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Non-infectious comorbidity in patients with multiple sclerosis: A national cohort study in Sweden

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Abstract

Background: Comorbidity is of significant concern in multiple sclerosis (MS). Few population-based studies have reported conditions occurring in MS after diagnosis, especially in contemporary cohorts.

Objective: To explore incident comorbidity, mortality and hospitalizations in MS, stratified by age and sex.

Methods: In a Swedish population-based cohort study 6602 incident MS patients (aged ≥18 years) and 61,828 matched MS-free individuals were identified between 1 January 2008 and 31 December 2016, using national registers. Incidence rates (IRs) and incidence rate ratios (IRRs) with 95% CI were calculated for each outcome.

Results: IRs of cardiovascular disease (CVD) were higher among MS patients than MS-free individuals, (major adverse CVD: IRR 1.42; 95% CI 1.12–1.82; hemorrhagic/ischemic stroke: 1.46; 1.05–2.02; transient ischemic attack: 1.65; 1.09–2.50; heart failure: 1.55; 1.15–2.10); venous thromboembolism: 1.42; 1.14–1.77). MS patients also had higher risks of several non-CVDs such as autoimmune conditions (IRR 3.83; 3.01–4.87), bowel dysfunction (2.16; 1.86–2.50), depression (2.38; 2.11–2.68), and fractures (1.32; 1.19–1.47), as well as being hospitalized and to suffer from CVD-related deaths ((1.91; 1.00–3.65), particularly in females (3.57; 1.58–8.06)).

Conclusion: MS-patients experience a notable comorbidity burden which emphasizes the need for integrated disease management in order to improve patient care and long-term outcomes of MS.

Keywords: Multiple sclerosis, comorbidity, cardiovascular diseases, depression, cohort study, incidence

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system primarily affecting younger and middle-aged individuals, with higher incidence reported among females.[1] Incidence rates also vary depending on ethnic and environmental factors, and the Nordic countries are considered high-risk areas.[1] The prevalence in Sweden has been estimated as 189/100,000 people with an incidence of 10.2 per 100,000 person-years.[2] Physical and mental comorbidities represent significant concerns in MS, since they negatively impact quality of life and clinical outcomes in patients and may contribute to increased adverse risks in patients receiving disease modulatory therapies (DMTs).[3] Compared to the general population, a higher proportion of MS patients are diagnosed with physical conditions such as inflammatory bowel disease, acute infections, malignancies, diabetes, fractures, and hyperlipidemia,[3–12] as well as mental disorders such as depression, bipolar disorders, and anxiety.[3,13–17]

Recent studies suggest an increased risk of cardiovascular events in patients with MS.[7,18–24] Although the literature is still incomplete and partially

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contradictory, some larger population-based studies suggest that MS patients have a higher prevalence of cardiovascular diseases (CVD) and a slightly increased CVD mortality risk.[18,19,22,25] In addition, a recent Swedish cohort study found that venous thromboembolic disorders in progressive MS accounted for a substantial proportion of this risk.[26]

As some DMTs have been found to increase the risk of comorbidity, such as hypertension, it is important to consider such conditions present before therapy is initiated.[3,27] In addition, as comorbidity increases risks of conditions requiring in-patient care, prevention and management of comorbidity can reduce overall health care costs.[28] A better understanding of the prevalence and incidence of comorbidity in MS patients is also important in light of risk-benefit assessments of newer DMTs with limited real-world experience outside of clinical trials. Despite some progress in recent years, significant knowledge gaps regarding comorbidity in MS remains. In particular, population-based studies focusing on incident conditions in MS are still rare,[18,20,29,30] and only a few published study reporting age- and sex-specific incidence estimates.[20,29,30] The objective of this study was to explore incident comorbidity, mortality and hospitalizations, stratified by age and sex, in a large national, population-based cohort of MS patients in Sweden.

Materials and methods

Study design

We performed a retrospective, population-based cohort study including incident MS patients (aged ≥18 years) and MS-free individuals registered in Sweden between the period 1 January 2008 and 31 December 2016. The study was designed to characterize comorbidity, causes of death, hospitalizations and medications among patients compared with a matched MS-free population. Data from four national health and population registers with mandatory reporting were used: A. The National Patient Register (NPR) which includes diagnoses from inpatient and outpatient specialist care coded according to the International Classification of Diseases (ICD). The NPR was established in 1964 with complete coverage across all hospitals in Sweden since 1987 and with comprehensive outpatient specialist care information available beginning in 2001.[20] B. The Cause of Death Register (CDR) comprises data on all deaths among individuals residing in Sweden since 1961. C. In the Prescribed Drug Register (PDR) information on dispensation of prescribed drugs in Sweden has been registered since 2005, with nearly 100% coverage of all dispensed drugs. D. The Total Population Register (TPR) is an administrative population register held by Statistics Sweden that includes information on vital status, region of residence, migration and civil status of all residents of Sweden beginning in 1968. Linkage of individual-level information was enabled across the national registers through unique personal identification numbers (PINs), which exist for each Swedish resident from birth or immigration.

The study was approved by the Uppsala Regional Ethics Committee (DNR 2017–261).

Study population and follow-up

Patients were included in the study if they were recorded in the NPR with a first primary diagnosis of MS (ICD-10: G35) during the inclusion period, which was later confirmed by a second primary MS diagnosis at a hospital neurology or internal medicine department at least 181 days (6 months) after first primary diagnosis. The index date was defined as the date of the first primary MS diagnosis during the study period. Patients with less than five years of continuous residency in Sweden prior to the index date were excluded, as well as patients with a primary diagnosis of MS (ICD-10: G35, ICD-9: 340, ICD-8: 340, and ICD-7: 345) in the NPR prior to the index date. Patients with a first, but not a second confirmatory MS diagnosis between 1 June 2016 and 31 December 2016 were excluded. In total, 6,602 incident MS patients were identified during the study period.

MS-free individuals were defined as those without an MS diagnosis in the NPR throughout the entire study period (ending 31 December 2016). For each MS patient identified, 10 individuals were randomly matched on age, sex, and region (county) of residency at the time of matching, using data from the TPR. MS-free individuals had to be alive and residing in Sweden on the date of the MS diagnosis confirmation of the matched patient to be eligible for inclusion. Each matched individual without MS was assigned the same index date as his or her corresponding MS patient. In total, 66,020 matched individuals were identified and after exclusions (≥1 primary or secondary MS diagnosis in NPR or EMR (N = 15), not alive or emigrated on the confirmation date of the MS patient (N = 624), <5 years of continuous residency prior to index date

(N = 3,553)), 61,828 MS-free individuals were included in the analyses.

Study subjects were followed from the index date until the end of the study observation period, emigration, or death, whichever occurred first.

Comorbidity, causes of death, hospitalizations and medications

Comorbidity data were collected from the NPR, and major disease categories of interest included both cardiovascular and non-cardiovascular diseases. CVD included a composite measure for major adverse cardiovascular events (MACE) which included diagnoses of stroke, myocardial infarction, and sudden death due to CVD. Non-cardiovascular diseases included diabetes, respiratory conditions, psychiatric disorders and liver disease. Only diseases with ICD-10 codes were assessed (see supplemental Appendix A). If a primary or secondary diagnosis prior to the index date was identified it was defined as a prevalent condition and that specific condition was subsequently excluded from incidence estimates during follow-up. In addition, CVDs diagnosed during follow-up were analyzed among those with no prior history of CVD (a CVD diagnosis or prescription of CVD medication) or CVD risk factors (a diagnosis of diabetes, obesity or alcohol liver disease, or prescription of diabetes medication), during one year prior to index date).

Information on mortality was retrieved from the CDR by using ICD-codes for underlying cause of deaths and was categorized as all-cause, MS-related, cardiovascular, cancer-related deaths and suicide. Data on hospitalizations were collected from the NPR and included only primary diagnosis at hospitalization and was categorized as all-cause, MS-related and CVD-related hospitalizations. Both mortality and hospitalizations were assessed from index date until the end of follow-up (Supplemental Appendix A).

In order to capture depression treated in primary care, data on anti-depressive medication with Anatomic Therapeutic Chemical classification (ATC) code N06A were collected from the PDR, both in the year before index-year and during follow-up.

Statistical analysis

For each comorbidity before the index date, the number and proportion of MS patients as well as MS-free individuals were calculated. The two groups were compared using a Chi-square test for comparisons of two population proportions. In the analysis of small numbers, Fisher's exact test was used.

Crude incidence rates (IRs) per 10,000 person-years (PY) with 95% confidence intervals (CI) among MS patients and MS-free individuals, respectively, were calculated for each comorbidity, hospitalization and mortality. Crude incidence rate ratios (IRRs) with 95% CIs were calculated to compare incidence between MS patients and matched individuals for each outcome.

The use of prescribed anti-depressive medications was assessed by the number and proportion of MS patients and MS-free individuals during the year before index date, and in 2-year time intervals during follow-up after cohort entry.

SAS software package version 9.4 was used in all data management and statistical analyses.

Results

Mean age among MS patients and the MS-free population was 40.9 and 41.2 years, respectively, and the proportion of females was 68.5% and 68.6%, respectively. MS patients had a slightly longer duration of historical data available in the patient register compared to the MS-free population (37.7 years vs. 35.9 years).

Non-infectious morbidity in MS patients and MS-free individuals before the index date

The prevalence of CVD before the index date was low among both MS patients and MS-free individuals given the age distribution, ranging from 0% to 2% (Table 1). However, the proportion of hemorrhagic and ischemic stroke, transient ischemic attack (TIA), venous thromboembolism (VTE) and peripheral vascular disease was higher among MS patients compared to the MS-free population. In addition, compared with the MS-free individuals, MS patients had higher prevalence of autoimmune disease, neuromuscular bladder dysfunction, optic neuritis, dyslipidemia, retinal disorders, bowel dysfunction, demyelinating disease other than MS, epilepsy and seizure, depression, anxiety, fracture, and osteoporosis.

Non-infectious comorbidity during follow-up

The IRs of several CVDs were higher among MS patients compared to MS-free individuals, i.e. MACE (IRR 1.42; 95% CI 1.12–1.82), hemorrhagic and ischemic stroke (1.46; 1.05–2.02), TIA (1.65;

Table 1. Prevalence of non-infectious comorbidity before multiple sclerosis (MS) diagnosis compared with MS-free matched individuals in a national, register-based cohort study in Sweden 2008–2016.

	MS patients N = 6602	Matched MS-free individuals N = 61,828	p[a,b]
Cardiovascular comorbidity			
Myocardial infarction	31 (0.5%)	362 (0.6%)	0.1866
Stroke, hemorrhagic and ischemic	133 (2.0%)	370 (0.6%)	**<0.0001**
Transient ischemic attack (TIA)	26 (0.4%)	148 (0.2%)	**0.0247**
Angina pectoris & unspecified ischemic heart disease	54 (0.8%)	604 (1.0%)	0.1507
Heart failure	19 (0.3%)	249 (0.4%)	0.1263
Venous thromboembolism	99 (1.5%)	676 (1.1%)	**0.0064**
Peripheral vascular disease	21 (0.3%)	116 (0.2%)	**0.0320**
Pericardial disease	n < 10	112 (0.2%)	0.3695
Bradycardia and heart block	n < 10	79 (0.1%)	0.0592
Paroxysmal tachycardia	29 (0.4%)	299 (0.5%)	0.5316
Atrial fibrillation and atrial flutter	48 (0.7%)	519 (0.9%)	0.2604
Other cardiac arrhythmias	37 (0.6%)	470 (0.8%)	0.0513
Non-cardiovascular comorbidity			
Autoimmune disease	84 (1.3%)	430 (0.7%)	**<0.0001**
Bladder dysfunction, neuromuscular	79 (1.2%)	142 (0.2%)	**<0.0001**
Optic neuritis	976 (14.8%)	28 (0.0%)	**<0.0001**
Chronic renal disease	10 (0.2%)	132 (0.2%)	0.2582
Diabetes type I	79 (1.2%)	645 (1.1%)	0.3444
Diabetes type II	92 (1.4%)	938 (1.6%)	0.3095
Dyslipidemia	112 (1.7%)	840 (1.4%)	**0.0483**
Retinal disorders	161 (2.4%)	697 (1.2%)	**<0.0001**
Asthma	212 (3.2%)	1838 (3.0%)	0.4665
Chronic obstructive pulmonary disease	26 (0.4%)	262 (0.4%)	0.6314
Bowel dysfunction	235 (3.6%)	1702 (2.8%)	**0.0007**
Crohn disease	34 (0.5%)	294 (0.5%)	0.7624
Ulcerative colitis	41 (0.6%)	436 (0.7%)	0.3492
Cancer	192 (2.9%)	2026 (3.4%)	0.0515
Breast cancer	46 (0.7%)	489 (0.8%)	0.3223
Prostate cancer	n < 10	130 (0.2%)	0.0615
Skin cancer	68 (1.0%)	621 (1.0%)	0.9999
Demyelinating disease other than MS	1418 (21.5%)	13 (0.0%)	**<0.0001**
Epilepsy and seizure	96 (1.5%)	512 (0.8%)	**<0.0001**
Depression	431 (6.5%)	3250 (5.4%)	**0.0001**
Anxiety	351 (5.3%)	2750 (4.6%)	**0.0056**
Fatigue	n < 10	73 (0.1%)	0.7368
Schizophrenia	60 (0.9%)	553 (0.9%)	0.9460
Bipolar affective disorders	64 (1.0%)	455 (0.8%)	0.0590
Fracture	834 (12.6%)	6849 (11.4%)	**0.0021**
Osteoporosis	34 (0.5%)	210 (0.3%)	**0.0329**
Viral liver disease (viral hepatitis)	16 (0.2%)	441 (0.7%)	<0.0001
Alcoholic liver disease	n < 10	29 (0.0%)	0.5234
Chronic liver disease/cirrhosis	n < 10	65 (0.1%)	0.7548
Acute liver disease or failure	0 (0.0%)	11 (0.0%)	0.2724
Toxic liver disease	n < 10	26 (0.0%)	0.9315
Liver diseases without viral or alcoholic cause	13 (0.2%)	150 (0.2%)	0.4170

[a]p-value for chi-squared test of difference in proportions between MS patients and matched MS-free individuals.
[b]In the analysis of small numbers (n < 30), Fishers exact test was used.
Note. Significant results (p<0.05) in bold numerals.

1.09–2.50), heart failure (1.55; 1.15–2.10) and VTE (1.42; 1.14–1.77) (Table 2). The risks of these CVDs were elevated for all ages, but the increased relative risks were most pronounced among those less than 40 years of age (Supplemental Table 1a). For MACE and TIA, respectively, increased IRRs were mainly found among females (MACE 1.66; 1.20–2.30. TIA 2.12; 1.32–3.41).

Also, the risk of developing several non-cardiovascular diseases was higher among MS patients compared to matched MS-free individuals. These comorbidities included autoimmune conditions (IRR 3.83; 95% CI 3.01–4.87; highest IRR among men and those under 60 years of age), retinal disorder (1.76; 1.44–2.16; highest risk among those under 40 years of age), asthma (1.29; 1.04–1.61), bowel dysfunction (2.16; 1.86–2.50), epilepsy and seizure (2.34; 1.66–3.31), depression (2.38; 2.11–2.68), anxiety (1.24; 1.07–1.45), fractures (1.32; 1.19–1.47); highest IRR among those aged 40 years or more), osteoporosis (1.77; 1.22–2.55) and toxic liver disease (3.12; 1.14–8.59) (Supplemental Table 1 b). Neuromuscular bladder dysfunction and optic neuritis are common in MS patients and may also be present before a formal diagnosis has been made. Diagnostic uncertainty at initial presentation also explains the substantially increased IRR of demyelinating diseases other than MS. Collectively, these three conditions accounted for the highest IRRs, ranging from 57.41 to 302.74.

Cardiovascular comorbidity during follow-up in MS patients with no previous CVD or CVD risk factors

MS patients had an increased risk of developing TIA (IRR 2.19; 95% CI 1.20–3.98) when compared with MS-free individuals (Table 3). This increased risk was mainly found in females (2.99; 1.53–5.86) and among those aged less than 60 years (Supplemental Table 2). For VTE the IRR was 1.50 (1.09–2.05), mostly conferred to females and those aged 40 years or older. The IRR of bradycardia and heart block was 2.81 (1.22–6.477), and this elevated IRR was only found in those aged less than 40 years. Notably, among females the IRR of MACE was 1.85 (1.15–2.97) and of myocardial infarction 2.73 (1.31–5.70), whereas no association was observed among men.

Hospitalization and mortality during follow-up

MS patients had a higher incidence rate of hospitalization overall than MS-free individuals (IRR 2.42; 95% CI 2.33–2.51), but IRs of hospital admission for CVD were similar in the two groups (Table 4). In contrast, the risk of CVD-related deaths was nearly twice as high among MS patients than among MS-free individuals (1.91; 1.00–3.65), and this increased risk was only found among females (3.57; 1.58–8.06) (Supplemental Table 3a). The IRR of suicide was 2.58 (1.18–5.65), although the number of events among MS patients was low.

Discussion

In this population-based, national cohort study, MS patients had an increased risk of several incident non-infectious types of comorbidity, when compared with matched MS-free individuals. While these differences were already detectable before the diagnosis of MS, disparities further increased after disease diagnosis. With regard to more serious consequences of comorbidity, MS patients experienced both an increased rate of hospitalizations and elevated mortality. Only a few previous population-based studies have focused on incident comorbid conditions in MS,[18,20,29,30] and we could only identify one with reported age- and sex-specific incidence estimates.[20,29,30] In this respect, the present study is the first to contribute evidence of patterns of comorbidity that characterize the period following a diagnosis of MS.

The existing literature suggests an increased prevalence of certain comorbid conditions in MS, but the overall understanding of the spectrum of comorbidity in population-based samples remains poorly investigated. The increased risk of specific comorbidities observed in this large population, such as a higher incidence of autoimmune disease among the MS patients, is consistent with earlier findings in previous studies.[3] However, in some areas, for example CVD-related outcomes, such studies have reported conflicting results.[18,19,22,25] Accordingly, it is important to emphasize that we found a clear increased risk across several CVD outcomes, as well as a higher risk of CVD-related mortality among Swedish MS patients when compared with matched MS-free individuals. While CVD-related events in this study were infrequent overall, and no increased rate of CVD-related hospitalization was observed, CVD-related death rates were nearly twice as high in incident MS patients, compared to the MS-free population. These results are also of interest in light of recent reports on the association between administration of alemtuzumab and intracerebral hemorrhages, not previously detected from its use in hematological conditions.[31] Regarding psychiatric disorders, previous studies found that depression is common in MS patients.[13,15,17] A Swedish study observed that MS patients had an

Table 2. The risk of incident non-infectious comorbidity after diagnosis of multiple sclerosis (MS) compared with MS-free matched individuals in a national, register-based cohort study in Sweden 2008–2016.

	MS patients N = 6602		MS-free individuals N = 61,828		
	Events	IR (95% CI)[a]	Events	IR (95% CI)[a]	IRR (95% CI)[a]
Cardiovascular comorbidity					
MACE	75	24.12 (18.66–29.57)	501	16.93 (15.45–18.41)	**1.42 (1.12–1.82)**
Myocardial infarction	35	10.99 (7.35–14.63)	252	8.45 (7.41–9.49)	1.30 (0.91–1.85)
Stroke, hemorrhagic and ischemic	42	13.40 (9.35–17.46)	274	9.19 (8.10–10.28)	**1.46 (1.05–2.02)**
Transient ischemic attack	26	8.15 (5.33–11.95)	148	4.94 (4.15–5.74)	**1.65 (1.09–2.50)**
Angina pectoris & unspecified ischemic heart disease	24	7.56 (4.85–11.25)	263	8.86 (7.79–9.93)	0.85 (0.56–1.30)
Heart failure	49	15.37 (11.06–19.67)	296	9.91 (8.78–11.04)	**1.55 (1.15–2.10)**
Venous thromboembolism	93	29.22 (23.28–35.16)	615	20.57 (18.95–22.20)	**1.42 (1.14–1.77)**
Peripheral vascular disease	13	4.07 (2.17–6.96)	90	3.00 (2.38–3.62)	1.36 (0.76–2.42)
Pericardial disease	12	3.75 (1.94–6.55)	62	2.07 (1.55–2.58)	1.81 (0.98–3.36)
Bradycardia and heart block	13	4.06 (2.16–6.94)	76	2.53 (1.96–3.10)	1.60 (0.89–2.89)
Paroxysmal tachycardia	19	5.95 (3.58–9.29)	165	5.52 (4.68–6.36)	1.08 (0.67–1.73)
Atrial fibrillation and atrial flutter	41	12.90 (8.95–16.85)	466	15.69 (14.27–17.12)	0.82 (0.60–1.13)
Other arrhythmias	37	11.63 (7.88–15.37)	309	10.38 (9.23–11.54)	1.12 (0.80–1.57)
Non-cardiovascular comorbidity					
Autoimmune disease	94	29.95 (23.90–36.01)	233	7.82 (6.82–8.82)	**3.83 (3.01–4.87)**
Bladder dysfunction, neuromuscular	334	109.14 (97.43–120.84)	57	1.90 (1.41–2.39)	**57.41 (43.35–76.02)**
Optic neuritis	279	105.98 (93.54–118.42)	12	0.40 (0.21–0.70)	**265.35 (148.89–472.91)**
Chronic renal disease	17	5.31 (3.09–8.50)	171	5.71 (4.85–6.56)	0.93 (0.57–1.53)
Diabetes, type I	15	4.74 (2.65–7.81)	141	4.75 (3.96–5.53)	1.00 (0.59–1.70)
Diabetes, type II	69	21.95 (16.77–27.13)	654	22.22 (20.51–23.92)	0.99 (0.77–1.27)
Dyslipidemia	67	21.34 (16.23–26.45)	701	23.80 (22.04–25.56)	0.90 (0.70–1.15)
Retinal disorders	112	36.17 (29.47–42.87)	606	20.50 (18.87–22.13)	**1.76 (1.44–2.16)**
Asthma	93	30.03 (23.92–36.13)	674	23.19 (21.44–24.95)	**1.29 (1.04–1.61)**
Chronic obstructive pulmonary disease	38	11.92 (8.13–15.71)	290	9.71 (8.59–10.83)	1.23 (0.88–1.72)
Bowel dysfunction	217	71.40 (61.90–80.89)	960	33.05 (30.96–35.14)	**2.16 (1.86–2.50)**
Crohn disease	11	3.45 (1.72–6.17)	84	2.81 (2.21–3.41)	1.23 (0.65–2.30)
Ulcerative colitis	21	6.60 (4.08–10.08)	147	4.93 (4.13–5.73)	1.34 (0.85–2.11)
Cancer	180	58.50 (49.95–67.04)	1657	57.72 (54.94–60.50)	1.01 (0.87–1.18)
Breast cancer	28	8.80 (5.85–12.72)	342	11.51 (10.29–12.73)	0.77 (0.52–1.12)
Prostate cancer	15	4.69 (2.62–7.73)	156	5.21 (4.39–6.02)	0.90 (0.53–1.53)
Skin cancer	78	24.67 (19.20–30.15)	586	19.78 (18.18–21.38)	1.25 (0.98–1.58)
Demyelinating disease other than MS	197	80.59 (69.33–91.84)	n < 10	0.27 (0.11–0.52)	**302.74 (149.30–613.86)**
Epilepsy and seizure	40	12.67 (8.75–16.60)	161	5.40 (4.57–6.24)	**2.34 (1.66–3.31)**
Depression	325	111.56 (99.43–123.69)	1326	46.94 (44.42–49.47)	**2.38 (2.11–2.68)**
Anxiety	193	64.30 (55.23–73.37)	1470	51.66 (49.02–54.30)	**1.24 (1.07–1.45)**
Fatigue	n < 10	0.31 (0.01–1.74)	18	0.60 (0.36–0.95)	0.52 (0.07–3.90)
Schizophrenia	17	5.35 (3.12–8.57)	142	4.77 (3.99–5.56)	1.12 (0.68–1.85)
Bipolar affective disorders	37	11.67 (7.91–15.44)	273	9.16 (8.08–10.25)	1.27 (0.90–1.80)
Fracture	390	143.12 (128.92–157.33)	2846	108.40 (104.42–112.38)	**1.32 (1.19–1.47)**
Osteoporosis	34	10.68 (7.09–14.27)	181	6.05 (5.17–6.93)	**1.77 (1.22–2.55)**
Viral liver disease (viral hepatitis)	12	3.75 (1.94–6.56)	110	3.69 (3.00–4.38)	1.02 (0.56–1.85)
Alcoholic liver disease	n < 10	0.94 (0.19–2.73)	50	1.66 (1.20–2.13)	0.56 (0.18–1.80)
Chronic liver disease/cirrhosis	n < 10	0.62 (0.08–2.25)	45	1.50 (1.06–1.94)	0.42 (0.10–1.72)

(continued)

Table 2. Continued.

	MS patients N = 6602		MS-free individuals N = 61,828		
	Events	IR (95% CI)[a]	Events	IR (95% CI)[a]	IRR (95% CI)[a]
Acute liver disease or failure	n < 10	0.94 (0.19–2.73)	35	1.16 (0.78–1.55)	0.80 (0.25–2.61)
Toxic liver disease	n < 10	1.56 (0.51–3.64)	15	0.50 (0.28–0.82)	**3.12 (1.14–8.59)**
Liver diseases without viral or alcoholic cause	15	4.69 (2.62–7.74)	99	3.30 (2.65–3.95)	1.42 (0.82–2.44)

[a]Per 10,000 person-years. Crude IR and IRR.
CI: confidence interval; IR: incidence rate; IRR: incidence rate ratio; MACE: major adverse cardiovascular events; N/A: not applicable.
Note. Significant results (p<0.05) in bold numerals.

Table 3. The risk of incident cardiovascular (CV) comorbidity (with no history of CV diseases (CVD) or CVD risk factors) after diagnosis of multiple sclerosis (MS) compared with MS-free matched individuals in a national, register-based cohort study in Sweden 2008–2016.

	MS patients N = 4539		MS-free individuals N = 47,527		
	Events	IR (95% CI)[a]	Events	IR (95% CI)[a]	IRR (95% CI)[a]
MACE	32	14.65 (9.58–19.73)	234	10.27 (8.95–11.58)	1.43 (0.99–2.07)
Myocardial infarction	16	7.31 (4.18–11.88)	102	4.47 (3.60–5.34)	1.64 (0.97–2.77)
Stroke, hemorrhagic and ischemic	16	7.31 (4.18–11.87)	133	5.83 (4.84–6.82)	1.25 (0.75–2.11)
Transient ischemic attack	13	5.94 (3.16–10.16)	62	2.72 (2.04–3.39)	**2.19 (1.20–3.98)**
Angina pectoris & unspecified ischemic heart disease	n < 10	3.65 (1.58–7.19)	107	4.69 (3.80–5.58)	0.78 (0.38–1.60)
Heart failure	13	5.94 (3.16–10.15)	76	3.33 (2.58–4.08)	1.78 (0.99–3.21)
Venous thromboembolism	44	20.18 (14.22–26.14)	307	13.48 (11.97–14.99)	**1.50 (1.09–2.05)**
Peripheral vascular disease	n < 10	3.19 (1.28–6.58)	39	1.71 (1.17–2.24)	1.87 (0.84–4.18)
Pericardial disease	n < 10	2.74 (1.01–5.96)	35	1.53 (1.02–2.04)	1.79 (0.75–4.25)
Bradycardia and heart block	n < 10	3.19 (1.28–6.58)	26	1.14 (0.74–1.67)	**2.81 (1.22–6.47)**
Paroxysmal tachycardia	n < 10	4.11 (1.88–7.80)	93	4.07 (3.25–4.90)	1.01 (0.51–2.00)
Atrial fibrillation and atrial flutter	14	6.40 (3.50–10.73)	190	8.33 (7.15–9.52)	0.77 (0.45–1.32)
Other arrhythmias	16	7.31 (4.18–11.87)	161	7.06 (5.97–8.15)	1.04 (0.62–1.73)

[a]Per 10,000 person-years. Crude IR and IRR.
CI: confidence interval; IR: incidence rate; IRR: incidence rate ratio; MACE: major adverse cardiovascular events; N/A: not applicable.
Note. Significant results (p<0.05) in bold numerals.

increased risk of suicide (HR 2.18; 95% CI 1.97–2.43),[32] a finding replicated in our results using a contemporary cohort. In addition, we also studied the rate of fractures, a common condition which contributes significantly to healthcare costs and is associated with potentially severe complications and even mortality. The increased risk of fractures observed in this study population (IRR 1.32; 95% CI 1.19–1.47) aligns with osteoporotic fracture risk previously observed among MS patients in the UK.[9] Our study expands previous knowledge by presenting data on a number of comorbidities occurring both before and after a diagnosis of MS. Interestingly with regard to the presumed target organ selectivity of MS, the incidence of a number of medical conditions was increased among MS patients compared to the MS-free population, and for certain conditions disparities were found between sexes and among ages groups.

The strengths of our study include the large sample size, the population-based cohort design with mandatory recorded data, including incident MS patients and matched, randomly selected, MS-free

Table 4. Hospitalizations and mortality after diagnosis of multiple sclerosis (MS) compared with MS-free matched individuals in a nationwide, register-based cohort study in Sweden 2008–2016.

	MS patients N = 6602		MS-free individuals N = 61,828		
	Events	IR (95% CI)[a]	Events	IR (95% CI)[a]	IRR (95% CI)[a]
Cause of hospitalization					
All hospitalizations	3414	1845.45 (1783.55–1907.36)	18,242	763.00 (751.93–774.07)	**2.42 (2.33–2.51)**
MS-related hospitalizations	1982	840.65 (803.64–877.66)	0	N/A	N/A
Cardiovascular-related hospitalizations	138	43.54 (36.27–50.80)	1205	40.55 (38.26–42.84)	1.07 (0.90–1.28)
Cause of death					
All-cause deaths	109	33.96 (27.59–40.34)	663	22.05 (20.38–23.73)	**1.54 (1.26–1.89)**
MS-related deaths	30	9.35 (6.00–12.69)	0	N/A	N/A
Cardiovascular deaths	11	3.43 (1.71–6.13)	54	1.80 (1.32–2.28)	**1.91 (1.00–3.65)**
Cancer-related deaths	27	8.41 (5.54–12.24)	254	8.45 (7.41–9.49)	1.00 (0.67–1.48)
Suicide	n < 10	2.49 (1.08–4.91)	29	0.96 (0.65–1.39)	**2.58 (1.18–5.65)**

[a]Per 10,000 person-years. Crude IR and IRR.
CI: confidence interval; IR: incidence rate; IRR: incidence rate ratio; N/A: not applicable
Note. Significant results ($p<0.05$) in bold numerals.

individuals from the general population, and the long and robust patient follow-up.

The registers used for identification of comorbidity, hospitalizations and mortality are nationwide with a high coverage for most of the conditions in our study. The NPR is a mandatory register that identifies hospital discharge diagnoses with approximately 80% accuracy (with variation for specific diagnoses).[33] It was implemented in 1964 with national coverage achieved in 1987 and outpatient diagnoses included since 2001. It has fewer diagnostic errors among younger patients and a high level of accuracy for MS diagnoses.[33] A recent study confirmed 92.5% of all MS diagnosis in the NPR[34] and previous validation studies have reported more than 99% of all somatic hospital discharges are registered in the register and 85-95% of all inpatient diagnoses are valid.[33] In our study we used two MS diagnoses separated by at least six months which notably increased the accuracy. As almost all MS patients have outpatient appointments at least once a year (often more frequently), the sensitivity of the patient register for MS diagnosis is high. The population register used for the selection of matched MS-free individuals is continuously updated and consists of all persons living in Sweden. In addition, the information contained in the registers enabled sex- and age-specific analyses. The comparably large size of the MS and non-MS populations included, and the nationwide coverage of the population included in Swedish national register data, strengthen the generalizability of the results and the ability to detect meaningful differences both across, and within groups.

Limitations of the study include that information on comorbidity for both MS patients and MS-free individuals was collected only from specialist care which leads to an underestimation of conditions commonly treated in primary care. Additionally, this study may be subject to surveillance bias, since after an MS diagnosis patients will be followed in specialized care which may facilitate earlier detection of a comorbidity, compared to MS-free individuals. The MS-free population may thus appear healthier, since they may be less likely to seek healthcare, leading to an overestimation of comorbidity incidence rate ratios. However, in an attempt to understand whether surveillance bias may be present, we performed a sensitivity analysis by restricting the definition of a comorbidity to only the primary diagnoses (i.e., excluding the secondary diagnoses), both for the follow-up and look-back periods. The inclusion of secondary diagnoses did not have a material impact on the magnitude of the IRRs compared to the use of only primary diagnoses. This suggests that the impact of any potential surveillance bias may be low. Although when restricting to only the primary diagnosis, smaller sample sizes limited the ability to draw firm conclusions, particularly for cardiovascular outcomes.

However, the higher risk of CVD-related deaths in MS patients could not be impacted by surveillance bias since cause of death is registered for both groups in a national register. Furthermore, the inclusion of patients in the study until 31 December 2016 meant that patients enrolled in later years had shorter follow-up times, and therefore had a smaller exposure windows to develop the outcomes under study. This may have caused an underestimation of these outcomes.

Finally, the potentially long prodromal period and time to diagnosis of MS might have misclassified incident comorbidity as prevalent conditions, and thus underestimated the observed IRRs.[35]

In conclusion, this population-based cohort study suggests that MS patients experience an additional clinical burden due to their disease already debuting prior to MS diagnosis and treatment. This burden extends beyond what is experienced among MS-free individuals, including an increased incidence of several cardiovascular, and other non-infectious diseases over time and an increased risk of mortality. This emphasizes the need for an integrated disease management, also taking into consideration the safety profile of newer DMTs, in order to improve patient care and long-term outcomes of MS.

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Supplemental Material

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