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Highlights

- Analysis included 147,933 adults aged ≥55 with MS from TriNetX data
- 8–12% of people with MS had a major adverse cardiovascular event (MACE) in 5 years
- MS was linked to higher stroke and mortality rates than rheumatoid arthritis
- Elevated CRP was strongly associated with future MACE in MS

Incidence and Associated Outcomes of Major Adverse Cardiovascular Events in Multiple Sclerosis versus Rheumatoid Arthritis

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Abstract

Aims: People with multiple sclerosis (pwMS) and rheumatoid arthritis (pwRA) have an increased cardiovascular disease (CVD) risk. As chronic inflammatory diseases with differing underlying mechanisms, they provide a useful comparison for understanding cardiovascular risk. We investigated major adverse cardiovascular event (MACE) incidence in pwMS, compared to pwRA.

Methods: A cohort study was conducted using anonymised healthcare data in TriNetX. PwMS or RA aged ≥55 years were diagnosed at least 5 years prior to the search and were 1:1 propensity-score matched for age, sex, ethnicity, pre-existing comorbidities, cardiovascular procedures and medications. Cox proportional hazard models determined 5-year incident MACE in pwMS, and associations between CVD risk factors and 5-year incident MACE were investigated. Associations were then compared between pwMS and pwRA.

Results: Among 147,933 pwMS, 8-12% experienced a MACE within 5-years of a recording of MS diagnosis in the database with or without CVD risk factors. PwMS and CVD risk factors, with no previously experienced MACEs, had a higher rate of MACE (HR 1.13, 95%CI 1.08, 1.19) compared to those without CVD risk factors. Among pwMS, a significantly higher rate of stroke (HR 1.28, 95% CI 1.22, 1.35) and all-cause mortality (HR 1.09, 95% CI 1.06, 1.12) was observed compared to pwRA. Normal CRP levels (<3mg/L) were associated with a lower rate of subsequent MACE compared to high CRP levels (≥3mg/L) (HR 0.62, 95% CI 0.58, 0.66) in pwMS.

Conclusions: Major adverse cardiovascular events are relatively common in pwMS; those with CVD risk factors have a higher 5-year MACE incidence. PwMS had a higher rate of stroke and all-cause mortality compared to pwRA. CRP may be an important variable influencing future MACE in pwMS.

Introduction

Multiple Sclerosis (MS) is an unpredictable, autoimmune condition in which the body's immune system destroys myelin in the brain, optic nerve and spinal cord. Whilst the aetiology of MS remains unknown, the estimated global prevalence of MS was 2.8 million in 2020 (1). Studies have consistently shown that people with MS (pwMS) exhibit a heightened susceptibility to cardiovascular disease (CVD) when compared to demographically matched counterparts without MS (2-6). Population-based data in 44,452 Canadians with MS estimated that the incidence rates of diabetes, hypertension, hyperlipidaemia, and ischaemic heart disease increased from 1995 to 2005 (7). A Mendelian randomisation study suggested a genetic link between the risk of MS and CVD (8). Additionally, the chronic recurrent episodes of inflammation and demyelination of the central nervous system in MS are believed to play a contributory role in the development of long-term cardiovascular dysfunction (9). Research into the relationship between MS and CVD requires greater attention to improve clinical care, early identification, optimise treatment strategies, and enhance the overall health outcomes and quality of life for pwMS.

Research into risk factors for CVD in pwMS is limited. Research using the Framingham risk score, a standardised algorithm widely employed in clinical practice to estimate the probability of cardiovascular events, has shown that a higher cardiovascular risk profile was associated with worse MS disability and disease course in 265 pwMS and 530 matched controls (10). Additionally, a cross-sectional study of 885 pwMS found that those with vascular comorbidities, such as hypertension, and diabetes were significantly associated with increased relapse rate over 2 years after adjusting for age (11). Research comparing major adverse cardiovascular events (MACE) in the MS population and non-MS control groups has found that incidence of acute myocardial infarction and stroke (5, 6, 12-14), as well as mortality rates (5, 15, 16), are greater in pwMS. The incidence of MACE has also been investigated in 19 of the most common autoimmune diseases, including MS, with around 15% of individuals with (*n*=446,449) and 11% in those without (*n*=2,102,830) autoimmune diseases developing incident CVD during a median follow-up of 6.2 years (17).

Autoimmune diseases are linked to an elevated rate of CVD, with the rate of CVD increasing with the number of autoimmune conditions present (17-19). A recent systematic review and meta-analysis in people with systemic autoimmune diseases, such as rheumatoid arthritis (RA), psoriasis, and lupus erythematosus has demonstrated an increased rate of MACE in comparison to the general population (20). Rheumatoid arthritis (RA) is an autoimmune disorder characterised by the immune system targeting healthy tissues (21). Despite ongoing research efforts, the aetiology for RA remains poorly understood. The global prevalence of RA was estimated to be approximately 17.6 million people in 2020 (22). RA is associated with a 50% increased risk of cardiovascular-related mortality and morbidity compared to healthy controls, which has been linked to chronic inflammation, similar to MS (18, 23). Given that MS and RA are chronic systemic inflammatory conditions associated with elevated cardiovascular risk, but with distinct pathophysiological mechanisms, RA provides a clinically relevant comparator for examining cardiovascular outcomes in MS. It is not known whether the rate of MACE between MS and RA is comparable, or whether cardiovascular risk factors in pwMS and pwRA have similar associations with MACE. This difference in cardiovascular risk is crucial for understanding how cardiovascular risk manifests across autoimmune diseases, and why it is necessary to investigate these diseases in parallel. Comparison of cardiovascular outcomes between RA and MS patients allows identification of specific risk factors unique to each condition, leading to more tailored and effective treatment strategies. Furthermore, such comparisons will help clarify the roles of immune modulation and inflammation in cardiovascular disease development, providing insights into how personalised approaches to managing cardiovascular risk can be developed for individuals with autoimmune diseases.

Overall, there remains a paucity of research on cardiovascular risk factors and long-term MACE for pwMS. We aimed to 1) investigate the 5-year incidence of MACE in pwMS, 2) identify the association between cardiovascular risk factors and MACE in pwMS, and 3) investigate whether the incidence of MACE, and the impact of cardiovascular risk factors, differ between pwMS and pwRA over a 5-year period.

Methods

Study design

This observational cohort study utilised anonymised data within TriNetX®, a global federated health research network with access to electronic medical records (EMRs) obtained from participating academic medical centres, specialty physician practices, and community hospitals, predominantly located in the USA (24). Upon submission of data to the network from participating institutions, it undergoes a process of mapping to a standardised and controlled set of clinical terminologies. Subsequently, the data is subjected to a comprehensive data quality assessment, including 'data cleaning' that excludes records failing to meet the predefined quality standards set by TriNetX®. The database conducts routine internal evaluations and extensive data quality assessments with every refresh based on conformance, completeness, and plausibility (25). As a federated network, research studies using TriNetX® do not necessitate ethical approval or informed consent as no identifiable data is acquired. The TriNetX® network was searched on May 27, 2026. The index date was defined as the date of the first recorded diagnosis of MS or RA in the database. For analyses involving cardiovascular risk factors, the index date was defined as the first date on which both MS (or RA) diagnosis and a cardiovascular risk factor were recorded in the database. Deidentified individuals were followed for up to 5-years from the index date. The EMR data included anonymised information on participant demographics, diagnoses, procedures, medication, and laboratory measurements. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (26) (see Supplementary material, Table S1). At the time of the search, 131 (primarily US-based) participating health care organisations had data available for individuals who met the study inclusion criteria. To adhere to legal frameworks and ethical guidelines that protect against data re-identification, identities of participating health care organisations and their individual contributions to each dataset are not disclosed.

Cohort

PwMS aged ≥55 years were included using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code G35. For comparisons with pwRA, pwRA without MS aged ≥55 years were included, using ICD-10-CM code M06.9 (Rheumatoid arthritis) to prioritise diagnostic specificity and minimise misclassification within the database. Those with RA were excluded if they had a record of optic neuritis (ICD-10-CM:H46),

acute transverse myelitis in demyelinating disease of central nervous system (ICD-10-CM:G37.3), encephalitis, myelitis and encephalomyelitis (ICD-10-CM:G04), unspecified parasitic disease (ICD-10-CM:B89), demyelinating diseases of the central nervous system (ICD-10-CM:G35-G37.9). These exclusion criteria were applied to remove conditions that may mimic demyelinating disease or introduce diagnostic uncertainty. RA was chosen as a comparison condition to MS due to the known increase in cardiovascular event rate in comparison to the general population. To reduce variability and enhance the detection of MACE, stratified by cardiovascular risk factors, younger individuals (<55) with MS or RA who may have fewer cardiovascular risk factors overall, were excluded. The age criterion for the study was applied based on the participants' age at the time of the most recent data access.

Exposures

Traditional cardiovascular risk factors including but not limited to hypertension, dyslipidaemia, smoking status, and inflammatory markers, were identified via codes included in Supplemental Table S2. These were defined as recordings present at any time up to and including the index date, which was itself defined as the first date on which both a diagnosis of MS or RA and a cardiovascular risk factor were recorded in the database.

. Second, these cardiovascular risk factors were further investigated in pwMS versus pwRA. Cardiovascular risk factors were based on clinically established thresholds (full list in supplemental table S2). For instance, high systolic blood pressure was defined as >140mmHg, diastolic blood pressure >90mmHg (27), HbA1c >6.5% (28), triglycerides >200mg/dl (29). Lastly, the associations of C-reactive protein (CRP) and MACE in pwMS vs pwRA was investigated. CRP levels in pwMS were stratified by normal (<3mg/L), and high levels (≥3mg/L) according to guidelines from the Centres for Disease Control and Prevention and the American Heart Association (30). Cardiovascular risk factors were treated as baseline covariates, established prior to the commencement of outcome follow-up, and were not modelled as time-varying exposures. Incident outcomes were assessed from one day after the index date, ensuring complete temporal separation between exposure ascertainment and outcome follow-up.

Statistical Analysis

All analyses were performed within the TriNetX platform, leveraging R's survival package v3.2–3. Forest plots for all analyses were created in R-Studio (2024.04.1+748). All analyses excluded participants with prior MACE that occurred before the 5-year follow-up period to minimise reverse causation. With adjustment for multiple hypothesis testing, statistical significance was set as $P < 0.001$. No imputations were performed for missing data. Censoring was applied by excluding a patient from the analysis after the occurrence of the last recorded event in their electronic health record.

Incidence of MACE and impact of cardiovascular risk factors in pwMS

5-year incidence of MACE during the 5-year follow-up period from the index date was investigated in pwMS with and without at least one CV risk factor after PSM. Using logistic regression, pwMS with traditional cardiovascular risk factors were 1:1 propensity score matched (PSM) for age, sex, ethnicity, analgesics, and antidepressants with pwMS without traditional cardiovascular risk factors. Cardiovascular procedures and medications were included in the propensity score model to improve balance between cohorts for underlying cardiovascular risk. These variables may also reflect baseline CVD burden and clinical management, which are important sources of confounding in observational analyses. To control for possible overmatching for cardiovascular procedures and medications, a sensitivity analysis was conducted excluding these variables from the model. The TriNetX platform utilises greedy nearest-neighbour matching, with a calliper of 0.1 pooled standard deviations. Covariate balance between groups was assessed using standardised mean differences (SMDs). Baseline characteristics with a SMD between cohorts score lower than 0.1 was considered well matched (31). Following PSM, Cox proportional hazards regression models produced hazard ratios (HR) with 95% confidence intervals (CIs) for 5-year incidence (from the index date) of all-cause mortality, ischemic stroke (cerebral infarction, ICD-10-CM:I63), acute myocardial infarction (ICD-10-CM:I21), and heart failure (ICD-10-CM:I50), as well as a composite of these variables (MACE), comparing pwMS and cardiovascular risk factors versus PSM controls with MS without risk factors.

MACE in pwMS versus pwRA

To investigate the difference in MACE incidence in pwMS and pwRA, people aged over 55 years were 1:1 PSM for age, sex, ethnicity, pre-existing comorbidities, cardiovascular

procedures (including electrocardiography, echocardiography, catheterisation, cardiac devices, and electrophysiological procedures), cardiovascular medications (including beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, and ACE inhibitors), analgesics, and antidepressants (codes used included in appendix 1) with people aged over 55 years with RA. Cox proportional hazards regression models produced HRs with 95% CIs for incidence of new MACE within the 5-year follow-up period, comparing pwMS versus propensity-matched pwRA. These analyses excluded participants with prior MACE that occurred before the index date.

Cardiovascular risk factors in pwMS versus pwRA

Subsequently, comparison of the impact of traditional cardiovascular risk factors on the risk of MACE in pwMS versus pwRA was analysed. PwMS with independent traditional cardiovascular risk factors were 1:1 PSM, using the same variables as above, with pwRA and traditional cardiovascular risk factors (Supplemental table S2). Cox proportional hazards regression models produced HRs with 95% CIs for 5-year incidence of new MACE, comparing pwMS versus propensity-matched pwRA.

C-Reactive Protein and MACE in pwMS

Cox proportional hazards regression models produced HRs with 95% CIs for 5-year incidence of new MACE, comparing pwMS and normal CRP levels (<3mg/L) versus propensity-matched pwMS and high CRP levels (≥3mg/L).

Results

Cohort Characteristics

In total, 147,933 people aged ≥55 with MS and at least 5-years of follow-up data were identified (56 ± 10 years, 74% female), whilst 657,138 people aged ≥55 with RA, without MS or other demyelinating diseases, were identified (66 ± 11 years, 73% female).

Impact of cardiovascular risk factors in pwMS

A total of 107,364 (75%) pwMS ≥55 years had at least one cardiovascular risk factor, and 35,612 (25%) pwMS had no risk factors. Following PSM, 32,760 pwMS were included in analyses in each group (Supplemental Table S3). There was a significantly higher rate of the

composite outcome of MACE among pwMS and any cardiovascular risk factor (HR 1.13, 95% CI 1.08, 1.19) (Figure S1) compared to pwMS and no risk factors during the 5-year follow-up period (rate of 3,669/30,113 vs 2,642/31,352, respectively). For the components of MACE, there was a significantly higher rate of 5-year incidence of stroke (HR 2.69, 95% CI 2.34, 3.10), acute myocardial infarction (HR 3.20, 95% CI 2.65, 3.86) and heart failure (HR 2.93, 95% CI 2.60, 3.31). There was a significantly lower rate of 5-year incidence of all-cause mortality (HR 0.79, 95% CI 0.75, 0.84) (Figure S1). Results of the sensitivity analyses that excluded cardiovascular procedures and medications from the PSM variables were consistent in direction and magnitude for all-cause mortality, stroke, acute myocardial infarction, heart failure and the composite outcome, MACE (Supplementary Table S4).

Incidence of MACE in pwMS

5-year incidence of MACE was 8.43%, and 12.18% in those with MS without and with at least one CV risk factor, respectively, after PSM. The difference between those without and with at least one CV risk factor was 3.80% (95%CI 3.30%, 4.20%) after PSM. 5-year incidence of MACE before PSM was 8.10%, and 13.90% in those with MS without and with at least one CV risk factor, respectively (5.80% risk difference, 95%CI 5.40%, 6.20%).

MACE in pwMS versus pwRA

Following PSM of pwMS to pwRA, there were *n*=129,497 included in each group. Although some variables were statistically different between cohorts (ischaemic heart diseases) following PSM, the cohorts were considered well-matched with small absolute differences (<0.1, Table 1).

During the 5-year follow-up period, pwMS had a significantly higher rate of all-cause mortality (HR 1.09, 95% CI 1.06, 1.12) and stroke (HR 1.28, 95% CI 1.22, 1.35) compared to propensity-matched pwRA (Figure 1). PwMS had a significantly lower rate of acute myocardial infarction (HR 0.79, 95% CI 0.74, 0.83) and heart failure (HR 0.69, 95% CI 0.66, 0.72) compared to propensity-matched pwRA (Figure 1). There was no difference in MACE across cohorts (rate of 13,859/121,474 vs 12,671/120,300, respectively).

[TABLE 1 INSERT HERE]

Cardiovascular risk factors in pwMS versus pwRA

There was a significantly higher rate of MACE over 5-years in pwMS and high CRP (HR 1.16, 95% CI 1.12, 1.21), low HDL cholesterol (HR 1.11, 95%CI 105, 1.16) compared to pwRA and high CRP and low HDL cholesterol, respectively (parameter definitions included in supplemental table S2, Figure 2). Whilst pwMS and low iron levels (HR 0.62, 95%CI 0.60, 0.65) had a significantly lower rate of MACE over 5-years compared to pwRA and low iron. There was a significantly higher rate of 5-year incidence of stroke among pwMS and high blood pressure (HR 1.25, 95% CI 1.19, 1.32), high body mass index (BMI) (HR 1.35, 95%CI 1.25, 1.45), high CRP (HR 1.12, 95%CI 1.03, 1.22), high HbA1c (HR, 1.22, 95% CI 1.10, 1.35), low HDL cholesterol (HR 1.21, 95%CI 1.10, 1.33), high triglycerides (HR 1.26, 95% CI 1.12, 1.41), high erythrocytes (HR 1.25, 95%CI 1.13, 1.40), and a history of smoking (HR 1.22, 95% CI 1.14, 1.32), in comparison to pwRA. Moreover, pwMS and high blood pressure (HR 1.03, 95%CI 1.00, 1.07), high BMI (HR 1.08, 95%CI 1.04, 1.13), high CRP (HR 1.36, 95% CI 1.30, 1.42), low HDL cholesterol (HR 1.14, 95%CI 1.08, 1.20), high triglycerides (HR 1.19, 95%CI 1.10, 1.28), high erythrocytes (HR 1.24, 95%CI 1.16, 1.32), and high HbA1c (HR 1.15, 95% CI 1.08, 1.23) showed a significantly higher rate of 5-year all-cause mortality in comparison to pwRA. However, pwMS and low iron showed a significantly lower rate of 5-year all-cause mortality in comparison to pwRA and low iron (HR 0.59, 95%CI 0.57, 0.62). Across all cardiovascular risk factors, pwRA were at an increased risk of acute myocardial infarction and heart failure in comparison to pwMS. PwMS and high blood pressure (HR 0.81, 95%CI 0.77, 0.85), high BMI (HR 0.87, 95%CI 0.80, 0.93), high CRP (HR 0.82, 95%CI 0.76, 0.89), low iron (HR 0.46, 95%CI 0.42, 0.50), high troponin (HR 0.74, 95%CI 0.65, 0.85), and a history of smoking (HR 0.85, 95%CI 0.80, 0.91) had a significantly lower rate of acute myocardial infarction compared to pwRA. Furthermore, pwMS and high blood pressure (HR 0.74, 95%CI 0.71, 0.77), high BMI (HR 0.80, 95%CI 0.76, 0.84), high CRP (HR 0.83, 95%CI 0.79, 0.88), high HbA1c (HR 0.83, 95%CI 0.77, 0.89), high total cholesterol (HR 0.81, 95%CI 0.73, 0.90), low iron (HR 0.45, 95%CI 0.42, 0.48), and a history of smoking (HR 0.79, 95%CI 0.75, 0.83) had a significantly lower rate of heart failure compared to pwRA. PSM data for individual cardiovascular risk factors can be found in supplementary materials (supplemental tables S5-16).

C-Reactive Protein and MACE in pwMS

High CRP levels were identified as having the strongest association with MACE among pwMS. CRP levels were stratified into normal (<3mg/L), and high (≥3mg/L) categories (Figure 3). Those with normal CRP levels showed a significantly lower rate of 5-year incidence of MACE (HR 0.62, 95% CI 0.58, 0.66, rate of 1,567/13,517 vs 2,309/13,117, respectively), all-cause mortality (HR 0.49, 95% CI 0.45, 0.53), acute myocardial infarction (HR 0.77, 95%CI 0.67, 0.88) and heart failure (HR 0.68, 95% CI 0.62, 0.75) compared to those with high CRP levels (Figure 3). PSM data can be found in supplementary materials (supplemental Table S17).

Discussion

To our knowledge, this observational cohort study represents the largest sample size to date. We found that between 8-12% of 147,933 pwMS aged ≥55 experienced a MACE within a 5-year of follow-up, at least 5-years after an MS diagnosis. Second, the presence of cardiovascular risk factors in pwMS was associated with significantly higher MACE compared to those without risk factors. Third, pwMS had a 28% higher rate of stroke and 9% higher rate of all-cause mortality compared to pwRA after exclusion of participants who had experienced a MACE prior to the follow-up period. This higher rate persisted across stratified cardiovascular risk factors. Notably, the current study identified CRP as having the strongest association with MACE in pwMS. Individuals with MS having normal CRP levels had a 38% lower rate of MACE compared to those with high CRP levels.

Incidence of MACE (8-12%) is substantially higher than previously reported (6). A systematic review of 249 studies and reported an overall prevalence of less than 5% for ischemic heart disease, congestive heart failure and stroke among pwMS (6). When defining MACE, the present study included a greater number of outcomes focussed exclusively on individuals aged over 55 with a recording of MS diagnosis on the database at least 5-years ago and investigated 5-year incidence of MACE excluding participants with prior MACE that occurred before the index date, whereas the previous systematic review included all age groups with varied follow-up periods, with and without prior CVD. It is widely acknowledged that ageing presents distinct challenges for pwMS due to the increased frequency of age-related and MS-related comorbidities (32). Moreover, as recruitment for the present study is mostly via research hospital sites, this may mean that the current sample is a higher risk group in comparison to other prospective cohort studies focussed solely on pwMS. Furthermore,

underreporting or misclassification of certain health conditions may be apparent in the present study in consequence of sourcing data from EMR databases of healthcare organisations.

The present study findings highlight the importance of managing cardiovascular disease risk in pwMS, with an added focus on those with at least one cardiovascular risk factor due to the significantly higher rate of MACE found compared to those without any cardiovascular risk factors (HR 1.13, 95% CI 1.08, 1.19). Additionally, the rate of stroke, acute myocardial infarction, and heart failure were significantly greater in those with cardiovascular risk factors. However, there was a significantly reduced rate of all-cause mortality found in pwMS with cardiovascular risk factors compared to those without (HR 0.79, 95% CI 0.75, 0.84). This unexpected association may be reflect improved primary and secondary CVD prevention arising from more frequent healthcare contact. Hemida and colleagues recently reported a significant rise in MS-associated cardiovascular mortality in US adults over a 25-year period, with age-adjusted mortality rates increasing from 0.78 to 1.21 per 100,000 between 1999 and 2023, and a particularly sharp increase observed between 2018 and 2021 (34). Taken together, these findings highlight the potential value of enhanced patient monitoring and integrated care to enable early detection and intervention. Interventions such as diligent blood pressure control, alongside lifestyle modification and pharmacological therapy, could offer a promising primary and secondary prevention approach for pwMS. However, alternative explanations must be considered. This finding may reflect surveillance bias, whereby individuals with documented risk factors have greater healthcare engagement, facilitating earlier detection and management of both cardiovascular and non-cardiovascular conditions. Selection bias may also be present, as those without recorded risk factors may include individuals with less frequent healthcare contact or under-documented comorbidities, representing a heterogeneous group of low-risk individuals and those with unrecorded or undiagnosed conditions. Additionally, misclassification bias may arise if risk factor recording is more likely in those already under closer clinical observation. Although statistically significant, the absolute mortality difference between groups was modest (~0.7%). This suggests limited clinical magnitude and reinforces the need for cautious interpretation, particularly in the context of a large cohort where small absolute differences

may reach statistical significance. Collectively, these biases may contribute to the apparent paradoxical mortality association and should be considered when interpreting these findings.

While pwMS and pwRA are known to have an increased CVD risk compared to general populations (4, 35-41), this is the first study to directly compare these two groups and investigate the impact of cardiovascular risk factors. Our findings demonstrate a 28% higher rate of stroke and 9% higher rate of all-cause mortality in pwMS versus matched pwRA, whilst there was a 21% lower rate of myocardial infarction and 31% lower rate of heart failure in pwMS versus matched pwRA. After stratifying for individual cardiovascular risk factors, stroke and all-cause mortality rate were consistently higher in pwMS. This study included all-cause mortality as a measure, so the increased mortality rate in pwMS may be driven by other conditions that are not cardiovascular in nature. While pwMS demonstrated a statistically significantly higher hazard of all-cause mortality than pwRA (HR 1.09), the magnitude of this relative difference was modest and clinical significance should be interpreted cautiously. A 2008 observational study of pwMS aged 40-84 years found that pwMS were less likely to be hospitalised for ischemic heart disease (OR 0.58, 95% CI 0.51, 0.66) or myocardial infarction (OR 0.78, 95% CI 0.64, 0.96), yet more likely to be hospitalised for ischemic stroke (OR 1.66, 95% CI 1.33, 2.09) compared to matched controls without MS (42). It could be speculated that these results may reflect important biological and clinical differences between MS and RA. Although both are immune-mediated inflammatory disorders, inflammation in MS occurs in the central nervous system, therefore neuroinflammation may lead to a higher rate of stroke (43), while inflammation in RA is systemic, leading to a potentially higher rate of acute myocardial infarction and heart failure. In addition, MS and RA differ in their age at onset, disease trajectories, comorbidity burden, and treatment strategies. For example, cardiovascular risk in RA may be modified by disease activity and antirheumatic therapies, while in MS it may be influenced by disability, reduced physical activity, autonomic dysfunction, and disease-modifying therapies. Moreover, there is a potential for misinterpretation of MS relapses as cerebrovascular events in pwMS, which may be responsible for the increase in stroke rate in this cohort (44). Therefore, the present findings should be interpreted as a comparison of cardiovascular outcomes across two clinically distinct inflammatory diseases rather than as evidence that one disease confers a greater intrinsic cardiovascular risk than the other. Nonetheless, comparing MS and RA provides

insight into whether cardiovascular risk manifests differently across autoimmune conditions with differing inflammatory mechanisms. Further research is necessary to elucidate the biological mechanisms behind these findings.

When looking at the individual risk factors, our findings showed BMI as having the strongest association with stroke (HR 1.35, 95% CI 1.25, 1.45), whilst CRP had the strongest association with composite MACE (HR 1.16, 95% CI 1.12, 1.21) and all-cause mortality (HR 1.36, 95% CI 1.30, 1.42) in pwMS versus pwRA. Our finding that CRP is associated with increased rate of MACE and all-cause mortality in pwMS supports previous literature that suggests the increased CVD rate in pwMS and pwRA is linked to chronic inflammation (41, 45-47). However, previous studies have shown conflicting results regarding CRP levels in pwMS (48-50). Whilst some previous work showed slightly lower CRP levels in pwMS during disease onset compared to healthy controls (48), others have found no clear correlation between CRP and MS (49, 50). Additionally, the current study is unable to determine causality. A study in pwRA (n=9,889) linked higher CRP with heart failure risk, whilst taking anti-inflammatory medications associated with a lowered risk (41). The present study highlights the potential role of CRP in MS-related CVD. Upon further investigation, after stratifying for normal and high CRP levels according to guidelines from the Centres for Disease Control and Prevention and the American Heart Association (30), pwMS with low CRP (<3mg/L) had a 38% lower rate of MACE compared to those with high CRP (≥3mg/L). This association remained for stroke, acute myocardial infarction, heart failure, and all-cause mortality with rate differences ranging from 9 to 51% (figure 3). CRP therefore seems to have a strong association with future CVD in pwMS and emphasises the need for comprehensive cardiovascular risk assessment and management. Future studies should validate this association and explore the mechanisms of this association.

Limitations

While the current study leverages a large patient cohort through TriNetX®, several limitations require consideration. First, the data were sourced from EMR databases of healthcare organisations, and there may be underreporting or misclassification of certain health conditions. Additionally, outcomes that occurred outside the TriNetX network are likely to be underrepresented. PSM mitigates the effects of age, sex, ethnicity, comorbidities, and

cardiovascular medication use, though confounding factors such as MS subtype, lifestyle factors (e.g. alcohol consumption, smoking behaviours, and levels of physical activity), disease-modifying MS therapies, and genetics could still influence the results. For instance, previous research suggests that different MS subtypes have varying risks for cardiovascular disease (51). Future studies should examine how MS subtypes and lifestyle factors impact cardiovascular rate and long-term outcomes. Research has found that physical activity in pwMS is not only beneficial for symptom management and potential disease modification (52, 53), but also for reduction of cardiovascular risk factors (54) and comorbidities (55). Yet, pwMS remain less physically active than those without MS (56, 57). Furthermore, certain variables included in the PSM process, such as cardiovascular medications and procedures, are likely markers of MACE. Their inclusion was necessary to ensure balance between the cohorts, though this approach could introduce bias in the estimated rates of incident MACE. This study compared the rate of MACE in pwMS to pwRA due to both being autoimmune conditions with established higher CVD risk compared to the general population. However, analysis of the rate of MACE directly among other autoimmune conditions may be of interest. Moreover, after PSM, the numbers of pwMS and pwRA did not reflect the population prevalence in the USA, which may introduce some bias. Diagnoses in TriNetX rely solely on ICD codes which may vary by healthcare organisation and lack detail about diagnostic processes (58). For analyses of cardiovascular risk factors, the index date was defined by the first recording of both the autoimmune disease and the risk factor. As cohort entry was therefore conditional on exposure ascertainment, selection bias may have been introduced. Accordingly, the estimated hazard ratios should be interpreted as associations among individuals with documented risk-factor status rather than as risk estimates from the time of MS or RA diagnosis. Additionally, the large number of comparisons made in the current study requires acknowledgement, as it increases the potential for type 1 error. To mitigate this risk associated with multiple hypothesis testing, statistical significance was set as $P < 0.001$. Finally, the study population, drawn predominantly from US healthcare organisations, may not represent the wider US population, or other populations and the generalisability of the results beyond this population is unclear.

Conclusions

This study with 147,933 pwMS aged 55 years and older, demonstrated that 8-12% pwMS (dependent on cardiovascular risk factors) experienced a MACE within a 5-year follow-up period that occurred at least 5-years after an MS diagnosis. Cardiovascular risk factors were also associated with significantly higher rate of MACE in pwMS. There was a higher rate of stroke and all-cause mortality in pwMS versus matched pwRA. Early identification and control of traditional risk factors, coupled with close monitoring of inflammatory markers, may improve long-term cardiovascular outcomes for pwMS.

Data Availability

A request can be made to TriNetX (https://live.trinetx.com) to access data in the research network but may require costs and necessitate a data sharing agreement. No patient identifiable information can be provided.

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Author contributions

BJRB, MFR, SLH, LAV, GMcD, AHAR, LMcC, and CAY were involved in conceptualisation and design of the study. MFR conducted the analyses with support from BJRB. All authors were involved in the interpretation of the results. MFR drafted the manuscript. All authors reviewed the results, revised it critically, approved the final version of the manuscript and agreed to be accountable for all aspects of this work.

Competing Interests

The authors declare that they have no competing interests.

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Table 1. Cohort characteristics for people with multiple sclerosis and people with rheumatoid arthritis before and after propensity score matching.

	Initial Populations			Propensity Score Matching		
	People with MS (n=147,933); % (n)	**People with RA (n=657,138); % (n)**	**Std diff.**	**People with MS (n=129,497); % (n)**	**People with RA (n=129,497); % (n)**	**Std diff.**
Age at Index; mean (SD)	57.2 +/- 9.8	66.1 +/- 11.3	0.843	57.7 +/- 9.6	57.7 +/- 9.7	0.008
Female	74 (98952)	0.732 (458822)	0.017	74 (95820)	74.4 (96282)	0.008
Male	25.8 (34568)	26.7 (167176)	0.019	25.9 (33485)	25.5 (33043)	0.008
Black or African American	10.9 (14551)	12.3 (76972)	0.044	11.1 (14342)	10.8 (14030)	0.008
White	73.2 (97915)	63.1 (395081)	0.219	72.6 (93961)	73 (94557)	0.010
Asian	0.9 (1161)	4.3 (26827)	0.217	0.9 (1161)	0.8 (1066)	0.008
American Indian or Alaska Native	0.3 (393)	0.5 (3298)	0.036	0.3 (393)	0.3 (393)	0.007
Native Hawaiian or Other Pacific Islander	0.1 (156)	0.3 (1831)	0.039	0.1 (156)	0.1 (123)	0.008

Other Race	2.2 (2935)	2.5 (15556)	0.019	2.2 (2896)	2.2 (2885)	0.001
Unknown Race	12.4 (16626)	17.1 (106910)	0.131	12.8 (16588)	12.7 (16491)	0.002
Hispanic or Latino	2.6 (3542)	5.4 (33852)	0.141	2.7 (3541)	2.7 (3477)	0.003
Not Hispanic or Latino	64.6 (86368)	60 (375801)	0.095	64.3 (83308)	65 (84137)	0.013
Unknown Ethnicity	32.8 (43827)	34.6 (216822)	0.039	32.9 (42648)	32.3 (41883)	0.013
Comorbidities						
Hypertensive diseases	0.7 (913)	0.7 (913)	0.068	0.7 (907)	0.6 (813)	0.009
Ischemic heart diseases	12.3 (16461)	33.3 (208460)	0.516	12.7 (16450)	12.4 (16071)	0.009
Cerebrovascular diseases	3.8 (5037)	6.9 (43360)	0.141	3.8 (4904)	3.4 (4462)	0.018
Type 2 diabetes mellitus	3.5 (4669)	12.2 (76614)	0.329	3.6 (4662)	3.6 (4667)	<0.001
Type 1 diabetes mellitus	4.8 (6477)	13.6 (85021)	0.305	5 (6466)	4.8 (6232)	0.008
Cardiovascular Care and Medications						
Cardiovascular Procedures	8.9 (11886)	22 (137887)	0.369	9.2 (11856)	8.9 (11573)	0.008
Cardiovascular Medications	20.4 (27262)	20.4 (27262)	0.469	21 (27200)	20.8 (26925)	0.005
Analgesics	21.2 (28319)	40.8 (255320)	0.433	21.8 (28257)	21.7 (28159)	0.002
Antidepressants	12 (16047)	18.2 (114093)	0.174	12.2 (15816)	12.1 (15676)	0.003

*PwMS; people with multiple sclerosis, PwRA; people with rheumatoid arthritis, SD; standard deviation. *Index; MS/RA with/without cardiovascular risk factor measurement recorded in database.*

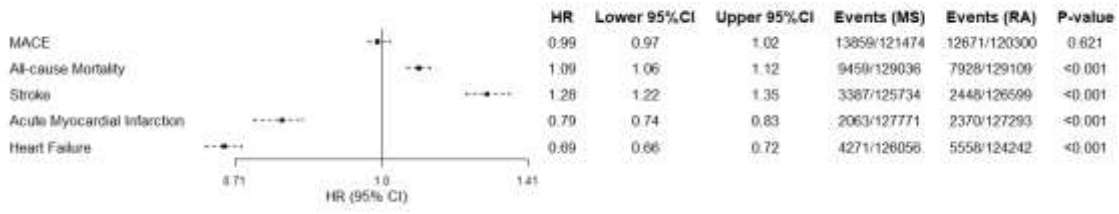
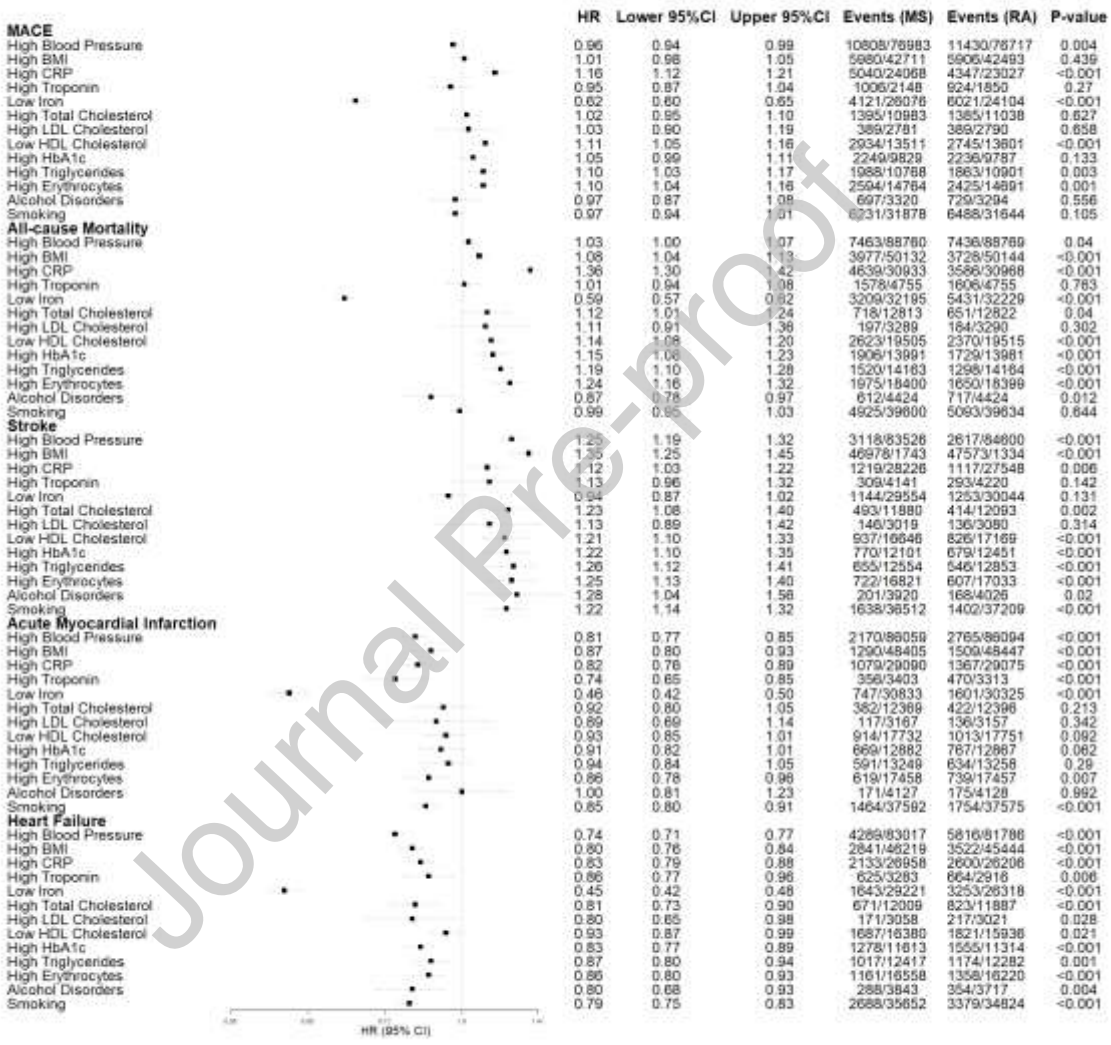


Figure 1. Forest plot presenting hazard ratios for 5-year incidence of MACE, all-cause mortality, stroke, acute myocardial infarction, and heart failure comparing people with MS

to propensity score matched people with RA, excluding participants with prior MACE that occurred before 2020. *CI; confidence interval, HR; hazard ratio; MACE; major adverse cardiovascular events, pwMS; people with Multiple Sclerosis, pwRA; people with Rheumatoid Arthritis*



	HR	Lower 95%CI	Upper 95%CI	Events (MS)	Events (RA)	P-value
MACE						
High Blood Pressure	0.96	0.94	0.99	10808/76983	11430/76717	0.004
High BMI	1.01	0.98	1.05	5980/42711	5906/42493	0.439
High CRP	1.16	1.12	1.21	5040/24068	4347/23027	<0.001
High Troponin	0.95	0.87	1.04	1006/2148	924/1850	0.27
Low Iron	0.62	0.60	0.65	4121/26076	6021/24104	<0.001
High Total Cholesterol	1.02	0.95	1.10	1395/10983	1385/11038	0.627
High LDL Cholesterol	1.03	0.90	1.19	389/2781	389/2790	0.658
Low HDL Cholesterol	1.11	1.05	1.16	2934/13511	2745/13601	<0.001
High HbA1c	1.05	0.99	1.11	2249/9829	2236/9787	0.133
High Triglycerides	1.10	1.03	1.17	1988/10788	1863/10901	0.003
High Erythrocytes	1.10	1.04	1.16	2594/14764	2425/14691	0.001
Alcohol Disorders	0.97	0.87	1.08	697/3320	729/3294	0.556
Smoking	0.97	0.94	1.01	6231/31878	6488/31644	0.105
All-cause Mortality						
High Blood Pressure	1.03	1.00	1.07	7463/88760	7436/88769	0.04
High BMI	1.08	1.04	1.13	3977/50132	3728/50144	<0.001
High CRP	1.36	1.30	1.42	4639/30933	3586/30968	<0.001
High Troponin	1.01	0.94	1.08	1578/4755	1606/4755	0.783
Low Iron	0.59	0.57	0.62	3209/32195	5431/32229	<0.001
High Total Cholesterol	1.12	1.01	1.24	718/12813	651/12822	0.04
High LDL Cholesterol	1.11	0.91	1.36	197/3289	184/3290	0.302
Low HDL Cholesterol	1.14	1.08	1.20	2623/19505	2370/19515	<0.001
High HbA1c	1.15	1.08	1.23	1906/13991	1729/13981	<0.001
High Triglycerides	1.19	1.10	1.28	1520/14163	1298/14164	<0.001
High Erythrocytes	1.24	1.16	1.32	1975/18400	1650/18399	<0.001
Alcohol Disorders	0.87	0.78	0.97	612/4424	717/4424	0.012
Smoking	0.99	0.95	1.03	4925/39600	5093/39634	0.644
Stroke						
High Blood Pressure	1.25	1.19	1.32	3118/83526	2617/84600	<0.001
High BMI	1.35	1.25	1.45	46978/1743	47573/1334	<0.001
High CRP	1.12	1.03	1.22	1219/28226	1117/27548	0.006
High Troponin	1.13	0.96	1.32	309/4141	293/4220	0.142
Low Iron	0.94	0.87	1.02	1144/29554	1253/30044	0.131
High Total Cholesterol	1.23	1.08	1.40	493/11880	414/12093	0.002
High LDL Cholesterol	1.13	0.89	1.42	146/3019	136/3080	0.314
Low HDL Cholesterol	1.21	1.10	1.33	937/16646	826/17169	<0.001
High HbA1c	1.22	1.10	1.35	770/12101	679/12451	<0.001
High Triglycerides	1.26	1.12	1.41	655/12554	546/12853	<0.001
High Erythrocytes	1.25	1.13	1.40	722/16821	607/17033	<0.001
Alcohol Disorders	1.28	1.04	1.58	201/3920	168/4026	0.02
Smoking	1.22	1.14	1.32	1638/36512	1402/37209	<0.001
Acute Myocardial Infarction						
High Blood Pressure	0.81	0.77	0.85	2170/88059	2765/88094	<0.001
High BMI	0.87	0.80	0.93	1290/48405	1509/48447	<0.001
High CRP	0.82	0.76	0.89	1079/29090	1367/29075	<0.001
High Troponin	0.74	0.65	0.85	356/3403	470/3313	<0.001
Low Iron	0.46	0.42	0.50	747/30833	1601/30325	<0.001
High Total Cholesterol	0.92	0.80	1.05	382/12369	422/12396	0.213
High LDL Cholesterol	0.89	0.69	1.14	117/3167	136/3157	0.342
Low HDL Cholesterol	0.93	0.85	1.01	914/17732	1013/17751	0.092
High HbA1c	0.91	0.82	1.01	669/12882	767/12867	0.062
High Triglycerides	0.94	0.84	1.05	591/13249	634/13258	0.29
High Erythrocytes	0.86	0.78	0.96	619/17458	739/17457	0.007
Alcohol Disorders	1.00	0.81	1.23	171/4127	175/4128	0.992
Smoking	0.85	0.80	0.91	1464/37592	1754/37575	<0.001
Heart Failure						
High Blood Pressure	0.74	0.71	0.77	4289/83017	5816/81786	<0.001
High BMI	0.80	0.76	0.84	2841/46219	3522/45444	<0.001
High CRP	0.83	0.79	0.88	2133/26958	2600/26206	<0.001
High Troponin	0.86	0.77	0.96	625/3283	664/2916	0.006
Low Iron	0.45	0.42	0.48	1643/29221	3253/26318	<0.001
High Total Cholesterol	0.81	0.73	0.90	671/12009	823/11887	<0.001
High LDL Cholesterol	0.80	0.65	0.98	171/3058	217/3021	0.028
Low HDL Cholesterol	0.93	0.87	0.99	1687/16380	1821/15936	0.021
High HbA1c	0.83	0.77	0.89	1278/11613	1555/11314	<0.001
High Triglycerides	0.87	0.80	0.94	1017/12417	1174/12282	0.001
High Erythrocytes	0.86	0.80	0.93	1161/16558	1358/16220	<0.001
Alcohol Disorders	0.80	0.68	0.93	288/3843	354/3717	0.004
Smoking	0.79	0.75	0.83	2688/35852	3379/34824	<0.001

Figure 2. Forest plots presenting hazard ratios for MACE, all-cause mortality, stroke, acute myocardial infarction, and heart failure comparing pwMS to propensity score matched pwRA with individual cardiovascular risk factors. *BMI; body mass index, BP; blood pressure, CRP; c-reactive protein, HbA1c; glycated haemoglobin, HDL; high-density lipoprotein, HR;*

hazard ratio, LDL; low-density lipoprotein, MACE; major adverse cardiovascular events, pwMS; people with Multiple Sclerosis, pwRA; people with Rheumatoid Arthritis. Parameter definitions included in supplemental table S2.

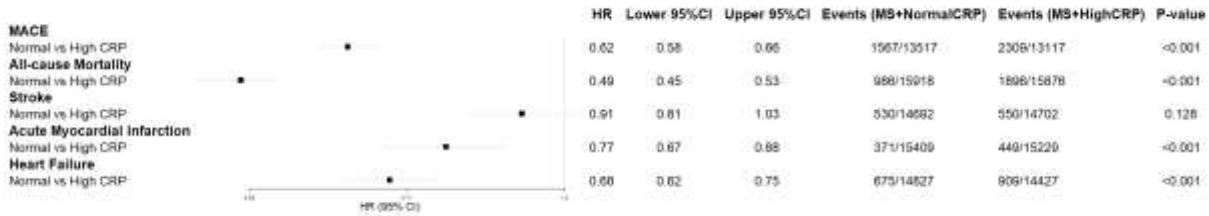


Figure 3. Forest plots presenting hazard ratios for MACE, all-cause mortality, stroke, acute myocardial infarction, and heart failure comparing people with MS and normal CRP levels to propensity score matched people with high CRP levels. *CRP; c-reactive protein, MACE; major adverse cardiovascular events, MS; multiple sclerosis.*
CRP defined as normal <3mg/L and high ≥3mg/L.

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Competing Interests

The authors declare that they have no competing interests.