Evaluating the Risk of Macrovascular Events and Mortality Among People With Multiple Sclerosis in England

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IMPORTANCE People with multiple sclerosis (MS) are associated with an increased risk of cardiovascular disease and mortality; however, evidence from population-based studies is sparse.

OBJECTIVE To assess whether the risk of macrovascular events and mortality differs among people with MS compared with a matched population without MS in England.

DESIGN, SETTING, AND PARTICIPANTS A population-based retrospective matched cohort study was conducted in general practices registered with the Clinical Practice Research Datalink in England between January 1, 1987, and September 30, 2018, with a mean (SD) follow-up of 11.3 (6.5) years. A total of 12 251 patients with MS were matched with up to 6 people without MS (n = 72 572) by age, sex, and general practice. People with 3 or more diagnoses of MS recorded during the study period were included. The first MS diagnosis was considered as index date.

EXPOSURES Multiple sclerosis status. Analyses were also stratified by sex.

MAIN OUTCOMES AND MEASURES Main outcomes were acute coronary syndrome, cerebrovascular disease, any macrovascular disease (including peripheral arterial disease), and mortality (all-cause mortality and cardiovascular disease–specific mortality). Cox proportional hazards regression and Fine and Gray proportional subhazard regression models were used to assess differences in rates.

RESULTS A total of 12 251 people with MS (66.9% women; mean [SD] age, 44.9 [13.3] years) were matched with 72 572 people without MS (69.8% women; mean [SD] age, 44.9 [13.3] years). As compared with people without MS, people with MS were associated with a 28% increased hazard of acute coronary syndrome (hazard ratio [HR], 1.28; 95% CI, 1.09-1.51), 59% increased hazard of cerebrovascular disease (HR, 1.59; 95% CI, 1.32-1.92), 32% increased hazard of any macrovascular disease (HR, 1.32; 95% CI, 1.15-1.52), 3.5-fold increased hazard of all-cause mortality (HR, 3.46; 95% CI, 3.28-3.65), and 1.5-fold increased hazard in cardiovascular disease mortality (HR, 1.47; 95% CI, 1.27-1.71). Differences in macrovascular events were more pronounced among women than men. Mortality risk was also higher for women than men. Treatment with lipid-lowering medications (mainly statins) was associated with lower mortality rates among people with MS.

CONCLUSIONS AND RELEVANCE This study suggests that MS is associated with an increased risk of cardiovascular and cerebrovascular disease that is not completely accounted for by traditional vascular risk factors. Given the adverse effects of these comorbidities on outcomes in patients with MS, further investigation is needed.

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he understanding of the importance of vascular risk factors and their management in multiple sclerosis (MS) has improved over time.1-6 Compared with the general population, people with MS were associated with a higher prevalence of hypertension and hyperlipidemia,1 being overweight or obese, having ever smoked, and having lower levels of physical activity.7

People with MS may also be at increased risk of macrovascular events, such as cerebrovascular disease and acute myocardial infarction, even after controlling for traditional vascular risk factors.1,8 However, most studies assessing the association between vascular risk factors and MS were not population based,1,9 and in many cases, they were conducted in specific settings with limited generalizability to the general population.9-11 Some studies did not control for health behaviors, while, for others, the study period terminated before the modern era of MS and cardiac treatments.12 In addition, some limited evidence suggests that women with MS may have a higher risk of vascular disease than men with MS.13

Mortality among people with MS remains higher than in the general population.7,14 Nevertheless, little is known about whether MS also confers an increased risk of vascular disease-related mortality and whether people with MS might benefit from tighter control of vascular risk factors.

Therefore, we used a large dataset representative of the English population to evaluate the association between vascular risk factors and the risk of macrovascular disease and mortality among people with MS compared with the general population.

Methods

Study Design

We conducted a population-based retrospective matched cohort study that included people with MS registered with general practices in England, diagnosed between January 1, 1987, and September 30, 2018. The Independent Scientific Advisory Committee of the UK Clinical Practice Research Datalink (CPRD) granted ethics approval (protocol number: 18_279R). Informed consent was not required for use of this anonymized data set.

Data Source

We used data from the CPRD, one of the largest databases of electronic medical records globally.15 The CPRD holds anonymized routinely collected longitudinal primary care records, covering approximately 7% of the UK population; it is representative in terms of age, sex, and race/ethnicity.16,17 Within the CPRD we focused on the English data set, as linkages to Hospital Episode Statistics and Office for National Statistics mortality data are available.15

Study Population

Similar to a previously adopted algorithm to identify people with MS in the CPRD,16 we identified possible cases of MS based on diagnostic and management primary care codes, International Statistical Classification of Diseases and Related Health

### Key Points

**Question** Do people with multiple sclerosis have an increased risk of macrovascular disease and mortality?

**Findings** In this population-based matched cohort study of 84,823 people with or without multiple sclerosis, those with multiple sclerosis were associated with an increased risk of macrovascular disease, even after controlling for sociodemographic variables and traditional vascular risk factors. People with multiple sclerosis were also associated with a 3.5-fold increased risk of all-cause mortality and a 1.5-fold increased risk of cardiovascular disease mortality; treatment with statins was associated with lower mortality rates among people with multiple sclerosis.

**Meaning** These findings show that multiple sclerosis is associated with an increased risk of cardiovascular and cerebrovascular disease, which is not completely accounted for by traditional vascular risk factors.

Problems, Tenth Revision (ICD-10) codes, and on prescription of disease-modifying therapies used exclusively to treat MS. To improve case finding, management primary care codes were also considered (eTable 1 in the Supplement). When linkage to secondary care data was available, Hospital Episode Statistics data were also considered to confirm the MS diagnosis (ICD-10 code G35). Based on prior work in the CPRD requiring 2 or more MS events and associated symptom and treatment codes19 as well as findings from other studies validating the use of administrative health care data to identify patients with MS,20 to reduce the risk of misclassification, we defined patients with MS as those with 3 or more MS events recorded in their available clinical history. Date of the first MS diagnosis was considered the index date.

Additional inclusion criteria for patients with MS were: (1) diagnosis after January 1, 1987, when magnetic resonance imaging was available to support the diagnosis; (2) continuous registration with the CPRD practice for 1 year or more before the first MS event to ensure that information regarding key covariates was available at onset; (3) defined sex (male or female); (4) valid date of birth; (5) age 18 years or older at cohort entry; (6) MS events recorded before the date of death; and (7) validity of patients’ clinical records in terms of continuous follow-up and data recording defined by the CPRD definition of “up to standard” (eFigure in the Supplement). Up to standard is deemed as the date at which the practice is considered to have high-quality data, based on continuity in data and death recording. Individuals were considered eligible if the clinical information recorded in the year before the index date and the follow-up were considered up to standard.

People with MS were randomly matched with up to 6 people without MS by age, sex, and general practice. Controls had up-to-standard clinical data recorded during the study period and did not have MS or any other demyelinating disease event recorded (eg, optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, and central nervous system demyelination not elsewhere classifiable), which minimized the possibility of including controls who might develop MS in the future. People with MS were matched with mul-
multiple controls to reduce variance.\textsuperscript{21} We assigned the controls the index date of their matched patient with MS. People were followed until their death or the end of the study period (September 30, 2018). People who survived to the end of the study period were censored at the date of last data collection for the CPRD practice.

**Study Variables**

Consistent with previous CPRD research,\textsuperscript{22-27} we defined study variables using comprehensive primary care code lists and ICD-10 codes (eTable 2 in the Supplement). Prescribing data were extracted using British National Formulary codes. Study outcomes included the following incident vascular events occurring after the index date: acute coronary syndrome, cerebrovascular disease, and macrovascular disease (either acute coronary syndrome, cerebrovascular disease, or peripheral arterial disease), as well as mortality, including all-cause mortality and cardiovascular disease–specific mortality.

Study covariates included individuals’ sociodemographic characteristics (age [continuous], sex, race/ethnicity [white or nonwhite], and index of multiple deprivation [quintiles]\textsuperscript{28}); vascular risk factors, including smoking status (current smoker, former smoker, or nonsmoker), diagnoses of type 2 diabetes and clinical depression, treatment with lipid-lowering, oral antidiabetic, antiplatelet, anticoagulant, and antihypertensive therapies in the index year; and year of MS diagnosis. Treatment with antihypertensive medications was used as a proxy for hypertension, consistent with previous studies.\textsuperscript{29} We also included the number of primary care visits in the year before the index year to account for differences in health care use between the MS and matched cohorts (surveillance bias).

**Statistical Analysis**

Differences in study variables between people with MS and controls in the index year were assessed using \( \chi^2 \) tests, \( t \) tests, and Kruskal-Wallis tests, as appropriate. We used multivariable Cox proportional hazards regression models to model differences in the hazard of each outcome of interest. For the analyses of incident vascular events, people with a history of the relevant outcome at baseline were excluded from the analysis. For analyses of cardiovascular–specific mortality we used competing-risk regressions based on the Fine and Gray proportional subhazard model where noncardiovascular disease mortality was the competing event and cumulative incidence functions were computed for subgroups of interest. The proportional hazards assumption was met as assessed using plots of log (-log survival time) against log survival time and Schoenfeld residuals against survival time. We also used linear regression of Schoenfeld residuals on time to test for independence between residuals and time. To better understand the role of each covariate in the regression models and avoid overfitting, models were first adjusted for presence of MS, age, and sex. Successively, models were adjusted for other sociodemographic characteristics (eg, ethnicity and deprivation), then for vascular risk factors and comorbidities, then for vascular treatments. Finally, models were adjusted for primary care visits and year of diagnosis. To compare fit of different models we used Akaike Information Criterion. We repeated these analyses after stratifying by sex to assess effect modification.

**Complementary Analyses**

We conducted a sensitivity analysis in which we included only patients with incident MS (and their matched controls) diagnosed from 2002 onward, the year of full implementation of the 2001 McDonald et al\textsuperscript{30} criteria for the diagnosis of MS in UK clinical practice. As lipid-lowering treatment at baseline was associated with all-cause and cardiovascular mortality but with opposite trajectories, we investigated a possible interaction between treatment with lipid-lowering medication and MS status by adding an interaction term between the 2 variables and repeated the regression analyses for all outcomes. Because the use of different vascular treatments and the occurrence of comorbidities during the study period might modify the risk of all-cause mortality and macrovascular events, we conducted an additional sensitivity analysis in which treatments and comorbidities were included as time-varying variables in the Cox proportional hazards regression models.

Results were presented as hazard ratios (HR) and subhazard ratios (SHR) and 95% CIs, as appropriate. We used the Nelson-Aalen cumulative hazard curves to plot the estimated risk of MS status on incident macrovascular disease and mortality. All \( P \) values were from 2-sided tests and results were deemed statistically significant at \( P < .05 \). We used Stata, version 15 MP (StataCorp LLC) to conduct statistical analyses.

**Results**

We identified 12,251 people with MS diagnosed between January 1, 1987, and September 30, 2018, and 72,572 matched controls. On average, each patient with MS was matched with a mean (SD) of 5.9 (0.3) controls. Mean (SD) follow-up time was 10.3 (6.3) years for people with MS and 11.5 (6.5) years for controls (Table). Among the patients with MS, 66.9% were women, and the mean (SD) age was 44.9 (13.3) years; among the controls, 69.8% were women, and the mean (SD) age was 44.9 (13.3) years. More patients with MS smoked than controls (37.9% vs 29.4%), while the proportion of individuals using cardiovascular medications in the 2 cohorts was broadly similar (anti-hypertensive medication, 5.6% vs 5.7%; lipid-lowering medication, 2.7% vs 2.9%; antiplatelet medication, 2.7% vs 2.0%; anticoagulant medication, 0.5% vs 0.5%). When restricting the study period to 2002-2018, a total of 7957 people with MS were included and matched with 47,175 controls. Characteristics of this subcohort were similar to those of the main cohort (Table).

**Incident Macrovascular Disease**

During the study period, the incidence among patients with MS per 100,000 person-years of acute coronary syndrome was 204.5 (95% CI, 179.6-233.0), of cerebrovascular disease was 159.6 (95% CI, 138.1-184.4), and of composite macrovascular events was 291.8 (95% CI, 261.2-326.0). The incidence of acute coronary syndrome was 116.8 (95% CI, 109.3-124.8) among controls, the incidence of cerebrovascular disease was 81.4 (95%
The incidence of composite macrovascular events was 159.1 (95% CI, 150.2-168.4) among controls (Figure 1; eTable 3 in the Supplement). Compared with controls, on multivariable analysis, people with MS had an increased hazard of acute coronary syndrome (HR, 1.28; 95% CI, 1.09-1.51), cerebrovascular disease (HR, 1.59; 95% CI, 1.32-1.92), and any macrovascular disease (HR, 1.32; 95% CI, 1.15-1.52). In stratified analyses, differences between cohorts were observed in women but not in men. Compared with women without MS, those with MS had an increased hazard of acute coronary syndrome (HR, 1.28; 95% CI, 1.09-1.51), cerebrovascular disease (HR, 1.59; 95% CI, 1.32-1.92), and any macrovascular disease (HR, 1.32; 95% CI, 1.15-1.52). In stratified analyses, differences between cohorts were observed in women but not in men.
coronary syndrome (HR, 1.42; 95% CI, 1.16-1.75), cerebrovascular disease (HR, 1.78; 95% CI, 1.41-1.23), and any macrovascular disease (HR, 1.49; 95% 1.26-1.77).

In the sensitivity analysis limiting the cohort to incident cases of MS diagnosed in 2002-2018, general findings were consistent. However, differences in rates of macrovascular disease were also observed in men. Compared with men without MS, men with MS had an increased hazard of acute coronary syndrome (HR, 1.81; 95% CI, 1.22-2.69) and any macrovascular disease (HR, 1.49; 95% CI, 1.15-2.43).

**All-Cause Mortality and Cardiovascular Disease Mortality**

During the study period, the observed mortality rate per 100 000 person-years was 2223.3 events (95% CI, 2140.5-2309.2) for people with MS and 619.5 events (95% CI, 602.5-637.0) for controls (eTable 3 in the Supplement). In adjusted analyses, compared with controls, people with MS had an increased risk of all-cause mortality (HR, 3.46; 95% CI, 3.28-3.65) and cardiovascular disease mortality (HR, 1.47; 95% CI, 1.27-1.71). When stratifying by sex, compared with women without MS, women with MS had a 3.5-fold increase in all-cause mortality (HR, 3.52; 95% CI, 3.28-3.77) and a 1.3-fold increase in cardiovascular disease mortality (SHR, 1.30; 95% CI, 1.04-1.62). As compared with men without MS, those with MS had a 2.7-fold increased risk of all-cause mortality (HR, 2.74; 95% CI, 2.35-3.18) and a 1.5-fold increased risk of cardiovascular disease mortality (SHR, 1.54; 95% CI, 1.06-2.23). Sensitivity analysis restricting the study period to 2002-2018 onward confirmed findings from the main analysis (Figure 2 and Figure 3).

**Complementary Analyses**

Almost 3% of the study population was taking lipid-lowering medications during the index year (2.7% for people with MS, statins in 94.6%; and 2.9% for controls, statins in 94.3%). In adjusted analyses for the people with MS taking lipid-lowering medications, mortality rates were relatively lower, while cardiovascular disease mortality rates were relatively higher than for those not taking them. Compared with controls not taking lipid-lowering medications, those with MS not taking lipid-lowering medications had 3.6-fold increased mortality rates (HR, 3.62; 95% CI, 3.43-3.83), while those with MS taking lipid-lowering medications had 2-fold increased mortality rates (HR, 1.95; 95% CI, 1.58-2.42). No sex-related differences were observed.

Compared with controls not taking lipid-lowering medications, patients with MS not taking lipid-lowering medications had 1.5-fold increased cardiovascular disease mortality rates (SHR, 1.48; 95% CI, 1.26-1.73) and those with MS taking lipid-lowering medications had 2.3-fold increased mortality rates (SHR, 2.28; 95% CI, 1.51-3.43). When stratified by sex, findings were broadly similar (Figure 4).

Findings from sensitivity analyses using time-varying Cox proportional hazards regression models confirmed those from main analysis (eTable 4 in the Supplement). In the sensitivity analysis, men with MS also had an increased risk of vascular disease (acute coronary syndrome: HR, 1.33; 95% CI, 1.02-1.76; cerebrovascular disease: 1.63; 1.20-2.24; and any macrovascular disease: 1.33; 1.04-1.71; eTable 4 in the Supplement). However, differences again remained less pronounced than for women with MS.

**Discussion**

We conducted a population-based matched cohort study of 84 823 people with or without MS. Even after controlling for sociodemographic factors and traditional vascular risk factors, people with MS still had an increased risk of macrovascular disease including acute coronary syndrome, cerebrovascular disease, and any macrovascular disease. Compared with the general population, those with MS were associated with a 3.5-fold increased risk of all-cause mortality and a 1.5-fold increased risk of cardiovascular disease mortality. Although there was no difference in incidence rates of macrovascular disease among men in the main analysis, differences were present among women.

Our findings regarding the increased risk of acute coronary syndrome (including unstable angina and acute myocardial infarction) and stroke are consistent with those of prior studies that used retrospective matched cohort designs, but did not account for smoking status. In a Swedish study, the risk of acute myocardial infarction was 85% higher and the risk of stroke was 71% higher in the population with MS, after adjustment for age, sex, birth country, and comorbidities. In a Danish study, the risk of acute myocardial infarction and stroke was also elevated in people with MS after adjustment for age, sex, diagnosis year, and comorbidity. In a Canadian study, the risk of acute myocardial infarction was 63% higher in the population with MS after adjustment for age, sex, socioeconomic status, diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease as a proxy for smoking status. Women with MS had a greater risk of macrovascular disease than men, consistent with previous findings from Swedish and Canadian studies. Although the risk of macrovascular disease was not increased in men in the main analyses, it was increased in the sensitivity analyses during the time period when MS was diagnosed via magnetic resonance imaging (2002-2018), and that accounted for changes in treatment and comorbidities over time, suggesting that these tem-
In our findings, the increased risk of cardiovascular disease even after accounting for the traditional risk factors that account for most of the risk of these conditions is not unique to MS. Systemic inflammation is a recognized risk factor for atherosclerosis, and other immune-mediated and inflammatory diseases confer an increased risk of cardiovascular disease, including psoriasis, rheumatoid arthritis, and severe atopic eczema. Further investigation is warranted to evaluate the mechanisms underlying our findings.

The increased all-cause mortality observed in the cohort with MS is consistent with prior studies, although few of these studies have accounted for health behaviors such as smoking. Comorbidity, including ischemic heart disease and stroke, confers an increased risk of death in MS, highlighting the importance of preventing and managing these conditions to improve survival. Cardiovascular-specific mortality rates have been the subject of less attention, although cardiovascular disease is the second or third leading cause of death in MS after MS itself.

Treatment with lipid-lowering medications (approximately 95% of which were statins) seemed to have a protective effect by preventing glutamate-mediated excitotoxic mechanisms. The effects of statins on neuroprotection in MS have been investigated during the last 2 decades, with numerous mechanisms postulated, such as direct vasculoprotection and enhanced perfusion and reduction in free radical damage either by improved blood flow and reducing hypoxia-mediated reactive oxygen species production or through direct inhibition of cytotoxic pathways. Also, statins may exert a neuroprotective effect by preventing glutamate-mediated excitotoxic effects. One direct association seen was the 43% reduction in brain atrophy in a cohort of people with secondary progressive MS randomized to receive high-dose simvastatin compared with controls.
Figure 4. Association Between Multiple Sclerosis (MS), Treatment With Lipid-Lowering Medications, and Risk of Macrovascular Disease and Mortality Between January 1987 and September 2018 in England

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Hazard ratio (95% CI)</th>
<th>Reduced risk</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Overall</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
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<td>Controls taking lipid-lowering medications</td>
<td>0.72 (0.44-1.20)</td>
<td>1.06 (0.79-1.42)</td>
<td>1.14 (0.53-2.46)</td>
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<td>Patients with MS</td>
<td>1.49 (1.20-1.84)</td>
<td>0.64 (0.29-1.43)</td>
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<td>Women taking lipid-lowering medications</td>
<td>0.84 (0.58-1.24)</td>
<td>1.03 (0.68-1.56)</td>
<td>1.06 (0.42-2.70)</td>
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<td>Cerebrovascular disease</td>
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<tr>
<td>Controls taking lipid-lowering medications</td>
<td>1.43 (0.89-2.31)</td>
<td>1.85 (1.46-2.33)</td>
<td>1.49 (1.20-1.84)</td>
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<td>Patients with MS</td>
<td>0.82 (0.26-2.57)</td>
<td>0.64 (0.29-1.41)</td>
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<td>Patients with MS taking lipid-lowering medications</td>
<td>0.92 (0.45-1.88)</td>
<td>1.69 (1.40-2.05)</td>
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<tr>
<td>Any macrovascular disease</td>
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<td></td>
<td></td>
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<tr>
<td>Controls taking lipid-lowering medications</td>
<td>0.87 (0.56-1.36)</td>
<td>1.09 (0.84-1.41)</td>
<td>0.84 (0.38-1.86)</td>
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<td>Patients with MS</td>
<td>1.48 (1.06-2.06)</td>
<td>1.85 (1.46-2.33)</td>
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<tr>
<td>Patients with MS taking lipid-lowering medications</td>
<td>0.97 (0.70-1.34)</td>
<td>1.56 (1.31-1.86)</td>
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<tr>
<td>Women taking lipid-lowering medications</td>
<td>0.64 (0.29-1.41)</td>
<td>0.93 (0.72-1.21)</td>
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<tr>
<td>Overall</td>
<td>1.20 (0.88-1.63)</td>
<td>1.69 (1.40-2.05)</td>
<td></td>
</tr>
<tr>
<td>Patients with MS</td>
<td>0.92 (0.45-1.88)</td>
<td>1.69 (1.40-2.05)</td>
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<tr>
<td>Patients with MS taking lipid-lowering medications</td>
<td>0.92 (0.45-1.88)</td>
<td>1.69 (1.40-2.05)</td>
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<td>All-cause mortality</td>
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<td>1.21 (1.01-1.45)</td>
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<td>Patients with MS</td>
<td>1.37 (1.18-1.58)</td>
<td>1.56 (1.31-1.86)</td>
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<td>Patients with MS taking lipid-lowering medications</td>
<td>1.37 (1.18-1.58)</td>
<td>1.56 (1.31-1.86)</td>
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<td>Women taking lipid-lowering medications</td>
<td>0.76 (0.44-1.31)</td>
<td>1.56 (1.31-1.86)</td>
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<td>Overall</td>
<td>1.43 (1.01-1.45)</td>
<td>3.57 (3.26-3.90)</td>
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<td>Patients with MS</td>
<td>1.37 (1.18-1.58)</td>
<td>1.56 (1.31-1.86)</td>
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<tr>
<td>Patients with MS taking lipid-lowering medications</td>
<td>0.76 (0.44-1.31)</td>
<td>1.56 (1.31-1.86)</td>
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<tr>
<td>Cardiovascular disease mortality</td>
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<td></td>
<td></td>
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<tr>
<td>Controls taking lipid-lowering medications</td>
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<td>1.26 (0.99-1.60)</td>
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<td>Patients with MS</td>
<td>1.83 (1.35-2.48)</td>
<td>1.74 (1.42-2.14)</td>
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<td>Patients with MS taking lipid-lowering medications</td>
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<td>Women taking lipid-lowering medications</td>
<td>1.60 (1.28-2.00)</td>
<td>1.48 (1.26-1.73)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.60 (1.28-2.00)</td>
<td>1.48 (1.26-1.73)</td>
<td></td>
</tr>
<tr>
<td>Patients with MS</td>
<td>2.28 (1.51-3.43)</td>
<td>2.28 (1.51-3.43)</td>
<td></td>
</tr>
</tbody>
</table>
Strengths and Limitations

This study had several strengths, including the population-based design, large sample size, and the use of more than 30 years of follow-up data from primary and secondary care settings. To our knowledge, this was the first study to explore at population level a possible protective role of lipid-lowering medications on all-cause mortality in people with MS.

Several limitations also merit discussion. First, we included data from January 1987 to September 2018, a period during which changes in the standard of care for MS and vascular disease occurred. However, we controlled our analyses for the year of MS diagnosis and we conducted a sensitivity analysis restricting our analyses to only patients with MS and matched controls with index year after the full implementation of the 2001 McDonald et al30 criteria in England. In addition, when using routinely collected data, miscoding, misclassification, and misdiagnosis may occur. However, the CPRD is a reliable, widely used data source and is subject to regular quality checks.35 Furthermore, we restricted MS diagnoses to people with 3 or more MS events recorded during the study period to improve case finding. We could not account for cardiovascular risk factors such as physical inactivity and obesity. Although they might be considered as proxies of MS disability, the associated risk of macrovascular disease for these risk factors is low and not enough to attenuate our findings of increased risk.48 Failure to account for these factors might have a greater association with mortality, although these associations are also modest.49,50

Conclusions

This study suggests that MS is associated with an increased risk of cardiovascular and cerebrovascular disease that is not completely accounted for by traditional vascular risk factors. Given the adverse effects of these comorbidities on outcomes in patients with MS, further investigation is needed.


