-2.3%; I^2=99.2%) in North America (figure S3). Men had higher MI prevalence of 2.1% (95% CI: 0.9%-4%; I^2=97.5%) compared to women (0.8% [95% CI: 0.4%-1.2%; I^2=93.8%]) (Figure S4).

The pooled odds ratio (Figure S5) estimate for MI (Table S2) was 1.41 (95% CI: 1.33-1.49; I2=96%), indicating that the MS increased the odds of MI by 41%. Approximately, 1.5 million cases of MI occur annually in the United States; the yearly incidence rate is approximately 600 cases per 100,000 people that means MI prevalence is estimated to be 0.6% among the whole population (Rogers et al., 2008). Therefore, the prevalence of MI was increased 2.8 times among MS patients.

4. Discussion

PwMS have a higher death rate than the overall population (Williams et al., 2012). Increased risk and incidence of CVDs could potentially be a contributing factor to this elevated death rate. However, the exact underlying processes that lead to more risk of CVDs among these patients are unclear yet. Possible pathophysiology of developing CVD in PwMS are as follows: Changes in myocyte function, cardiovascular autonomous nervous system dysfunction, physical infirmity, oxidative stress, and endothelial dysfunction. Moreover, the development of early atherosclerosis in MS could theoretically increase the risk of MI in this population (Mincu et al., 2015). The incidence of cardiovascular events is almost doubled in PwMS compared to the general population (Persson et al., 2020) The pooled odds ratio estimate for MI was 1.41 (95% CI: 1.33-1.49; I2=96%), indicating that the MS increased the odds of MI by 41% in the analysis.

The range of reported prevalence of MI were from 0.003 (Persson et al., 2020) to 0.074% (Lindegard, 1985) in different studies. All of the studies were conducted in Europe, Australia, and North America. We did

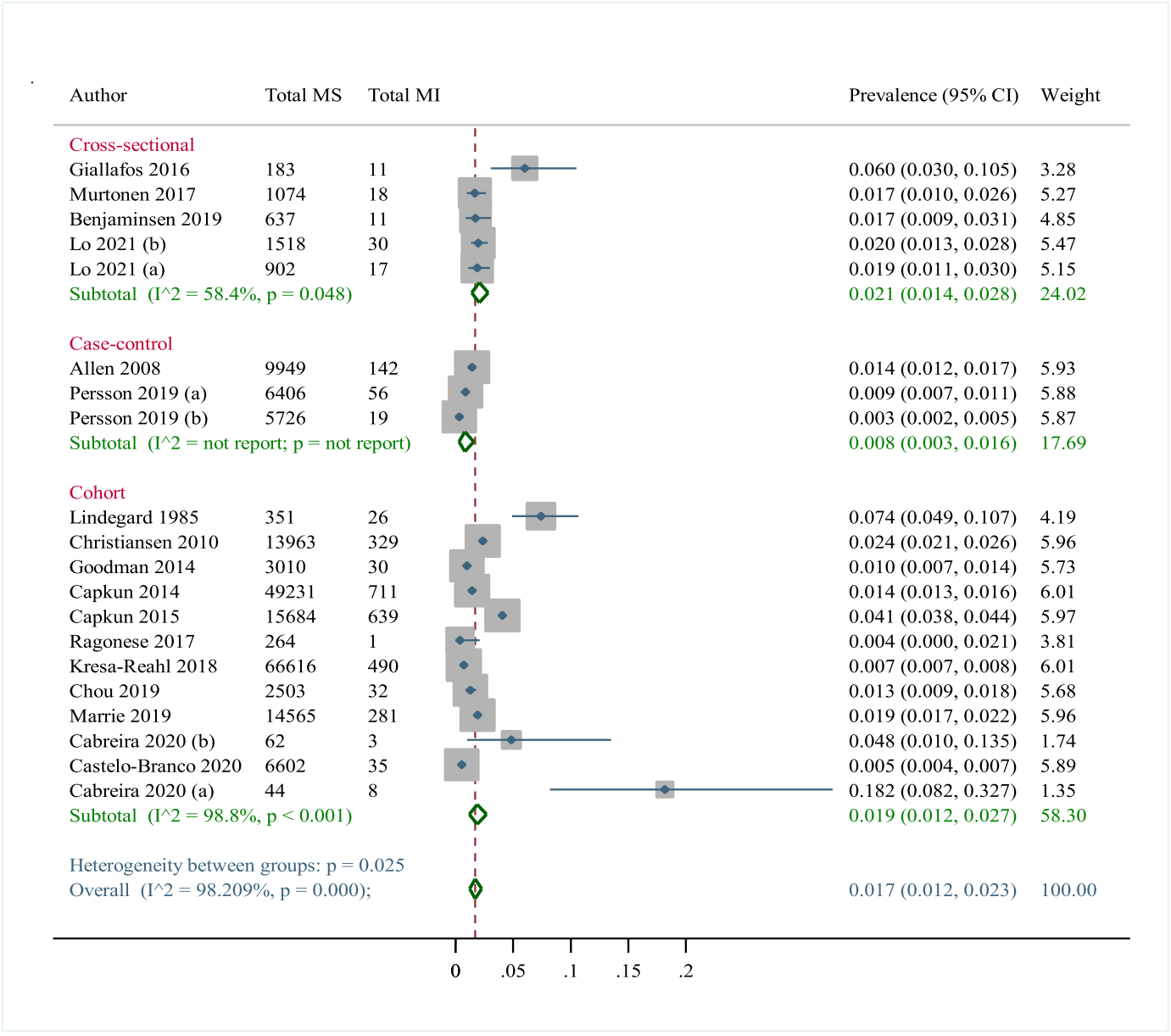

Fig. 2. Overall prevalence of estimated MI in different types of studies in MS patients

not find any data about MI among PwMS in Asia, Africa, and South America.

When looking at the pooled data on prevalence of MI among PwMS, it is important to interpret findings cautiously. The collected data in many of these studies may underestimate the occurrence of MI in people suffering from several chronic illnesses because of several reasons, including coding biases or the limited number of diagnoses per visit (Information CIfH 2003). Moreover, a number of the included studies did not validate their MS or MI case definitions. Further methodological work is thus necessary when using administrative data for the assessment of the incidence and prevalence of MI among PwMS.

To enhance search sensitivity, we initially looked for any study reporting data on MI among PwMS, regardless of being focused on the incidence and/or prevalence. This most certainly increased the heterogeneity of the included citations because of studies with poorer quality. However, we limited our meta-analysis to population-based studies to overcome the problem of heterogeneity. Despite doing this, we found considerable heterogeneity across studies.

This study has some limitations as follows: The included citations rarely reported estimates on age- and sex-specific prevalence/incidence of MI among cases. This is important given the variability of CVDs in different regions, age groups, and genders. Furthermore, the estimated MI prevalence in the general population was not available in all regions where the studies have been conducted. Moreover, many of the patients were presumably taking disease-modifying medications in the included studies, however, this was rarely reported. The quality and methodology of studies included in our systematic review and meta-analysis varied widely. This is important given the possible effect of some of these medications on the cardiovascular system.

Despite the increasing interest in studies on CVDs among PwMS, there is still a big data gap on this subject. There is a scarcity of high-quality data on the incidence and/or prevalence of MI among PwMS cases. Future studies should focus on population-based design for the assessment of MI in this population. In addition, studies investigating the incidence and prevalence of MI in this population need to report gender, age, ethnicity, medications, and disease-modifying therapies and their possible effect on the incidence and/or prevalence rates.

5. Conclusion

In summary, this systematic review and meta-analysis show an increased prevalence of MI in individuals with MS. This highlights the need for clinicians to be more careful in the face of an increased MI burden in PwMS. Future research on the relation between MS and MI is suggested.

Declaration of Competing Interest

All of the authors declared no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103292.

References

Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R.A., et al., 2020. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS. third edition Mult Scler 26 (14), 1816–1821.

Capkun, G., Dahlke, F., Lahoz, R., Nordstrom, B., Tilson, H.H., Cutter, G., et al., 2015. Mortality and comorbidities in patients with multiple sclerosis compared with a population without multiple sclerosis: An observational study using the US Department of Defense administrative claims database. Mult Scler Relat Disord 4 (6), 546–554.

Kaufman, D.W., Reshef, S., Golub, H.L., Peucker, M., Corwin, M.J., Goodin, D.S., et al., 2014. Survival in commercially insured multiple sclerosis patients and comparator subjects in the U.S. Mult Scler Relat Disord 3 (3), 364–371.

Kingwell E., van der Kop M., Zhao Y., Shirani A., Zhu F., Oger J., Montgomery S., Hillert J., Bahmanyar S. et al.Hospital admission due to infections in multiple sclerosis patients. Eur J Neurol. 2013;20(8):1153-60.

Christiansen, C.F., Christensen, S., Farkas, D.K., Miret, M., Sørensen, H.T., Pedersen, L., 2010. Risk of arterial cardiovascular diseases in patients with multiple sclerosis: a population-based cohort study. Neuroepidemiology 35 (4), 267–274.

Jadidi, E., Mohammadi, M., Moradi, T., 2013. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. Mult Scler 19 (10), 1336–1340.

Christiansen, C.F., 2012. Risk of vascular disease in patients with multiple sclerosis: a review. Neurol Res 34 (8), 746–753.

Berkovich, R., , Assistant Professor of Clinical Neurology KSoMUoSC, Subhani, D., , Clinical Research Assistant UoSCMSCCC, Steinman, L., Professor of N, 2011. Autoimmune Comorbid Conditions in Multiple Sclerosis. US Neurology 07 (02), 132.

Marrie, R.A., Garland, A., Schaffer, S.A., Fransoo, R., Leung, S., Yogendran, M., et al., 2019. Traditional risk factors may not explain increased incidence of myocardial infarction in MS. Neurology 92 (14), e1624–e1e33.

Nilsson, P.M., Nilsson, J.A., Berglund, G., 2006. Population-attributable risk of coronary heart disease risk factors during long-term follow-up: the Malmö Preventive Project. J Intern Med 260 (2), 134–141.

Marrie, R.A., Bernstein, C.N., Peschken, C.A., Hitchon, C.A., Chen, H., Fransoo, R., et al., 2014. Intensive care unit admission in multiple sclerosis: increased incidence and increased mortality. Neurology 82 (23), 2112–2119.

Marrie, R.A., Elliott, L., Marriott, J., Cossoy, M., Blanchard, J., Leung, S., et al., 2015. Effect of comorbidity on mortality in multiple sclerosis. Neurology 85 (3), 240–247.

Brønnum-Hansen, H., Koch-Henriksen, N., Stenager, E., 2004. Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain 127 (Pt 4), 844–850.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., et al., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015. statement. Systematic Reviews. 4 (1), 1.

Ma, L.-L., Wang, Y.-Y., Yang, Z.-H., Huang, D., Weng, H., Zeng, X.-T., 2020. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Military Medical Research 7 (1), 7.

Allen, N.B., Lichtman, J.H., Cohen, H.W., Fang, J., Brass, L.M., Alderman, M.H., 2008. Vascular disease among hospitalized multiple sclerosis patients. Neuroepidemiology 30, 234–238.

Benjaminsen, E., Myhr, K.M., Grytten, N., Alstadhaug, K.B., 2019. Comorbidity in patients with multiple sclerosis from Nordland, Norway. European Journal of Neurology 26, 475.

Cabreira, V., Abreu, P., Maia, C., Costa, A., Sá, M.J., 2020. Trends in hospital readmissions in Multiple Sclerosis patients between 2009 and 2015. Mult Scler Relat Disord 45, 102396.

Capkun, G., Lahoz, R., Chen, W., Moore, A., Bischof, D., Geissbuehler, Y., et al., 2014. Comorbidities in patients with multiple sclerosis compared with the general population: retrospective analysis of the US MarketScan Database. Multiple Sclerosis Journal 20, 147.

Castelo-Branco, A., Chiesa, F., Bengtsson, C.E., Lee, S., Minton, N.N., Niemcryk, S., et al., 2020. Non-infectious comorbidity in patients with multiple sclerosis: A national cohort study in Sweden. Mult Scler J Exp Transl Clin 6, 2055217320947761.

Chou, I.J., Kuo, C.F., Tanasescu, R., Tench, C.R., Tiley, C.G., Constantinescu, C.S., et al., 2020. Comorbidity in multiple sclerosis: its temporal relationships with disease onset and dose effect on mortality. Eur J Neurol 27, 105–112.

Giallafos, E., Kokkotis, P., Katsanos, S., Haina, V., Andreadou, E., Anagnostouli, M., et al., 2016. Prevalence of myocardial infarction with normal coronary artery in patients with multiple sclerosis. A new type of diastolic heart failure. European Journal of Heart Failure 18, 65.

Goodman, M., Healy, B., Cai, T., Weiner, H.L., Chitnis, T., De Jager, P.L., et al., 2014. Leveraging electronic health records for a phenomewide examination of the comorbidity burden associated with multiple sclerosis disease outcome. Multiple Sclerosis 20, 164.

Jick, S., Persson, R., Lee, S., Minton, N., Niemcryk, S., Lindholm, A., 2018. Cardiovascular disease (CVD) in patients diagnosed with multiple sclerosis (MS): A study in the UK Clinical Practice Research Database (CPRD). Multiple Sclerosis Journal 24, 375–376.

Kresa-Reahl, K., Edwards, N.C., Phillips, A.L., 2017. Prevalence of comorbidities in patients with and without multiple sclerosis by age and sex: a US retrospective claims database analysis. Multiple Sclerosis Journal 23, 488.

Lindegard, B., 1985. Diseases associated with multiple sclerosis and epilepsy. A population cohort study of 159,200 middle-aged, urban, native Swedes observed over 10 years (1970-79). Acta Neurologica Scandinavica 71, 267–277.

Lo L.M.P., Taylor B.V., Winzenberg T., Palmer A.J., Blizzard L., Ahmad H., et al. Estimating the relative contribution of comorbidities in predicting health-related quality of life of people with multiple sclerosis. Journal of Neurology.

Lo L.M.P., Taylor B.V., Winzenberg T., Palmer A.J., Blizzard L., van der Mei I. Change and onset-type differences in the prevalence of comorbidities in people with multiple sclerosis. Journal of Neurology.

Murtonen, A., Kurki, S., Hänninen, K., Soilu-Hänninen, M., Sumelahti, M.L., 2018. Common comorbidities and survival in MS: Risk for stroke, type 1 diabetes and infections. Mult Scler Relat Disord 19, 109–114.

Persson, R., Lee, S., Yood, M.U., Wagner, M., Minton, N., Niemcryk, S., et al., 2020. Incident cardiovascular disease in patients diagnosed with multiple sclerosis: A multi-database study. Mult Scler Relat Disord 37, 101423.

Ragonese, P., Aridon, P., Realmuto, S., Vazzoler, G., Alessi, S., Portera, E., et al., 2017. Cardiovascular comorbidity in multiple sclerosis patients treated with Mitoxantrone therapy: a cohort study. Multiple Sclerosis and Demyelinating Disorders 2.

Rogers, W.J., Frederick, P.D., Stoehr, E., Canto, J.G., Ornato, J.P., Gibson, C.M., et al., 2008. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 156 (6), 1026–1034.

Williams, T., van Staa, T., Puri, S., Eaton, S., 2012. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf 3 (2), 89–99.

Mincu, R.I., Magda, L.S., Florescu, M., Velcea, A., Mihaila, S., Mihalcea, D., et al., 2015. Cardiovascular Dysfunction in Multiple Sclerosis. Maedica (Bucur) 10 (4), 364–370.

Information CIfH, 2003. Discharge Abstract Database (DAD)/CMG/Plx Data Quality: Re-abstraction Study. Canadian Institute for Health Information, Ottawa, Ontario.