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What is This?
High risk of cardiovascular diseases after diagnosis of multiple sclerosis

Elham Jadidi¹, Mohammad Mohammadi¹ and Tahereh Moradi¹,²

Abstract
Background: Studies of the risk of cardiovascular diseases (CVDs) in patients with multiple sclerosis (MS) have the potential to improve our understanding of the etiology of and the heterogeneity of prognosis and outcomes.

Objectives: To investigate the risk of myocardial infarction (MI), stroke, heart failure (HF), and atrial fibrillation (AF) or Flutter in MS patients with different ethnicity, both female and male.

Methods: Using Poisson regression, we performed a nationwide study in Sweden to investigate the association between the diagnosis of MS and the risk of MI, stroke, HF, or AF/Flutter in 8281 patients who were hospitalized due to MS from 1987 through 2009, plus 76,640 matched control individuals. We performed stratified analyses by sex, age at follow-up and country of birth.

Results: Among MS patients, the incidence rate ratio for MI was 1.85 (95% confidence interval (CI) 1.59 to 2.15), for stroke was 1.71 (95% CI 1.46 to 2.00), for HF was 1.97 (95% CI 1.52 to 2.56) and for AF/Flutter was 0.63 (95% CI 0.46 to 0.87), as compared with individuals without MS. The increased risks were particularly prominent for women. These associations remained after stratification by sex, age and country of birth.

Conclusion: We recommend careful surveillance and preventive CVDs measures among MS patients, particularly among the women.

Keywords
Multiple sclerosis, cardiovascular disease, myocardial infarction, stroke, heart failure, atrial fibrillation, flutter, Sweden, ethnicity, immigrants, epidemiology, risk factors

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Introduction
Studies to investigate the risk of cardiovascular diseases (CVDs) in patients with multiple sclerosis (MS) have important clinical and public health implications. Such studies could increase our understanding of the etiology of MS and determine whether the underlying causes are similar to those of CVDs, as well as lead to these CVDs having preventive measures, and to prognostic and treatment strategies for MS patients. Despite these important applications, few studies have been performed and their results have been inconsistent.¹⁻⁴ In addition, although men and women are differently affected by MS and CVDs, with MS predominantly affecting young women⁵ and the most common type of CVDs, myocardial infarction (MI), affecting mostly men,⁶ no study to date has examined the risk of CVDs in male and female MS patients separately.

Furthermore, despite a wide variation in the incidence and prevalence between countries, regions and different ethnic groups for MS⁷⁻¹⁰ and for CVDs,⁶¹¹⁻¹³ to our knowledge no data are available regarding the risk of CVDs in MS patients according to immigration status.

In this large cohort study, we estimated the risk of first-time MI, stroke, heart failure (HF) and atrial fibrillation (AF)/flutter among all patients in whom MS had been diagnosed within a demographically and ethnically diverse population in Sweden.

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Materials and methods

Study database

We used the Migration and Health Cohort (M&H Co) database, which was established in 2005 and contains over 15 Swedish national registers that are linked by the 10-digit personal identification number unique to all Swedish residents. Three registers within the M&H Co database were used in our study:

1. The Swedish National Inpatient Register, including clinical data for hospitalized patients with a diagnosis of disease, as well as patients diagnosed with MS, CVDs and comorbid diseases, according to the International Classification of Diseases (ICD) codes. This in-patient register was established in 1964 and reached nationwide coverage in 1987. The positive predictive value for most diseases included in this register is between 85% and 95%.14
2. The Total Population Register at Statistics Sweden, which contains demographic information, country of birth and data on emigration and immigration.15
3. The Cause of Death Register, which since 1952 has recorded the date of death and both the underlying and contributing cause of death.16

The study was approved by the Stockholm Regional Ethical Committee.

Study population

In this population-based comparison cohort study, we identified all 8281 cases of first diagnosis of MS (ICD-8: 340; ICD-9: 340 and ICD-10: G35) between 1 January 1987 and 31 December 2009. We excluded 23 individuals with incorrect information on the date of diagnosis of MS and 594 MS patients who had a prior history of any CVDs (ICD-8: 400–456; ICD-9: 390–448; ICD-10: 100–125, 127–179) before their first registered diagnosis of MS.

For each case, we randomly selected 10 sex- and date-matched individuals from the Total Population Register who were alive and without MS at the date of MS diagnosis of their matched case; thus, we identified a total of 76,640 individuals for the comparison group. We defined the date of first MS diagnosis for the case as the start date of follow-up for the matched group of 10 control subjects. We excluded a total of 3198 individuals with a diagnosis of any CVDs before the date of diagnosis of their matched case. We further excluded 7 227 individuals with incomplete data on their dates of death and emigration. Thus, our final cohort included 7 664 patients with MS and 66,215 control subjects who were without MS.

Follow-up

For the MS patients, follow-up was from the date of diagnosis of MS until the date of their first-time MI (ICD-8 and ICD-9: 410; ICD-10:121), HF (ICD-8: 427.0, 427.1; ICD-9: 428; ICD-10: 150), AF/flutter (ICD-8: 427.4; ICD-9: 427.3; ICD-10: 148), or stroke (defined as subarachnoid hemorrhage, intracerebral hemorrhage and cerebral infarction (ICD-8 and ICD-9: 430, 431, 433, 434, 436; ICD-10: 160–164), death, first emigration, or the end of the study (December 2009), whichever came first. We followed the comparison group from the date of diagnosis of MS in the matched case until the date of diagnosis of MI, HF, AF/flutter, or stroke, the censuring or closing date for the matched case, diagnosis of MS, death, emigration, or the end of the study (December 2009), whichever occurred first.

Statistical methods

We first used Poisson regression, estimated by the maximum likelihood method, to estimate incidence rate ratios (IRRs) and their 95% confidence intervals (CIs) for MI, stroke, HF and AF/flutter in MS patients in the study cohort, as compared with matched control subjects. We further performed stratified analyses by sex, age at follow-up (≤ 60 and > 60 years) and country of birth (Sweden and outside of Sweden).

All our analyses were adjusted for age at the end of follow-up in 5-year categories and calendar period of follow-up (1987–1998 and 1998–2009). We further adjusted for sex and country of birth (within/outside Sweden), when applicable. Because the presence of some comorbid conditions such cardiac valve disease, diabetes mellitus, deep vein thrombosis or pulmonary embolism, chronic obstructive pulmonary disease (COPD), hypertension, renal failure and liver disease might affect the risk of CVDs, we performed additional adjustments for these disorders. These adjustments did not change the risk estimates (change in IRR < 10%); therefore, they were not included in the final model. All statistical analyses were 2-sided and we used SAS V9.1 software (SAS Institute Inc., Cary, NC).

Results

Basic characteristics of the cohort of MS patients and their sex- and date of birth-matched comparison group are shown in Table 1. The majority of MS patients were women (68.1%), younger than 60 years of age (88.4%) and were born in Sweden (90.1%). There was little difference between the prevalence of comorbid diseases between individuals with and without MS, with the exception of deep vein thrombosis/pulmonary embolism, which was slightly higher in MS patients (2.4%) compared with control subjects (0.9%). Mean age at diagnosis (± SD) was 68.1 (± 11.9) years for MI, 68.82 (±12.8) for stroke, 74.0 (± 11.5) for HF and 68.4 (± 11.9) for AF/flutter.

The were 522 CVDs events among MS patients during 71,695 years of follow-up and 2,500 CVDs events among matched control individuals during 636,744 years of follow-up. We found an overall increased risk of MI
Table 1. Characteristics of the cohort of patients with MS and their sex- and date of birth-matched comparison group without MS.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with MS, n (%)</th>
<th>Comparison group, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5215 (68.05)</td>
<td>45,602 (68.87)</td>
</tr>
<tr>
<td>Male</td>
<td>2449 (31.96)</td>
<td>20,612 (31.13)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60 years</td>
<td>6622 (88.40)</td>
<td>58,862 (88.90)</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>1042 (13.60)</td>
<td>7352 (11.10)</td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swedish-born</td>
<td>6906 (90.11)</td>
<td>55,103 (83.22)</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>758 (9.89)</td>
<td>11,111 (16.78)</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>105 (1.37)</td>
<td>689 (1.04)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (0.42)</td>
<td>447 (0.68)</td>
</tr>
<tr>
<td>COPD</td>
<td>59 (0.77)</td>
<td>425 (0.64)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>181 (2.36)</td>
<td>590 (0.89)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>27 (0.35)</td>
<td>242 (0.37)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>41 (0.54)</td>
<td>293 (0.44)</td>
</tr>
<tr>
<td>Cardiac valve disease</td>
<td>11 (0.14)</td>
<td>182 (0.27)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7664</td>
<td>66,214</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; DVT: Deep vein thrombosis; MS: multiple sclerosis; PE: pulmonary embolism.

In our nationwide cohort study that included more than 8000 MS patients in Sweden, we found that a diagnosis of MS increased the risk of MI, stroke and HF; while it reduced the risk of AF/flutter, as compared with a large cohort of matched individuals without MS. These observed associations were consistent in both men and women, younger and older patients, and patients born within or outside Sweden. However, the increased risks were more elevated among women than men. To the best of our knowledge, our study is the first to investigate the risk of important subcategories of CVDs in male and female MS patients, separately, and in immigrants.

The observed increased risk of MI, stroke and HF among MS patients in our study and the noticeably elevated risk in female MS patients, as compared with male patients, may in part be due to a higher prevalence of several unmeasured, but shared CVDs risk factors such as physical inactivity, alcohol and illegal drug consumption, smoking, excessive dietary fat intake, plus depression and anxiety disorders; among MS patients and particularly among women, when compared with individuals without MS and male MS patients.17–21

Common etiological factors in MS and CVDs, such as immune system dysfunction and inflammation, can to some extent explain our findings.22 Identification of several clinical risk factors for CVDs in patients with MS, such as higher plasma levels of homocysteine,23,24 altered thrombogenic factors,25 endothelial dysfunction,26 cardiovascular autonomic dysfunction27 and lower arterial compliance28 may also support the findings of a higher risk of CVDs among the MS patients in our study. It has been suggested that inflammation, oxidative stress and raised levels of homocysteine in MS will lead to endothelial dysfunction, which represents an early step toward atherosclerosis. In addition, the cerebral hypoperfusion29 found in MS increased the risk of CVDs.33,34 The effect of new MS drugs such as fingolimod on the risk of CVDs has yet to be explored. The observed increases in risk of MI, stroke and HF; and decreased risk of AF, in the MS patients in our study were in line with the results of the only reported cohort study (a Danish study1) and also are comparable with the results of a small case-control study showing the increased risk of cerebrovascular disease and congestive HF among 820 ethnic Chinese patients with MS, in Taiwan;3 however, our findings are in contrast with the results of both a cross-sectional and a hospital-based study in the US.2,4

In our study, the observed increased risk of CVDs among MS patients may also lead to increased CVDs-related mortality in MS patients. A higher mortality from CVDs among MS patients, as compared with the general population, was observed in some studies, with a more pronounced increase among women.35,36 However, others show CVDs to be a more frequent cause of death among male than female MS patients.37

Discussion

In our nationwide cohort study that included more than 8000 MS patients in Sweden, we found that a diagnosis of MS increased the risk of MI, stroke and HF; while it reduced the risk of AF/flutter, as compared with a large cohort of matched individuals without MS. These observed associations were consistent in both men and women, younger and older patients, and patients born within or outside Sweden. However, the increased risks were more elevated among women than men. To the best of our knowledge, our study is the first to investigate the risk of important subcategories of CVDs in male and female MS patients, separately, and in immigrants.

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Some limitations of this study should be considered. We excluded from our analyses all patients with a diagnosis of any CVDs before the diagnosis of MS; however, we did not have any information about previous diagnoses of CVDs for the foreign-born individuals before their immigration to Sweden; thus, we may have overestimated the true risk among individuals born outside of Sweden. In addition, we lacked information on some CVDs risk factors such as smoking and alcohol consumption, obesity, hyperlipidemia, and family history of CVDs; however, the adjustment for comorbidities such as diabetes mellitus, deep vein thrombosis/pulmonary embolism, COPD and hypertension, which may be related to these risk factors, did not affect our risk estimates.

The observed significant rise in the risk of MI, stroke and HF, and the reduced risk of AF/flutter among patients with MS, as compared with matched control subjects, suggested that careful surveillance and preventive CVDs measures are warranted among MS patients. In addition, further research should be conducted to explore the etiology of MS and the cause of this observed association between MS and CVDs. The stronger, increased risk of MI, stroke and HF in women, plus the greater risk of stroke between MS and CVDs. The stronger, increased risk of MI, stroke and HF, and the reduced risk of AF/flutter among patients with MS, as compared with matched control subjects, suggested that preventive measures are warranted among MS patients. In addition, further research should be conducted to explore the etiology of MS and the cause of this observed association between MS and CVDs. The stronger, increased risk of MI, stroke and HF, and the reduced risk of AF/flutter among patients with MS, as compared with matched control subjects, suggested that preventive measures could be particularly important for these subgroups of MS patients.

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Conflict of interest
None declared.

References


