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Hospital admission due to infections in multiple sclerosis patients

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Background and purpose: Multiple sclerosis (MS) patients are at increased infection risk. Here the influences of susceptibility, severity and surveillance bias on infection-related hospital admission are assessed.

Methods: Swedish registers identified 20 276 patients with MS, matched with 203 951 people from the general population without MS. Risk of first hospital admission for infection and mortality over 36 years was estimated by Poisson regression.

Results: Multiple sclerosis was associated with an increased hospital admission risk for all infections, with an adjusted relative risk (and 95% confidence interval) of 4.26 (4.13–4.40). A proportion of this raised risk was probably due to surveillance and referral bias, although a raised risk remained when MS was compared with other immune-mediated diseases. The 1-month mortality rate following hospital admission for infection was higher in MS patients than in the comparison cohort, with a relative risk of 4.69 (4.21–5.22). There was no clear temporal trend in the results, and risks were higher in males and varied by MS phenotype.

Conclusions: Higher hospital admission rates among MS patients for infection are likely to be due to a combination of surveillance bias, cautious medical management and greater susceptibility to severe infections. MS-related functional limitations may increase infection risk and this should be considered in MS management.

Background and purpose

A raised risk of infections among multiple sclerosis (MS) patients has potential implications for clinical management and resource use and is a concern as infections may increase the risk of MS relapses [1–5]. Also, immunotherapy in MS [6] may increase infection risk. Although a lower rate of common viral infections has sometimes been reported in MS [7], excess infection-related mortality has been well documented [8–11]. Previous studies examined hospital admission and infections in MS patients [12,13]. This Swedish register study extends earlier work by focusing specifically on infection type and considers the potential roles of susceptibility, surveillance bias and referral patterns. Severity is investigated through mortality risk following hospital admission. Variation of admission risk by calendar period was used to assess potential variations in exposures over time. Associations with MS phenotype and sex were also examined as some studies have found an excess male mortality risk [14].

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Methods

Subjects

Patients who received a diagnosis of MS in Sweden between 1969 and 2005 were identified through two complementary sources: the Patient Register and the Multiple Sclerosis Register. The Patient Register has recorded the main and secondary hospital discharge diagnoses since 1964. Initially national coverage was partial, with only 15 Swedish counties (from a total of 26) reporting to the register by 1970. Coverage increased to 20 counties reporting by 1980 and full national coverage was achieved by 1987 [15]. The Swedish Multiple Sclerosis Register has recorded information on patients with MS since 1996, although the proportion of patients registered increased more notably from 2001 [16,17]. The coverage of the Multiple Sclerosis Register varies by county, and during the

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earlier period of its coverage it was more likely to include patients receiving immunomodulatory therapy [17]. Prevalent MS patients recorded in this register are on average younger than those in the Patient Register due to the relatively recent founding of the Multiple Sclerosis Register [17]. Both registers are used as the Patient Register identifies a large number of MS patients diagnosed over several decades while the Multiple Sclerosis Register identifies a smaller number of patients but with confirmed high diagnostic accuracy.

A total of 20 543 individuals with a diagnosis of MS were identified, including 7957 through the Multiple Sclerosis Register. The Multiple Sclerosis Register provided information on MS phenotype for the subset of patients identified by this register. Phenotype was defined once at registration and is unavailable for a proportion of patients (see Table 1) as phenotype may be difficult to assign for some at diagnosis. Linkage between data sources was possible using the personal identity number issued to all Swedish residents [18].

The design was that each patient with MS should be individually matched with 10 Swedish residents without an MS diagnosis, thus creating two cohorts. Matching was performed by the government agency, Statistics Sweden [19], using data from the Total Population Register which also provided dates of death and emigration to define follow-up time. The matching criteria, based on characteristics at the time of the MS diagnosis, were county of residence in Sweden, year of birth and sex. For each person with MS, individuals without MS who had the appropriate characteristics for matching were identified, and from them 10 were selected at random. For a minority of subjects with MS fewer than 10 MS-free subjects with the

Table 1 Characteristics of the MS and non-MS cohorts

	Entire study population		Subset from the Multiple Sclerosis Register	
	With MS (%)	Without MS (%)	With MS (%)	Without MS (%)
Total	20 276	203 951	7958	89 102
Sex				
Female	13 218 (65.2)	13 2638 (65.0)	5633 (70.8)	63 683 (71.5)
Age at MS diagnosis/entry (years)				
<20	440 (2.2)	5828 (2.2)	323 (4.1)	3360 (3.8)
20–29	2836 (14.0)	28 640 (14.0)	1698 (21.3)	18 600 (20.9)
30–39	4412 (21.6)	44 056 (21.6)	2250 (28.3)	25 128 (28.2)
40–49	4762 (23.3)	47 309 (23.2)	2008 (25.2)	22 439 (25.2)
≥50	7826 (38.2)	78 118 (38.3)	1679 (21.1)	19 578 (22.0)
Mean (SD)	45.8 (15.5)	45.8 (15.6)	39.5 (12.2)	39.8 (12.4)
Age at final follow-up (years)				
<30	902 (4.5)	10 407 (5.1)	701 (8.8)	7615 (8.6)
30–39	2056 (10.1)	21 506 (10.5)	1625 (20.4)	17 766 (19.9)
40–49	3407 (16.8)	31 655 (15.5)	2087 (26.2)	22 522 (25.3)
50–59	4592 (22.7)	40 421 (19.8)	2075 (26.1)	22 916 (25.7)
60–69	4372 (21.6)	38 628 (18.9)	1110 (14.0)	13 318 (15.0)
70–79	3220 (15.9)	31 661 (15.5)	307 (3.9)	4150 (4.7)
>80	1727 (8.5)	29 673 (14.6)	53 (0.7)	815 (0.9)
Mean (SD)	55.2 (15.9)	57.9 (17.6)	46.8 (13.5)	47.2 (13.8)
Follow-up, years				
<5	7103 (35.0)	50 981 (25.0)	3636 (45.7)	39 504 (44.3)
5–10	5441 (26.8)	49 453 (24.2)	2365 (29.7)	26 558 (29.8)
11–15	3609 (17.8)	37 123 (18.2)	873 (11.0)	10 134 (11.4)
>15	4390 (21.7)	66 608 (32.7)	1084 (13.6)	12 906 (14.5)
Mean (SD)	9.9 (8.3)	12.7 (9.6)	7.6 (7.3)	7.9 (7.6)
Calendar period				
<1980	5264 (26.0)	52 599 (25.8)	486 (6.1)	6764 (7.6)
1980–1989	4912 (24.2)	48 372 (23.7)	983 (12.4)	11 038 (12.4)
1990–1999	5320 (2.6)	52 924 (25.9)	2666 (33.5)	29 398 (33.0)
2000–2005	5047 (24.9)	50 268 (24.6)	3182 (40.0)	35 134 (39.4)
MS phenotype				
Primary progressive	–	–	601 (7.6)	–
Progressive relapsing	–	–	66 (0.8)	–
Relapsing–remitting	–	–	3428 (43.1)	–
Secondary progressive	–	–	2104 (26.4)	–
No phenotype recorded	–	–	1759 (22.1)	–

same characteristics were available; where this occurred all appropriate MS-free subjects were used. A total of 204 163 people without MS were included in the matched (non-MS) comparison cohort. We subsequently excluded 267 people with MS and 212 without MS due to missing information.

A six-category socioeconomic index (SEI) was constructed from census data, with categories for manual workers, non-manual workers, professionals, self-employment, farmers and others. The census used was nearest in time to first MS diagnosis in patients and the same time-point for the individually matched members of the non-MS cohort.

Hospital admissions

Inpatient infectious diagnoses between 1969 and 2005 were identified through the Patient Register using ICD codes. During this period the version of ICD varied both over time and by county, so the specific codes used differed by period and region. Infections were identified using ICD-10 codes: A00-B99, G00-G02, G06-G07, J00-J22, J32, J35-J37, M00-M01, L00-L02, L08, H66, N10 and N300. The analysis examined all infections combined, by organ system or specific diagnosis, in the groups and diagnoses presented in Table 2. The individual infections and grouped infections were chosen on an *a priori* basis and results for all of these infections are presented, except for five. We did not present results for infections that were too rare, as the diagnostic accuracy for some rare conditions can be unacceptably low in the Patient Register, making the risk of producing spurious results far greater. The criterion that we used to define rarity was where fewer than 50 diagnoses of a specific infection were identified in each cohort. The infections that were not presented due to rarity are viral pneumonia, pneumocystis pneumonia, progressive multifocal leucoencephalopathy, infectious mononucleosis and *Pseudomonas aeruginosa*.

Multiple sclerosis is a chronic disease, usually resulting in more frequent contact with health services, and incidental diagnoses are more often recorded than among the general population, which can result in *surveillance bias*. To reduce potential surveillance bias, infections were only included if they were recorded as the primary hospital admission diagnosis and thus likely to be the main reason for hospital admission. Further analysis took into account the number of all hospital admissions between the time of first MS diagnosis and outcome infection. This was designed to indicate and adjust for the effects of chronic disease and related referral patterns. Additionally, MS patients were compared with a subset of the non-MS cohort comprising subjects with other immune-mediated diseases. The smaller comparison cohort (n = 13 731) included only those with a diagnosis of ulcerative colitis (n = 819), Crohn's disease (n = 669), psoriasis (n = 800), type 1 diabetes (8611), rheumatoid arthritis (n = 2130), polyarteritis nodosa (n = 45), temporal arteritis and polymyalgia rheumatica (n = 1077), Addison's disease (n = 112) or pemphigoid (n = 68). Individuals could have more than one of these diagnoses.

Table 2 The risk of infection-related hospital admissions for MS patients

	Events: MS cohort (n = 20 276)	Events: non-MS cohort (n = 203 951)	Unadjusted relative risk (95% CI)	Adjusted[a] relative risk (95% CI)	Adjusted[b] relative risk (95% CI)
All infections	5167	19 148	3.64 (3.52–3.75)	4.26 (4.13–4.40)	2.36 (2.28–2.43)
Sex					
Male	2178	7932	4.15 (3.95–4.35)	4.95 (4.72–5.20)	2.67 (2.54–2.81)
Female	298	11 216	3.37 (3.24–3.51)	3.86 (3.70–4.02)	2.15 (2.05–2.24)
Respiratory infections	3095	10 177	3.87 (3.71–4.03)	4.74 (4.55–4.94)	2.55 (2.44–2.66)
Influenza	284	564	6.06 (5.25–6.99)	7.23 (6.25–8.36)	3.57 (3.06–4.15)
Bacterial pneumonia	455	1126	4.99 (4.47–5.57)	6.13 (5.48–6.85)	2.73 (2.43–3.06)
Pneumonia in bacterial diseases	323	1214	3.17 (2.80–3.58)	3.83 (3.38–4.34)	1.96 (1.72–2.23)
Gastrointestinal infectious diseases	604	2312	3.09 (2.82–3.38)	3.39 (3.09–3.71)	1.59 (1.45–1.75)
Viral and other specified gastrointestinal infections	174	670	3.06 (2.59–3.61)	3.45 (2.91–4.09)	1.46 (1.22–1.74)
Infections of the skin and subcutaneous tissue	493	2064	2.84 (2.58–3.14)	3.16 (2.86–3.49)	1.51 (1.36–1.67)
Infectious arthropathies	76	487	1.85 (1.45–2.36)	2.10 (1.65–2.68)	0.98 (0.76–1.26)
Septicaemia	923	2198	5.13 (4.75–5.54)	6.20 (5.73–6.70)	2.89 (2.66–3.13)
Infections of the urinary system	1513	2571	7.23 (6.79–7.71)	8.22 (7.71–8.77)	4.08 (3.81–4.36)

[a]Adjusted for duration, sex, age at entry, period at entry, region and SEI.
[b]Adjusted for all of the above and total number of hospital admissions during the follow-up period.

Mortality

Infectious causes of death were identified through the Cause of Death Register [20] which uses information recorded on death certificates. Despite low accuracy for some diagnoses on death certificates, there is evidence that infectious causes such as pneumonia and influenza have a relatively high accuracy: a study confirmed an accuracy of 83% for these diagnoses [21]. The data received from this register were abbreviated so that it was possible to identify infectious causes but not more specific diagnoses. Although date of death was available for the entire study period, causes of death were only available for between 1969 and 1997. Mortality during the 30 days following hospital admission for infection among MS and non-MS patients was assessed to determine risk of life-threatening infection.

Statistical analysis

The main analyses compared the MS and non-MS cohorts with follow-up time beginning at first recorded MS diagnosis (and the same time-point for the individually matched members of the comparison cohort) and ending at the first inpatient diagnosis of infection, emigration, death or study end in 2005, whichever occurred first. Relative risk for the first relevant infectious event was estimated by Poisson regression with adjustment for follow-up duration, year at entry and age at entry (under 5 years, then in 5-year age groups to 84 years and with a final category for 85 years or older), sex, county and SEI. Stratification by period of outcome infection was all infections grouped together and also for one of the common infections, influenza. Additional adjustment was for the total number of admissions for any diagnosis between the dates of first MS diagnosis and infection or study exit. The above analyses were repeated using a subset of the non-MS cohort comprising only people with other immune-mediated diseases.

The Multiple Sclerosis Register contains some information not available from the Patent Register, including MS phenotype. Also, the accuracy of an MS diagnosis is more readily verifiable using the Multiple Sclerosis Register [22]. Therefore, some analyses were limited to the subset of MS patients identified in the Multiple Sclerosis Register and the relevant matched members of the non-MS cohort. Due to the reduction in numbers, the analysis was limited to all infectious diagnoses grouped as the outcome. MS patients were compared with the non-MS cohort for each MS phenotype separately and then the phenotypes were compared only among the MS patients.

Analysis of infection-related mortality was performed using Poisson regression for the period from study entry to death, emigration or 1997, whichever occurred first. Adjustment was for duration, sex, region, age at entry, period at entry and SEI. Similar methods examined whether there was a raised risk of all-cause mortality in the 30 days following hospital admission for infection.

Ethics approval

This study was approved by the Karolinska Institutet ethics committee.

Results

The characteristics of the cohorts are shown in Table 1. The first two columns describe the entire study population (MS and non-MS cohorts) and the second two columns are for the subset of MS patients from the Multiple Sclerosis Register and members of the non-MS cohort matched with them. As the MS and non-MS cohorts were matched, there were no notable differences in sex, age at study entry or calendar period. Duration of follow-up and age at exit tended to be greater for the non-MS cohort. Compared with the entire study population, those from the Multiple Sclerosis Register tended to be younger at diagnosis, showed a higher proportion of women and entered the study at a more recent calendar period. The commonest MS phenotype was relapsing–remitting.

Infection-related hospital admissions

There was a statistically significant association between MS and hospital admission for any infection before and after adjustment for potential confounding factors (Table 2). The magnitude of association was higher among men. After adjustment for the potential confounding factors, except total number of admissions for any cause, MS was statistically significantly associated with a raised risk for all infections and the grouped and individual infections resulting in hospital admission, with the highest risks observed for urinary tract infections and influenza. The largest magnitude sex difference was for urinary tract infections, with adjusted relative risks (and 95% confidence intervals) of 13.87 (12.5–15.39) for males and 6.02 (5.53–6.55) for females. There was also a sex difference for influenza, with adjusted relative risks of 9.93 (7.98–12.35) for males and 5.69 (4.67–6.93) for females.

After additional adjustment for total number of admissions, the magnitude of the associations between

MS and infections was attenuated but remained raised and statistically significant, with the exception of infectious arthropathies which showed no association with MS (Table 2). Exclusion of events in the first 5 years following first recorded MS diagnosis yielded statistically significant and similar estimates (data not shown), indicating that the results were not explained by admissions that coincided with the first MS diagnosis.

When MS patients were compared with subjects who had another hospital-diagnosed immune-mediated disease (Table 3), the associations of MS with hospital admission for infections were attenuated to a greater extent than those in Table 2. Statistically significant raised risks for infectious admissions remained except for gastrointestinal infections, infectious arthropathies and infections of the skin and subcutaneous tissue. Statistically significant inverse associations with MS were observed for the last two outcomes. Further adjustment for total number of all hospital admissions did not alter any of the associations noticeably (data not shown).

Among the subset of MS patients identified through the Multiple Sclerosis Register and their matched non-MS cohort, MS was statistically significantly associated with a raised risk of hospital admission for any infection diagnosis, with a higher magnitude association among males (Table 4). There was a statistically significant raised risk of hospital admission for infections for each of the four phenotypes, with the highest risk for primary and secondary progressive phenotypes. When comparisons were made *between MS patients*, with the secondary progressive phenotype as reference, the only statistically significant

Table 3 Infection-related hospital admissions among subjects with MS compared with a group of patients with other immune-mediated diseases[a]

	Events: MS cohort (n = 19 022)	Events: other immune-mediated disease cohort[a] (n = 13 731)	Unadjusted RR (95% CI)	Adjusted RR[b] (95% CI)
All infections	4558	3616	1.82 (1.74–1.91)	1.78 (1.70–1.87)
Respiratory infections	2761	1947	2.13 (2.01–2.27)	2.05 (1.92–2.18)
Influenza	248	121	2.70 (2.14–3.40)	2.57 (2.03–3.25)
Bacterial pneumonia	401	192	3.13 (2.61–3.75)	2.01 (1.66–2.42)
Pneumonia in bacterial diseases	293	266	1.68 (1.41–2.00)	1.81 (1.51–2.16)
Gastrointestinal infectious diseases	509	528	1.11 (0.98–1.27)	0.99 (0.87–1.14)
Viral and other specified gastrointestinal infections	144	175	0.96 (0.76–1.22)	0.82 (0.64–1.04)
Infections of the skin and subcutaneous tissue	397	550	0.88 (0.77–1.01)	0.84 (0.73–0.96)
Infectious arthropathies	63	144	0.56 (0.41–0.77)	0.48 (0.35–0.66)
Septicaemia	783	615	1.88 (1.68–2.1)	1.60 (1.43–1.8)
Infection of urinary system	1312	530	3.38 (3.04–3.76)	3.18 (2.86–3.55)

[a]Members of the comparison cohort have a diagnosis of ulcerative colitis (n = 819), Crohn's disease (n = 669), psoriasis (n = 800), type 1 diabetes (8611), rheumatoid arthritis (n = 2130), polyarteritis nodosa (n = 45), temporal arteritis and polymyalgia rheumatica (n = 1077), Addison's disease (n = 112) or pemphigoid (n = 68).
[b]Adjusted for sex, area, duration, age at entry, period and SEI. Further adjustment for total number of hospital admissions did not change the results.

Table 4 The risk of infection-related hospital admissions by MS phenotype

	Events: Multiple Sclerosis[b] Register cohort (n = 7958)	Events: non-MS[b] cohort (n = 89 105)	Unadjusted relative risk (95% CI)	Adjusted[a] relative risk (95% CI)
All infections	992	3353	3.39 (3.16–3.64)	3.49 (3.25–3.74)
Sex				
Male	388	1023	4.47 (3.98–5.03)	4.54 (4.03–5.11)
Female	604	2330	2.94 (2.69–3.22)	3.05 (2.79–3.33)
MS phenotype				
Primary progressive	124	338	4.45 (3.61–5.47)	4.46 (3.62–5.50)
Progressive relapsing	8	37	2.79 (1.29–6.02)	2.64 (1.21–5.78)
Relapsing– remitting	150	851	1.90 (1.60–2.27)	1.92 (1.60–2.92)
Secondary progressive	522	1562	3.97 (3.59–4.38)	4.02 (3.63–4.44)

[a]Adjusted for duration, sex, age at entry, period at entry, region and SEI.
[b]These results are limited to the subset of patients identified through the Multiple Sclerosis Register and the relevant individually matched members of the comparison cohort.

Table 5 Temporal variation in infection-related hospital admissions for MS patients

	Events: MS cohort (n = 20 276)	Events: non-MS cohort (n = 203 951)	Unadjusted relative risk (95% CI)	Adjusted[a] relative risk (95% CI)
All infections				
<1980	702	1726	3.49 (3.33–3.67)	4.14 (3.95–4.35)
1980–1989	1411	4743	3.54 (3.36–3.73)	4.29 (4.06–4.52)
1990–1999	1744	7438	4.03 (3.75–4.32)	4.40 (4.09–4.72)
2000–2005	1310	5241	4.11 (3.56–4.76)	4.25 (3.66–4.92)
Influenza				
<1980	113	239	5.13 (4.13–6.38)	6.24 (5.00–7.79)
1980–1989	92	169	6.12 (4.74–7.89)	7.58 (5.85–9.83)
1990–1999	70	88	8.31 (6.07–11.38)	9.13 (6.64–12.55)
2000–2005	9	14	6.51 (2.82–15.05)	6.98 (3.01–16.17)

[a]Adjusted for duration, sex, age at entry, region and SEI.

Table 6 Infection-related mortality risk for MS patients

	Events: MS cohort (n = 20 276)	Events: non-MS cohort (n = 203 951)	Unadjusted relative risk (95% CI)	Adjusted[a] relative risk (95% CI)
Infection-associated mortality	1601	4808	3.97 (3.75–4.20)	5.19 (4.90–5.50)
Sex				
Male	730	2221	4.21 (3.87–4.58)	5.60 (5.14–6.11)
Female	871	2587	3.84 (3.55–4.14)	4.86 (4.49–5.25)
Age at study exit (years)				
<40	96	133	6.09 (4.66–7.97)	5.16 (3.92–6.80)
40–59	534	785	5.55 (4.97–6.20)	4.10 (3.66–4.59)
60–79	798	2206	4.06 (3.74–4.40)	3.41 (3.14–3.70)
≥80	173	1684	2.43 (2.08–2.84)	2.81 (2.40–3.30)

[a]Adjusted for duration, sex, age at entry, period at entry, region and SEI.

difference after adjustment was with the relapsing–remitting phenotype which had a lower infection risk, producing a relative risk of 0.39 (0.32–0.48).

Stratification by calendar period (Table 5) found non-conclusive evidence of a modest rise of infection risk over the first three periods but not in the fourth, which was the least precisely estimated as the duration was shorter.

Infection-related mortality

Multiple sclerosis patients were statistically significantly more likely to have infection-related mortality (Table 6). The risk was higher for males and the relative risk for infection-related mortality associated with MS was greatest at younger ages.

Mortality during the 30 days following hospital admission for an infection involved 443 deaths among the MS cohort and 1629 in the non-MS cohort, producing an unadjusted relative risk of 4.60 (4.13–5.12). Adjustment for the potential confounding factors, except total number of admissions, increased the risk to 4.69 (4.21–5.22), and further adjustment for total number of admissions attenuated it somewhat to 4.18 (3.73–4.68). There were no notable sex differences (data not shown).

Discussion

In this study patients with MS were admitted to hospital for a range of infectious diseases significantly more often than matched members of the general population (the non-MS cohort). They were also more likely to have died from infectious causes and to have died during the month following a hospital admission for infection.

Disease associations using hospital diagnoses are potentially subject to inflation by surveillance bias, particularly for chronic conditions involving frequent contact with health services when incidental diagnoses can be recorded. To tackle this, infectious outcomes were limited to the primary diagnosis and thus the most likely reason for hospital admission. To avoid the results being driven by multiple admissions among a subset of the study population, the analyses examined risk of *first* hospital admission for infections. To further address surveillance bias, the total number of admissions for any cause during the follow-up period

was adjusted for, as a marker of frequency of contact with health services. This adjustment reduced the magnitude of association between MS and infections but significantly raised risks remained. Cautious management of MS patients could result in a form of referral bias. Comparison of MS patients only with subjects who had another immune-mediated disease was undertaken to reduce the relative influence of surveillance and referral bias further: this produced the lowest magnitude estimates of association between MS and hospital admission for infection, but they remained statistically significant. The different methods to tackle surveillance and referral bias produced a range of estimates, the highest indicating the high use of inpatient health services by MS patients but inflated by surveillance and referral bias, whilst the lowest estimates show that a significant association persists even after more robust efforts to eliminate the effect of these biases. The results are consistent both with a higher risk of infection and greater likelihood of hospital admission for infection.

Despite an overall positive association of MS with hospital admission in comparison with the reduced non-MS cohort of those with immune-mediated diseases, a minority of the infection groups were inversely associated with MS. This is likely to reflect higher risk for some infection types associated with diseases in the comparison cohort. Using several comparison diseases allowed adequate statistical power and provided comparison with diseases imparting susceptibility to a wider range of infections.

There was a raised risk for infection-related mortality among MS patients. Relative risks for infection-related mortality in MS were higher for younger age groups. People with MS admitted to hospital with an infection were significantly more likely to have died within a month compared with people without MS also admitted to hospital for infections, indicating greater average infectious disease severity among the MS patients.

The lack of clear temporal patterns suggests that a major part was not played by treatments such as interferon beta, which can produce febrile symptoms [23]. Interferon beta was introduced in Sweden for MS in 1996 and its use increased over the subsequent years [24]. Other MS treatments that may potentially increase some types of infection risk include glatiramer acetate (Copaxone), which was licensed for use in Sweden in 2001 but the agreement that costs for this prescribed medication would be refunded took effect in July 2004. Thus glatiramer acetate could only influence results noticeably during the last period of our study. Vaccination programmes may be important in controlling infection in this patient group. Guidelines to promote influenza vaccination in Sweden were introduced in 1997 and the numbers vaccinated in the general population began to increase noticeably from 2003. MS patients would be more likely to be vaccinated than the general population, and the greatest coverage is likely to have been during the latter years of our study period.

The risk of urinary tract and gastrointestinal infections may be raised by the bladder and bowel dysfunction experienced by MS patients [25–27], while an inability to cough and clear the lungs [28] may increase respiratory infection risk. It is unlikely that MS patients have a life-long increased susceptibility to infections prior to MS onset even though the pattern of infections may be relevant for MS risk [29–31] as frequency of childhood infections prior to MS onset is not significantly increased. The higher risk for infection-related hospital admission in men was unexpected and the speculation is that, if not due to chance, it may reflect greater MS severity or increased susceptibility to infections. Immunizations may help to reduce infection risk and are not generally associated with increased MS relapse rates [32], although they may not prevent all relevant infections.

Data from the Multiple Sclerosis Register were available only for a subset of MS patients used in this study, but provided useful complementary information. The majority of MS diagnoses were identified through the Patient Register, which despite acceptable levels of diagnostic accuracy may contain a proportion of misdiagnoses [15]. For this reason our main findings were replicated using Multiple Sclerosis Register patients to ensure that the results were not driven by a poorly defined patient population. There are some differences in characteristics between patients identified through the Multiple Sclerosis and Patient Registers relevant to age, phenotype and treatment [17], but we previously demonstrated that the Multiple Sclerosis Register is accurate for over 95% of diagnoses [22].

Patients with MS are at a noticeably raised risk of serious infections leading to hospital admission and infection-related mortality, even at younger ages. A component of the raised infection risk may be due to MS-related functional limitations. There is no evidence of substantial change in relevant environmental exposures over time. These findings emphasize the continuing importance of prevention strategies including through urological care.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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