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Associations between multiple sclerosis and incidence of heart diseases: Systematic review and meta-analysis of observational studies

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ABSTRACT

Background: Observational studies have described associations between multiple sclerosis (MS) and heart diseases, but the results were mixed.
Methods: Medline, Embase, and Cochrane CENTRAL were searched up to 5 October 2020 according to a protocol (PROSPERO registration number CRD42020184493). We included longitudinal non-randomized studies of exposure comparing the incidence of acquired heart diseases between people with multiple sclerosis (pwMS) and people without multiple sclerosis. We used ROBINS-E and the GRADE approach to assess risk of bias and the certainty of evidence, respectively. Data were pooled using random-effect models.
Results: Of 5,159 studies, nine studies met the inclusion criteria. MS was associated with an increased risk for myocardial infarction (HR 1.6, 95% CI 1.2 to 2.0, I2 86%, $n = 1,209,079$) and heart failure (HR 1.7, 95% CI 1.3 to 2.2, I2 49%, $n = 489,814$). The associations were more pronounced among women and younger people in subgroup analyses. We found no difference for ischemic heart disease (HR 1.0, 95% CI 0.8 to 1.4, I2 86%, $n = 679,378$) and bradycardia (HR 1.5, 95% CI 0.4 to 5.0, I2 50%, $n = 187,810$). The risk of atrial fibrillation was lower in pwMS (HR 0.7, 95% CI 0.6 to 0.8, I2 0%, $n = 354,070$), but the risk of bias was high, and the certainty of evidence was rated as very low. One study found more cases of infectious endocarditis among pwMS (HR 1.2, 95% CI 1.0 to 1.4, $n = 83,712$).
Conclusions: Myocardial infarction and heart failure should be considered in people with multiple sclerosis during follow-up examinations.

Introduction

A plethora of studies have described associations between multiple sclerosis (MS) and cardiovascular diseases. A systematic review and meta-analysis of administrative mortality data found a roughly 30%-increased mortality due to cardiovascular diseases in people with MS (pwMS) compared with the general population (Manouchehrinia et al., 2016). PwMS showed an increased occurence of ischemic heart disease and congestive heart failure (Marrie et al., 2015) and several case reports have described a close temporal association between cardiomyopathy and MS relapses (Valencia-Sanchez et al., 2019). However, past studies exhibited a high risk of bias due to cardiovascular risk factors (Ewanchuk et al., 2018; Handel et al., 2011; Marrie et al., 2015; Motl et al., 2005), potential cardiotoxicity of disease modifying treatments for MS (Findling et al., 2020; Kingwell et al., 2010; Vargas and Perumal, 2013) and further sources of bias (Cohen et al., 2020). The question whether MS is a risk factor for cardiovascular diseases hence remains elusive.

This systematic review and meta-analysis of non-randomised studies aimes to investigate the association between MS and acquired heart diseases. We included longitudinal studies comparing incident heart diseases between people with and without MS.

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List of abbreviations

AF	Atrial fibrillation
AMSTAR-2	a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DMT	Disease modifying therapy
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HF	Heart failure
HR	Hazard Ratio
IHD	Ischemic heart disease
IRR	Incidence rate ratio
MI	Myocardial infarction
MOOSE	Meta-analysis of observational studies in epidemiology
MS	Multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
pwMS	People with multiple sclerosis
ROBINS-E	Risk Of Bias In Non-randomized Studies - of Exposures

Methods

Protocol and registration

This study is in accordance with the reporting guidelines Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009), Meta-analyses Of Observational Studies in Epidemiology (MOOSE) (Stroup, 2000), and Appraisal Tool for Systematic Reviews That Include Randomised or Non-Randomised Studies of Healthcare Interventions, or Both (AMSTAR-2) (Shea et al., 2017). A study protocol was registered a priori at the PROSPERO database (CRD42020184493). Deviations from the study protocol and guideline checklists are outlined in the Appendix.

Eligibility criteria, and data extraction

The research question was conducted using the PECO framework (population, exposure, comparison, outcome) (Morgan et al., 2018). The inclusion criteria were: (1) The study included MS-patients and MS was treated as exposure, and (2) pwMS were compared to people without MS. (3) We included only longitudinal, non-randomised observational studies of exposure reporting incident heart diseases. A further inclusion criterion was that the eligible study included a specific statement saying that participants with heart disease prior to the index date (MS diagnosis or study entry by controls) were excluded. We selected five acquired heart diseases as outcomes, namely (i) ischemic heart disease, (ii) heart failure, (iii) myocardial infarction, (iv) cardiac arrhythmia, and (v) infectious heart disease. Inclusion and exclusion criteria are outlined in Table 1. Two authors (DR, SM) independently screened titles, abstracts, and full texts for eligibility and extracted data to a piloted data extraction form. Disagreement was resolved by discussion with a third author (MaS).

Information sources

The search was conducted in collaboration with a trained research librarian. We searched three information sources via Ovid: (1) Medline, (2) Embase, (3) Cochrane Controlled Register of Trials (CENTRAL) and manually screened reference lists of eligible studies and reviews. The search was conducted on the 5 May 2020 and was updated on the 5 October 2020. We used no age- or language-restriction. The part of the search term to detect studies on MS was adapted by the Cochrane Collaboration Multiple Sclerosis and Rare Diseases of the CNS-group's search strategy (Cochrane Multiple Sclerosis and Rare Disease of the CNS, 2020). The final search term can be accessed via the Appendix. Five studies were extracted from an earlier systematic review prior to our literature search to evaluate whether the search term was sufficiently sensitive (Marrie et al., 2015). All five of the five selected studies were found by our search strategy.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1) MS treated as exposure	1) Cross-sectional study
2) Participants without MS are comparator	2) Not incidence but mortality reported
3) Acquired heart disease among outcome variables	3) No statement that participants with heart disease before MS-onset were excluded
4) Study design is longitudinal non-randomized study of exposure	

Synthesis and data analysis

We used R software version 4.0.3 for data analysis. The package meta (Balduzzi et al., 2019) was used for data synthesis and robvis 2021 (McGuinness, 2021) for visualization of risk of bias. After log-transforming all effect estimates and the corresponding confidence interval bounds, summary estimates were derived from random-effects models using the restricted-maximum-likelihood estimator and the Hartung-Knapp adjustment. When studies reported several effect measures, adjusted for a different number of covariables, we used the maximally adjusted model. We used hazard ratios (HR) and incidence rate ratios (IRR) interchangeably and pooled both effect measures in meta-analyses (Symons and Moore, 2002). Heterogeneity across included studies was assessed using the I^2 (0 to 100%) statistic (Higgins, 2003). We did not investigate whether publication bias was present using funnel plot for two reasons: firstly, this study investigated heart diseases among pwMS which are rare events. Therefore, a sufficient sample size is required, and this question cannot be addressed by small studies. Secondly, the overall number of included studies was lower than ten per outcome. In this case the power of funnel plot asymmetry analysis is not sufficient (Higgins et al., 2020).

Statistical significance was assumed for p-values of less than 0.05 or when 95% confidence intervals did not include the null effect using a 5% α-level.

Risk of bias and evidence assessment

We used the Risk Of Bias In Non-Randomized Studies of Exposures (ROBINS-E) tool for assessment of risk of bias (Higgins et al., 2020; Morgan et al., 2019; Schwingshackl et al., 2020). In ROBINS-E, a hypothetical target trial with no risk of bias is constructed and selected studies are compared with this target trial. Risk of bias is then assessed by seven categories: (1) Bias due to confounding, (2) Bias in selection of participants into the study, (3) Bias in classification of exposures, (4) Bias due to deviations from intended exposures, (5) Bias due to missing data, (6) Bias in measurement of the outcome, and (7) Bias in selection of the reported results. Each category is rated using the levels "low risk of bias", "moderate risk of bias", "serious risk of bias", or "critical risk of bias". The overall risk of bias of the whole study is equal to the most adverse risk of bias in one of the seven categories. An adaption of this tool for the present study can be accessed via the Appendix.

Risk of bias was independently assessed by two authors (DR, SM) and disagreement was resolved by discussion with a further author (JS).

Grading of recommendations assessment, development, and evaluation (certainty of the evidence)

Traditionally, GRADE classifies RCTs with an initial score of high and classifies observational studies (e.g. cohort studies) with a score of low. Recently, guidance on how to assess the certainty of evidence within GRADE when ROBINS-I is being used was published in 2018. RoB instruments, such as ROBINS that allow for the comparison of a body of evidence from observational studies to RCTs eliminate the GRADE requirement for starting an assessment of a body of evidence as "high" or "low" certainty based on study design.

For ischemic heart disease, myocardial infarction, heart failure, atrial Fibrillation, and bradycardia one GRADE experienced author (LS) and DR rated the certainty of evidence. Each outcome was evaluated with the following GRADE domains: risk of bias by using the ROBINS tool, indirectness, inconsistency, imprecision, and publication bias, dose-response, and large magnitude of effect. Overall GRADE specifies four levels of certainty of evidence: high, moderate, low, and very low (Schünemann et al., 2019).

Results

Our search retrieved 5159 articles. Nine studies met the inclusion criteria and were therefore considered for synthesis (Fig. 1). One study reported acute coronary syndrome as an outcome measure and was therefore not meta-analysed (Palladino et al., 2020). Likewise, one study reported acute infectious endocarditis (Roshanisefat et al., 2014). Both studies were used for qualitative purposes. Another study reported the results of two databases, namely the CPRD-data from the United Kingdom and the DOD-data based on members of the United States military (Persson et al., 2020). We treated the results of both databases as distinct studies in our synthesis because they yielded considerable heterogeneity (Table 2).

PwMS were identified using inpatient and outpatient data, data from general practitioners, or prescription claims in most studies. One of nine studies used only inpatient hospital data for identification of pwMS (Jadidi et al., 2013).

All studies meeting our inclusion criteria were population-based studies using administrative data such as health claims. A summary of used ICD codes can be accessed via the Appendix. Furthermore, all included studies were matched retrospective cohort studies that considered at least age and sex as possible confounders by using these characteristics as matching variables. Three of nine studies reported

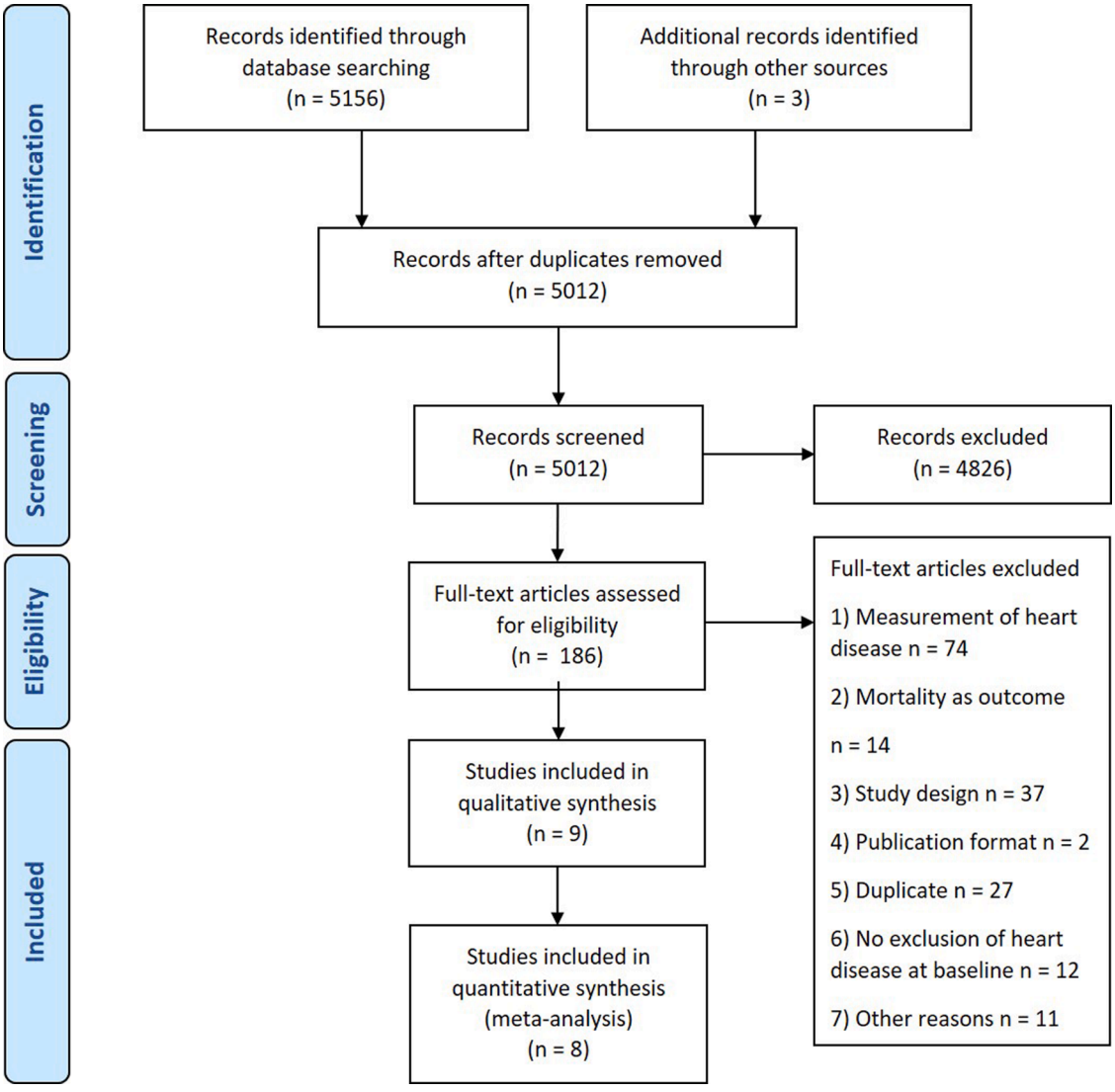

Fig. 1. PRISMA Flow diagram of selected studies.

Table 2
Characteristics of included studies.

Study	Country / database	Study design	Covariables	Study period	Study population	Number of pwMS / controls	Follow-up duration	Age / Gender	MS definition	Definition of heart disease	Type of controls	Overall risk of bias
Castelo-Branco et al., 2020	**Sweden** / The Swedish National Patient Register	MRCS	MV: A, S, R	Study entry: 2008–2016 End of follow-up: 2016	-Population-based -≥18y	4539 / 47,527	Range of mean follow-up: 3.4 to 4.8 years*	Mean age at entry MS : 41y C : 41y Proportion of women MS: 69% C: 69%	Incident MS-cases during study entry period. MS defined as ICD-10: G35	-Incident ICD-codes during follow-up - Inpatient and outpatient	Population-based	Serious
Christiansen et al., 2010	**Denmark** / Danish National Registry of Patients	MRCS	MV: A, S AV: A, S, DM, AHT, COPD, further[c]	Study entry: 1977–2006 End of follow-up: 2006	General population of Denmark	13,963 / 66,407	NA	Age at entry (weighted median)[a] MS : 45y Proportion of women MS: 64% C: 64%	Hospital claim (ICD) of MS Including outpatient data since 1995	Hospital claim (ICD) of heart disease, stratified analyses for first year of follow-up	Population-based	Serious
Jadidi et al., 2013	**Sweden** / Migration and Health Cohort (M&H Co): 1)The Swedish National Inpatient Register 2)The Total Population Register at Statistics Sweden 3) The Cause of Death Register	MRCS	MV: A, S AV: A, S, country of birth (Sweden, yes/no), calender period Considered for adjustment: DM, AHT, COPD, further[b]	Study entry: 1987–2009 End of follow-up: 2009	General population of Sweden	7664 / 66,214	NA	% younger than 60y of age at entry MS: 88% C: 89% Proportion of women MS: 68% C: 69%	Hospital claim (ICD) of MS	Hospital claim (ICD) of heart disease	Population-based	Serious
Marrie et al., 2016	**Canada** / Claims data (population registry, hospital, phasician) British Columbia, Manitoba, Quebec, Nova Scotia	MRCS	MV: A, S, R AV: A, S	Study entry: 1995–2005 End of follow-up: 2005	Population of British Columbia, Manitoba, Quebec, Nova Scotia, covering nearly 43% of the Canadian population	44,452 / 220,849	NA	Age at entry (weighted mean)[a] MS: 44y C: 44y Proportion of women MS: 71% C: 71%	≥3 hospital or physician claims for MS (ICD-9/10 5 340/G35)	≥1 hospital claim or ≥2 physician ICD-claims	Population-based	Critical
Marrie et al., 2019	**Canada** / Claims data (population registry, hospital, physician, drug prescription) of British Columbia (BC) and Manitoba (M)	MRCS	MV: A, S, R AV: S, SEI, DM, AHT, HLA, COPD	Study entry: BC: 1985–2016 M: 1979–2016 End of follow-up: BC: 2016 M: 2016	-Inpatient and outpatient -≥20 years at index date -individuals taking Mitoxantrone excluded	14,565 / 72,825	NA	Mean age at entry MS : 44y C : 44y Proportion of women MS: 73% C: 73%	Incident MS-cases during study entry period, having ≥3 ICD or prescription claims.	ICD code of myocardial infarction in hospital discharge diagnoses	Population-based	Moderate
Palladino et al., 2020	**England** / Clinical Practice	MRCS	MV: A, S, R AV: A, S,	Study entry: 1987–2018	≥18 years General practices	12,251 / 72,572	Mean follow-up	Mean age at entry MS: 45y	≥3 diagnostic primary care codes, ICD, drug	Recorded heart disease	General practices	Moderate

(*continued on next page*)

Table 2 (*continued*)

Study	Country / database	Study design	Covariables	Study period	Study population	Number of pwMS / controls	Follow-up duration	Age / Gender	MS definition	Definition of heart disease	Type of controls	Overall risk of bias
	Research Datalink (CPRD)		ethnicity, smoking, DM, depression, HLA, AHT, further[d]	End of follow-up: 2018			overall: 11.3 years	C: 45y Proportion of women MS: 67% C: 70%	prescription, hospital statistics for MS			
Persson et al., 2020	**United Kingdom** / Clinical Practice Research Datalink (CPRD) GOLD	MRCS	MV: A, S, R	Study entry: 2001–2016 End of follow-up: 2016	General practices, Inpatient and outpatient	5726 / 57,331	Range of mean follow-up: 2.7 to 5.7 years*	Median age at entry MS : 41y C : 41y Proportion of women MS: 72% C: 72%	Incident MS-cases during study entry period.	One record (read code) of CVD	General practices	Serious
Persson et al., 2020	**United States** / Department of Defense (DOD) military health care system	MRCS	MV: A, S, R	Study entry: 2004–2017 End of follow-up: 2017	US-DOD members, Inpatient and outpatient	6406 / 66,281	Range of mean follow-up: 6.0 to 6.0 years*	Median age at entry MS : 38y C : 38y Proportion of women MS: 71% C: 71%	Incident MS-cases (ICD) during study entry period.	At least five ICD-records of CVD	US-DOD members	Serious
Roshanisefat et al., 2014	**Sweden** / MS: Swedish Multiple Sclerosis Register (SMSreg) Comorbidities: Patient Register	MRCS	MV: A, S, R AV: A, S, R, SEI, AHT, year at entry, follow-up duration	Study entry: 1964–2005 End of follow-up: 2005	Swedish residents	7667 / 76,045	Mean follow-up: 11.1 years*	Mean age at entry MS : 40y C : 40y Proportion of women MS: 71% C: 70%	Incident MS-cases during study entry period.	Only primary ICD-diagnosis at hospital discharge; First year of follow-up excluded	Population-based	Serious
Thormann et al., 2016	**Denmark** / MS: The Danish Multiple Sclerosis Registry Comorbidities: 1) The Danish National Patient Register (NPR) 2) Danish Register of Causes of Death	MRCS	MV: A, S, R	Study entry: 1980–2005 End of follow-up: 2012	Born in Denmark	8838 / 44,111	NA	Mean age at entry: 35y Proportion of women MS: 66% C: 66%	Incident MS-cases during study entry period	-Incident ICD-codes during follow-up -Inpatient and outpatient	Population-based	Critical

A age, AHT arterial hypertension, AV adjusting variables, C: Non-MS controls, DM diabetes mellitus, HLA hyperlipidaemia, MRCS Matched retrospective cohort study, MV matching variables, NA data not available, SEI socioeconomic index, S sex, R region of residence, Y years of age,.

[a] Weighted mean/median: calculated follows: ∑(mean or median of subgroup * number of cases in subgroup) / number of cases overall.

[b] Jadidi 2013 considered the following covariables but did not adjust for in the final model since the change of IRR was <10%: DM, AHT, COPD, cardiac valve disease, deep vein thrombosis/ pulmonary embolism, renal failure, liver disease.

[c] Christiansen 2010 further adjusted for cancer, cardiac valve disease, renal failure, liver disease, gout, deep vein thrombosis, pulmonary embolism, year of first MS-diagnosis.

[d] index of multideprivation; antiplatelet/anticoagulation medications, number of primary care visits in the year before the diagnosis of MS, year of diagnosis of MS.

[*] Mean follow-up was estimated by dividing number of person years of observation time for a specific outcome by the number of study participants (pwMS and controls).

crude effect measures, and six studies reported effect measures adjusted for potential confounders such as arterial hypertension or diabetes mellitus.

The number of included pwMS ranged between 4,539 and 44,452 participants. Mean age at study entry ranged from 35 to 45 years and the mean duration of follow-up ranged between 2.7 and 11.3 years. Two studies excluded the first year of follow-up to control for detection bias (Christiansen et al., 2010; Roshanisefat et al., 2014).

The overall risk of bias of the included studies was high (Fig. 2). Two of nine studies were judged as "critical risk of bias", five studies as "serious risk of bias", and two studies as "moderate risk of bias", respectively. The risk of bias domain scoring the worst judgements was "bias due to confounding" (Fig. 1).

Our meta-analyses found an increased risk in pwMS for myocardial infarction (HR 1.6, 95% CI 1.2 to 2.0, I^2 86%) and heart failure (HR 1.7, 95% CI 1.3 to 2.2, I^2 49%). The risk was not significantly different for ischemic heart disease (HR 1.0, 95% CI 0.8 to 1.4, I^2 86%) and bradycardia (HR 1.5, 95% CI 0.4 to 5, I^2 50%). The risk of atrial fibrillation was decreased in pwMS (HR 0.7, 95% CI 0.6 to 0.8, I^2 0%). Furthermore, one study found an increased risk of acute coronary syndrome (HR 1.3, 95% CI 1.1 to 1.5) (Palladino et al., 2020) and another study found an increased risk for acute infective endocarditis (HR 1.2, 95% CI 1.0 to 1.4) (Roshanisefat et al., 2014) in pwMS.

Sensitivity analyses revealed that the effect of MS on heart disease was more pronounced in women and younger participants. The increased risk in pwMS for myocardial infarction was 2.3-fold in women and 1.3-fold in men. Likewise, the increased risk in pwMS for heart failure was 2.2-fold in women and 1.5-fold in men. This association could not be examined for other outcome measures, since the number of studies reporting sex-specific results was too low. Furthermore, we performed a sensitivity analysis for heart failure using Roshanisefat et al. (2014) instead of Jadidi et al. (2013). Both studies were based on the Swedish population and covered roughly the same time period. We used the results from Jadidi et al. in the primary analysis since Roshanisefat et al. excluded the first year of follow-up and only used primary hospital diagnosis to define heart diseases. When we used the results from Roshanisefat et al. instead of Jadidi et al., the summary-HR of heart failure changed from 1.7 (95% CI 1.3 to 2.2) to 1.4 (95% CI 0.9 to 2.2). The heterogeneity measured by I^2 was increased from 49% to 65% when the results of Roshanisefat et al. were used. Christiansen et al. (2010) reported results separately for the first year of follow-up and the years two to 30 of follow-up. We used the latter results in our primary analysis and performed a sensitivity analysis using the first year of follow-up (Appendix). The affected summary-HRs (AF, HF, and MI) were higher in sensitivity analyses and remained statistically significant.

The certainty of evidence of our meta-analyses was low or very low. Downgrading of the evidence was mostly based on very serious risk of bias. The meta-analysis of IHD also revealed inconsistency based on high I^2 and imprecision due to wide confidence intervals (Table 3).

Discussion

We investigated the relationship between MS and acquired heart diseases in this systematic review and meta-analysis of observational studies. Real-world data contribute important insights in the field of MS-comorbidities (Cohen et al., 2020).

Myocardial infarction (MI) and heart failure (HF)

Our meta-analysis showed that MS was associated with a 57% and

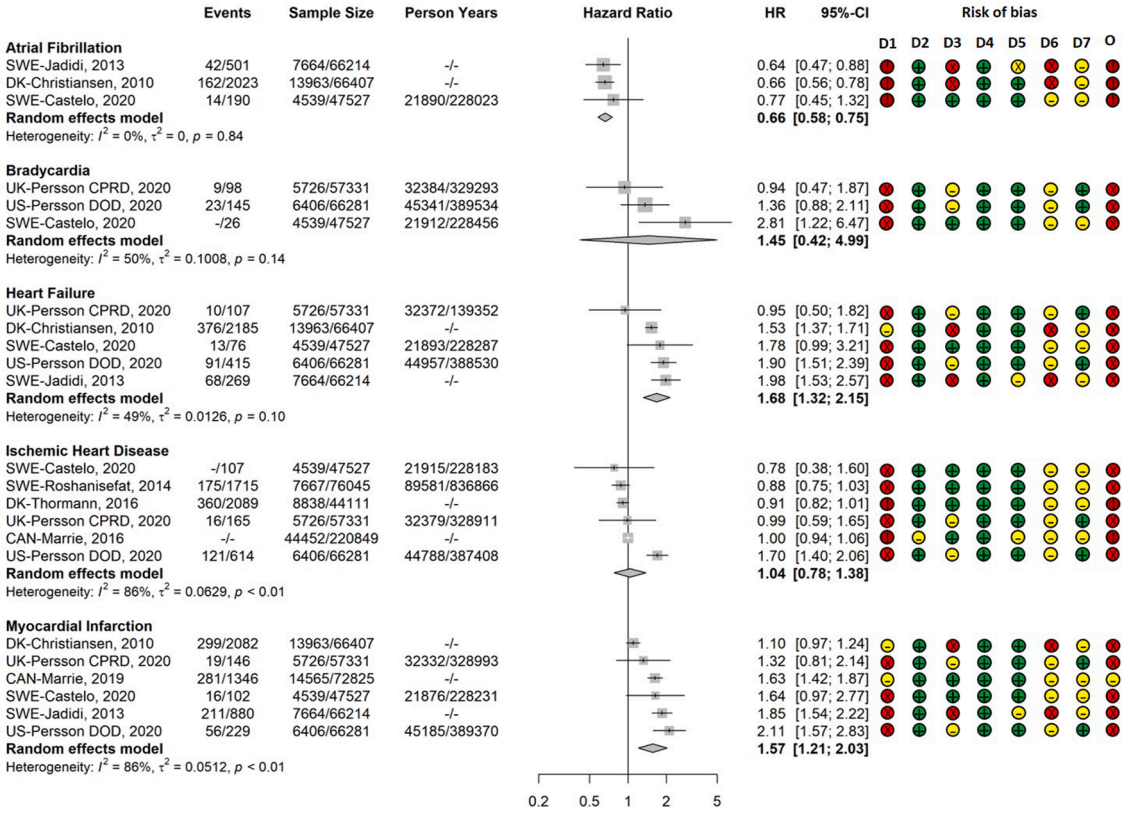

Fig. 2. Forest plots and traffic light plots of included studies.
Note: Risk of Bias domains: D1: Bias due to confounding, D2: Bias in selection of participants into the study, D3: Bias in classification of exposures, D4: Bias due to deviations from intended exposures, D5: Bias due to missing data, D6: Bias in measurement of the outcome, D7: Bias in selection of the reported results. O: overall risk of bias. Risk of bias legend: + low, - moderate, X serious, ! critical. Annotation: Some 95% CI are different from publication data due to estimation of standard error in the meta-analysis.

Table 3
Summary of findings.

Outcome	Effect (95% CI)	No of participants (studies)	Certainty of evidence (GRADE)	Informative statements
Ischemic heart disease	**HR 1.04** (0.78 to 1.38)	679,378 (6)	⨁◯◯◯ VERY LOW[a,b,c]	The evidence is very uncertain about the effect of multiple sclerosis on ischemic heart disease
Myocardial infarction	**HR 1.57** (1.21 to 2.03)	1209,079 (6)	⨁⨁◯◯ LOW[a,b,d]	The evidence suggests a slightly increased risk of myocardial infarction in pwMS
Heart failure	**HR 1.68** (1.32 to 2.15)	489,814 (5)	⨁⨁◯◯ LOW[a,d]	The evidence suggests an increased risk of heart failure in pwMS
Atrial fibrillation	**HR 0.66** (0.58 to 0.75)	354,070 (3)	⨁◯◯◯ VERY LOW[a]	The evidence is very uncertain about the effect of MS on atrial fibrillation
Bradycardia	**HR 1.45** (0.42 to 4.99)	187,810 (3)	⨁◯◯◯ VERY LOW[a,e,f]	The evidence is very uncertain about the effect of MS on bradycardia

[a] Downgraded by two levels since most or all (heart failure and bradycardia) included cohort studies were rated with a serious risk of bias; mainly due to risk of confounding. Atrial fibrillation by three levels due to critical risk of bias (Schünemann et al., 2019).
[b] Downgraded by one level due the high statistical inconsistency (I2=86%; $p<0.01$); Moreover, point estimates varied between included studies, and 95% CI did not completely overlap (Guyatt et al., 2011b).
[c] Downgraded by one level since 95% CI overlaps null effect and includes potential harm (HR: >1.25). We downgraded, although the number of events was high (>400, information on number of events missing in two studies) (Guyatt et al., 2011a).
[d] We did not downgrade for inconsistency although I^2=86%, since the point estimates were often mainly similar, and 95% CI overlaps mainly overlaps between studies (Guyatt et al., 2011b).
[e] Downgraded by one level for inconsistency since I^2=50%; and $\tau^2 = 0.1$; and point estimates varied strongly between studies (Guyatt et al., 2011b).
[f] Downgraded by one level since 95% CI overlaps null effect and includes potential benefit (RR: <0.75) and potential harm (HR: >1.25). Moreover, number of events was low (<400) (Guyatt et al., 2011a).

68% increased risk for MI and HF, respectively (Fig. 2). The risk of MI and HF was increased by 133% and 124% in women with MS and by 31% and 52% in men with MS. Furthermore, there was a tendency of higher HRs in younger pwMS (Appendix). Since the age groups differed between studies, the results of the subgroup analyses considering age are only explorative.

One possible explanation how MS could increase the risk of heart failure is by causing stress cardiomyopathy. Several case reports have described a temporal association between MS onset or relapse and stress cardiomyopathy, and found no further risk factors except MS (Valencia-Sanchez et al., 2019). Neurological diseases are among the known risk factors for stress cardiomyopathy. Moreover, the typical onset is at a younger age compared to ischemic heart disease, and the risk is higher in women (Ghadri et al., 2018). This might be in line with the higher effect sizes in women and younger age groups detected by our study. Christiansen et al. (2010) found a stronger association between MS and heart diseases during the first year of follow-up compared with the rest of the follow-up period. However, this could be explained by detection bias since pre-existing heart diseases might be discovered at the time of MS-diagnosis due to diagnostic workup. Other possible explanations of higher incidences of HF and MI among pwMS are that biological aging is accelerated in pwMS (Bühring et al., 2021) or that systemic inflammation and small vessel diseases (Geraldes et al., 2020) could increase the cardiovascular risk among pwMS.

In addition, DMT may be a relevant risk factor in MS. Some drugs are associated with increased risk of cardiovascular risk factors (Cocco and Marrosu, 2014; Findling et al., 2020; Kingwell et al., 2010). Especially Mitoxantrone is well known for its cardiotoxicity. In a study of 163 pwMS treated with Mitoxantrone 14% developed de novo reduced left ventricular ejection fraction (Kingwell et al., 2010). Although, the effect of MS on MI was also present when pwMS taking Mitoxantrone were excluded in another study (Marrie et al., 2019). Furthermore, Mitoxantrone is now only rarely used to treat MS, so that this effect might be rather low.

Aside from direct effects of MS on MI and HF, we assume that residual confounding is responsible for a part of the reported associations. Smoking and physical inactivity was more common among pwMS in past studies (Ewanchuk et al., 2018; Handel et al., 2011; Motl et al., 2005; Sasaki et al., 2018). The impact of classical cardiovascular risk factors on the association between MS and MI has been investigated by several studies (Marrie et al., 2019; Palladino et al., 2020). These studies showed that the association of MS and heart disease persisted after adjustment.

Ischemic heart disease (IHD)

We did not find an increased incidence of IHD among pwMS. In contrast to MI and HF, we could not detect differences between sexes. The summary-HR was 1.0 (95% CI 0.8 to 1.4) and the studies yielded considerable heterogeneity. Persson et al. (2020), for example, reported the results of the DOD database including US military servants and the CPRD database including pwMS from UK general practices. The IRRs derived from both databases were 1.7 (95% CI 1.4 to 2.1) and 1.0 (95% CI 0.6 to 1.7), respectively. No other included study except from the US-DOD database found a significantly increased risk of IHD among pwMS and the inclusion of this study therefore increased the between-study heterogeneity. In contrast to our results, an earlier systematic review by Marrie et al. (2015) found an increased occurrence of ischemic heart disease in pwMS. We assume that several methodological properties differed between the two meta-analyses since Marrie et al. included studies reporting prevalences and yielded a higher heterogeneity. Another consideration is that the age at study entry ranged between 35 and 45 years and the mean follow-up ranged between 2.7 and 11.3 years. Since age is a major influential factor for IHD, longer follow-up periods are needed in future studies to detect potential differences between pwMS and controls.

Cardiac arrhythmias

AF was the only heart disease associated with a decreased risk in pwMS. The meta-analysis yielded a 44% decreased risk of AF and the included studies showed low heterogeneity. This might be because all three studies were based on Scandinavian samples. The rationale of this association, however, is not obvious. AF shares some important risk factors with heart failure and myocardial infarction (Hindricks et al., 2020), and AF has been linked with HF in other studies (Santhanakrishnan et al., 2016). One possible explanation is that cardiac valve disease and hypertension were less frequent among pwMS in the study samples (Christiansen et al., 2010; Jadidi et al., 2013). Both are known risk factors for AF (Hindricks et al., 2020). However, adjustment for

these characteristics did not alter the effect estimates substantially (Jadidi et al., 2013). Since hypertension and cardiac valve disease are the most common risk factors for AF, the lower risk of atrial fibrillation among pwMS must be considered with caution and the certainty of evidence was rated "very low" (Table 3).

In contrast to AF, we found no significant association of MS and bradycardia. This is particularly interesting, because the disease-modifying drug fingolimod is known to cause bradycardia (Vargas and Perumal, 2013). Three studies reported results on this association, but the confidence interval of the summary-HR was wide, and the heterogeneity was high. This was probably because the definition of bradycardia was vaguer compared to the other outcomes and the considered ICD codes were more diverse.

Further heart diseases

In addition to the studies used for quantitative synthesis, we identified single studies reporting further associations of MS and heart diseases. Palladino et al. (2020) found a 30% increased risk for acute coronary syndrome (HR 1.3, 95% CI 1.1 to 1.5). This study also showed higher effects in women compared with men (HR 1.4 and 1.1, respectively). Roshanisefat et al. (2014) found a 20% increased risk of endocarditis in pwMS (IRR 1.2, 95% CI 1.0 to 1.4). This finding might be explained by the usage of immunosuppressive disease modifying therapies. The risk of infectious disease overall seems to be higher in pwMS (Luna et al., 2020).

Further subgroups

Roshanisefat et al. (2014) performed subgroup analyses by pattern of disease progression but there were no statistically significant differences between courses. However, it must be considered that the number of IHD-events were low in each subgroup and ranged between 27 and 85.

Two studies compared the incidence of cardiovascular diseases between pwMS and people without MS during the time before MS diagnosis. Thormann et al. (2016) found an increased hazard of cardiovascular diseases in pwMS after MS onset (HR 1.08 95% CI 1.02 to 1.15). The hazard of cardiovascular disease of people who will later be diagnosed with MS, however, was not significantly different from people who will not be diagnosed with MS (HR 0.87, 95% CI 0.71 to 1.07). Piehl et al. (2019) investigated whether there were differences of prescribed drugs before MS diagnosis. The authors restricted the analysis to the year before MS diagnosis. Drugs that are commonly prescribed for cardiovascular diseases were more common in people who will later develop MS (1635/6602; 24.8%) than in people who will not be diagnosed with MS (13,007/61,828; 21%).

We identified another study which assessed the risk of major adverse cardiovascular events in pwMS compared with controls (Frisell et al., 2019). Subgroup analysis were performed for different disease modifying treatments. However, there was no statistically significant differences between included DMTs.

Comparison of our results with mortality data

Our meta-analysis suggests an increased risk of some heart diseases in pwMS. Manouchehrinia et al. (2016) performed a meta-analysis using mortality data and found an increased mortality in pwMS. The overall standardized mortality ratio was 2.8, meaning that overall mortality in pwMS was 2.8-fold compared to the general population. The mortality due to cardiovascular diseases was increased by 29% (SMR 1.29, 95% CI 1.20 to 1.38). Furthermore, the authors found a survival disadvantage in women compared to men with MS. These results are in line with the results of our study showing that the association between some heart diseases are accentuated in women. An important goal for future studies could be to compare DMT. Neither the meta-analysis by Manouchehrinia et al. (2016) nor our results allow comparison of incidences or mortality between pwMS with or without DMT because of a lack of data in primary studies.

Limitations

The most serious limitation is the high risk of bias. Especially the effect of MS on AF must be considered with caution due to critical bias by confounding. All eligible studies might also be distorted by detection bias since pwMS are likely to see medical professionals more regularly than people without MS. This distortion might be especially serious because of the strong associations between gender and MS as well as gender and heart diseases. Since heart diseases are known to be underdiagnosed in women (Mehta et al., 2016), regular follow-up examinations among pwMS could yield a particularly serious detection bias among women. This could also explain at least part of the stronger associations in women and younger persons. Additionally, this study is based on administrative data. Validation studies of the included databases reported diagnostic accuracies between 85% and 98%, potentially yielding misclassification and bias. The acquisition of study participants and definition of heart diseases differed between included studies (Table 2). While some studies were population-based and used nationwide data, other studies used data from general practices or hospital claims. This leads to considerable heterogeneity among included studies. This is represented by rather high I2-values in Fig. 2. Furthermore, all included studies were based on western countries and the overall number of included studies was low. Lastly, the effect of disease modifying treatments and patterns of MS progression on cardiovascular events could not be investigated due to the scarcity of data.

Conclusions and implications for future research

Our meta-analysis provides evidence for an association between MS and myocardial infarction as well as heart failure. This relationship was stronger in women and tendentially stronger in younger people. We could not identify an association with ischemic heart disease and only ambiguous evidence for cardiac arrhythmias. The decreased risk of atrial fibrillation must be considered with caution because it is likely that critical confounding was present. The association between MS and myocardial infarction as well as heart failure especially in women and young persons should be considered by clinicians treating MS patients.

Future studies should aim to adjust for relevant cardiovascular risk factors. The inclusion of tobacco smoking, and physical activity is warranted, and subgroup analyses should consider gender, age, and disease modifying treatments. It is a challenge that a long follow-up period is needed to observe a sufficient number of heart events. Among the included studies of this review, the number of person years to observe one case of myocardial infarction among pwMS ranged between 807 and 1702 years of follow-up time. This means that roughly 1700 pwMS must be followed over a period of ten years to observe ten cases of myocardial infarction. Hence, large study arrangements are needed to further investigate the impact of MS on heart diseases.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

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

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The author received no specific funding for this work.

Authors' contributions

DR and SM contributed equally as first authors. DR originated the idea, designed the study, conducted the literature research, conducted study screening, extracted data, assessed risk of bias, assisted with GRADE, performed statistical analyses, and wrote the manuscript draft. SM conducted the literature research, designed the study, conducted study screening, extracted data, assessed risk of bias, and wrote the manuscript draft. JS conducted statistical analyses and advised on risk of bias assessment. LS performed GRADE assessment and advised on risk of bias. HT contributed in concept formation. MaS originated the idea and supervised the study. All authors read and approved the final manuscript.

Declaration of Competing Interest

DR: none declared.

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Supplementary materials

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