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# High nationwide prevalence of multiple sclerosis in Sweden

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## Abstract

**Background:** Few nationwide multiple sclerosis (MS) prevalence studies have been published. In Scandinavia, the nationwide MS prevalence was 173/100,000 in Denmark 2005 and 100/100,000 in Iceland 1990.

**Objective:** Our aim with the present study was to determine the first population-based nationwide MS prevalence in Sweden, based on observed, registered patients and to investigate the presence of a north–south gradient of MS prevalence.

**Methods:** By linking the Swedish National Patient Register, the Swedish Multiple Sclerosis Registry and the Swedish Total Population Register we obtained the number of patients who were diagnosed with MS before 2009, and who were registered, alive and resident in Sweden on the prevalence date 31 December 2008. We calculated the gender-specific nationwide MS prevalence in 1-year age intervals. The relationship between MS risk and latitude was studied in a logistic regression model including all individuals in the population of Sweden.

**Results:** The number of registered MS patients in 2008 was 17,485 out of the Swedish population of 9,256,347. The overall MS prevalence was 188.9/100,000 (95% CI 186.1–191.7), 113.4 (95% CI 110.3–116.5) for men and 263.6 (95% CI 258.9–268.3) for women. The female to male ratio was 2.35:1. The prevalence of MS significantly increased for each degree of north latitude with 1.5% in men ( $p = 0.013$ ) and 1% in women ( $p = 0.015$ ).

**Conclusions:** The MS prevalence of 188.9/100,000 in Sweden is among the highest nationwide prevalence estimates in the world. In Sweden, the risk of MS increases with increasing north latitude for both men and women.

## Keywords

epidemiology, latitude, multiple sclerosis, prevalence, Sweden

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## Introduction

Few nationwide multiple sclerosis (MS) prevalence studies have been published. Nationwide prevalence estimates have either been calculated from observed MS patients in national MS registries,<sup>1–4</sup> from multiple sources, including nationwide health data registries,<sup>5</sup> from nationwide health insurance systems,<sup>6</sup> or generalized from more or less representative population samples.<sup>7,8</sup>

The nationwide prevalence of MS in Sweden has not been studied before, except for a rigorous, hospital-based survey in the 1930s, which showed a prevalence of 21.2/100,000.<sup>9</sup> Regional MS surveys in Sweden showed MS prevalence estimates of 96/100,000 in 1988,<sup>10</sup> 154/100,000 in 1997<sup>11</sup> and 170.1/100,000 in 2002.<sup>12</sup> Our primary aim with the present study was to determine the first population-based nationwide MS prevalence in Sweden, based on observed, registered patients.

An additional aim was to investigate the presence of a north–south latitude gradient of MS prevalence in Sweden. It has been observed that the prevalence of MS tends to be higher at higher degrees of latitude in both hemispheres.<sup>5,13–15</sup> A large meta-analysis, including age- and gender-specific population figures, confirmed a latitude gradient of the incidence of MS, although this gradient was attenuating over time.<sup>16</sup> In another large meta-analysis the finding of an

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association between MS prevalence and latitude was questioned by the authors.<sup>17</sup> In Norway, the MS prevalence was paradoxically lowest in regions north of the Arctic Circle.<sup>18</sup> In the present study, the analysis of a latitude gradient of MS was based on data that related each inhabitant of Sweden with latitude at municipality level.

## Materials and methods

### Area and population

Sweden lies between latitudes 55° and 69° north in Northern Europe. There are 290 municipalities in Sweden. The population density is low, 23 inhabitants per square kilometre, and it is considerably higher in the southern part of the country. Despite its northern latitude, Sweden has a temperate climate. In 2008, the mean age of the Swedish population was 41 years, the birth rate was 12/1000, the mortality was 10/1000, the immigration rate was 11/1000, and 5/1000 persons emigrated. At the end of 2008, approximately 14% of the population of Sweden had been born abroad, 21% of these in other Nordic countries, 36% in non-Nordic European countries and the remaining 43% in non-European countries (<http://www.scb.se>).

### Ethics approval

All individual data from the different sources were made anonymous to the authors by the replacement of the personal identity numbers by unique number codes for use in the present study. Thus, informed consent was not obtained. The study was approved by the regional ethical review board in Gothenburg.

### The Swedish National Patient Register (NPR)

Information on patients admitted to hospital has been collected since the 1960s in Sweden. The Swedish National Patient Register (NPR) at the National Board of Health and Welfare (<http://www.socialstyrelsen.se>) contains information on all inpatient care (Inpatient NPR) from 1987 and also all outpatient visits (Outpatient NPR) from 2001. The NPR was searched for patients diagnosed with MS, coded as G359, 340 and 340.99 according to the International Classification of Diseases (ICD) 10, 9, and 8.

### The Swedish Multiple Sclerosis Registry (SMSreg)

The Swedish Multiple Sclerosis Registry (SMSreg) (<http://www.msreg.net>) started in 1996 in order to promote MS research and the quality of MS care, as one of the national quality registries in the Swedish health and

medical services (<http://www.kvalitetsregister.se>). Patients with MS or Possible MS according to the McDonald criteria<sup>19,20</sup> have been prospectively and retrospectively registered and followed at each visit. The main variables relevant for the present study were personal identity number, gender, diagnosis of MS and the date of diagnosis.

### The Swedish Total Population Register (TPR)

Since 1947, every individual who has resided in Sweden on a permanent basis has been recorded in the *Swedish Total Population Register* (TPR) kept by Statistics Sweden (<http://www.scb.se>). Each individual has been assigned a personal identity number. This mandatory 10-digit unique identity number, which includes the date of birth and the gender of the individual, makes it possible to link registries and to follow an individual over time. Information in the TPR about the residence for each year and date of death of all individuals diagnosed with MS was relevant to the present study.

### Included MS patients

Patients were included if they (1) were registered with an MS diagnosis according to ICD 8, 9 or 10, in one or more of: older inpatient registries from the 1960s, the Inpatient NPR after its start in 1987, the Outpatient NPR after its start in 2001; and/or (2) were registered with MS according to the criteria of Poser<sup>21</sup> or MS or Possible MS according to the criteria of McDonald<sup>19,20</sup> in the SMSreg after its start in 1996. Use of the unique 10-digit personal identity number, mandatory in Sweden since 1947, ensured that MS patients who were registered in several registries were counted only once in the present survey.

### Statistics

By linking data from the NPR, the SMSreg and the TPR, we obtained the number of patients who were diagnosed with MS before 2009 and were alive and resident in Sweden on the prevalence date 31 December 2008. Thus, the prevalence of MS was determined by counting observed patients, registered in both or either of NPR and SMSreg. We calculated the gender-specific nationwide MS prevalence in 1-year age intervals and the overall gender-specific prevalence with 95% confidence intervals (CIs). We studied the relationship between MS prevalence and latitude by use of a logistic regression model, including age with 1-year precision, gender and latitude of residence (the population centre of the municipality of residence). The dependent variable of the model was a zero–one variable indicating whether or not MS was present on the

prevalence date. The value of each variable was obtained for each of the 9,256,347 inhabitants of Sweden on the prevalence date.

## Results

### Number of patients with MS

The total number of patients with MS registered in the NPR was 17,058 (11,974 women, 5084 men), and in the SMSreg 10,484 (7,506 women, 2978 men). The numbers of MS patients identified from either the NPR only, the SMSreg only, or both registries were 7001, 427 and 10,057, respectively. In the SMSreg a total of 9150 patients were diagnosed with MS, 677 with Possible MS and in 657 cases it was not specified whether the diagnosis was MS or Possible MS. Of the patients registered in the SMSreg only, 165 were diagnosed with Possible MS.

### Gender ratio

The female to male MS ratio was 2.35:1. The numbers of female and male MS patients on the prevalence date were 12,265 and 5220, respectively.

### Nationwide MS prevalence

The total number of MS patients alive and resident in Sweden on 31 December 2008 was 17,485. The overall MS prevalence in the Swedish population of 9,256,347

was 188.9/100,000 (95% CI 186.1–191.7), 113.4 (95% CI 110.3–116.5) for men and 263.6 (95% CI 258.9–268.3) for women (Figure 1).

### Age distribution

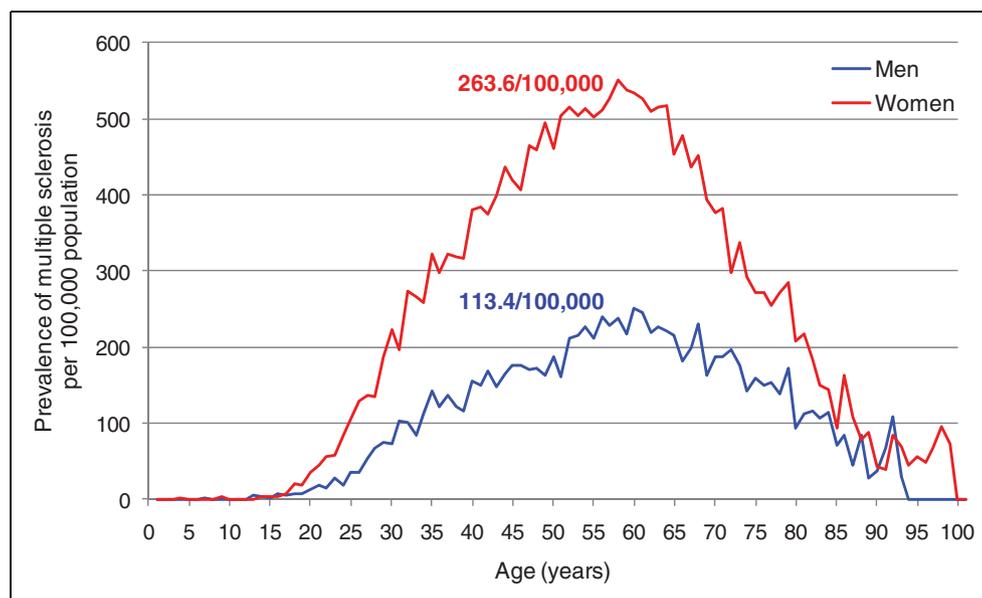
The gender- and age-specific prevalence of MS is shown in Figure 1. The mean age was 52.6 years (range 3–98), 52.9 years in men (range 6–92 years) and 52.5 years in women (range 3–98 years). The mean age of the patients registered in the NPR only was 57.6 years, while it was 49.2 years in the SMSreg. Patients older than 60 years of age comprised 31% of all registered patients. Among patients who were registered in the NPR only, this age group represented 45%, and among all patients in the SMSreg 22%.

### MS prevalence at county level

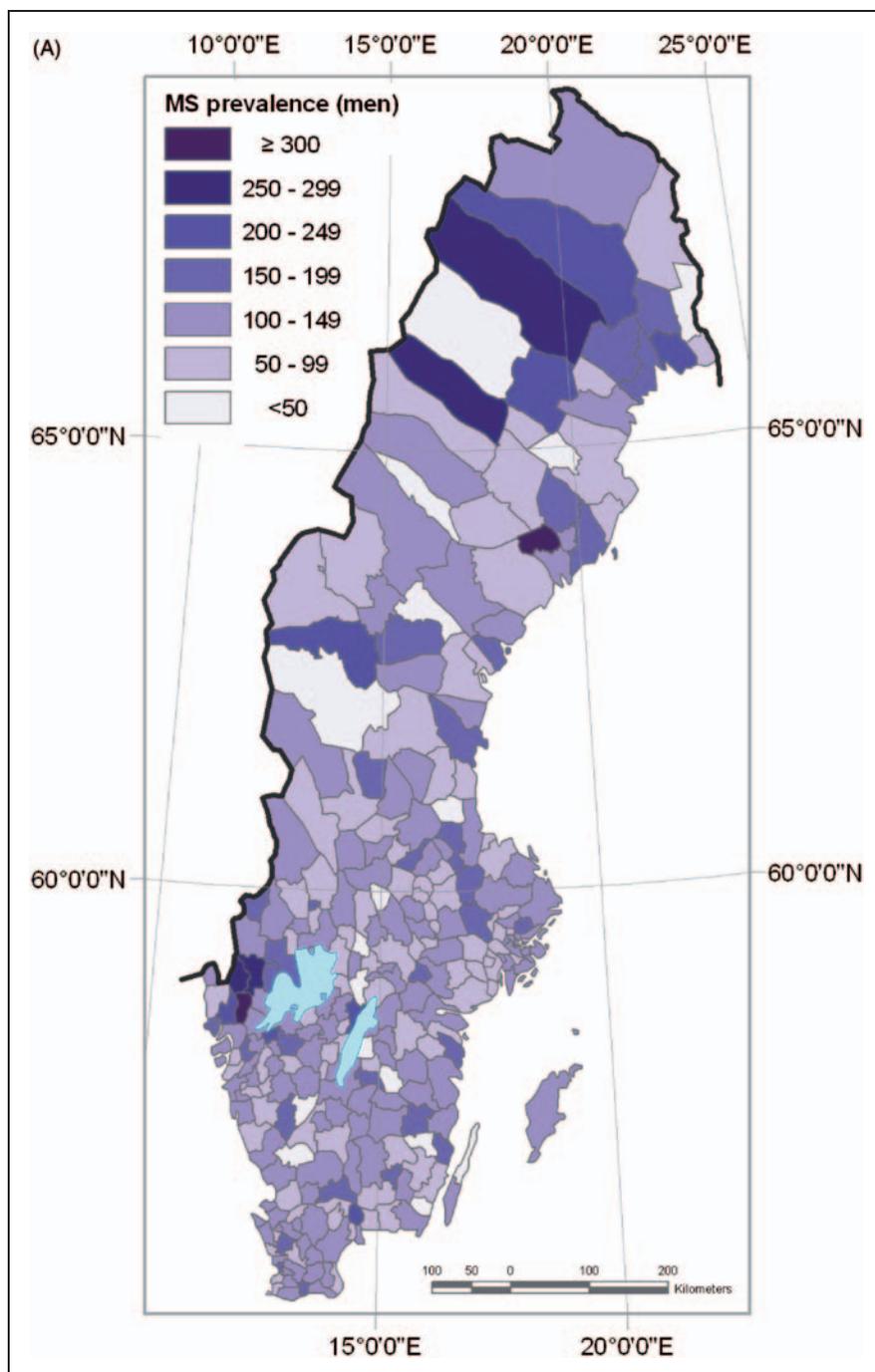
The prevalence of MS for both genders in the 21 counties ranged from 168–227/100,000. It was highest at latitude 66° north and lowest at latitude 57° north. The SMSreg coverage at county level varied between 10% and 83% of the total number of the registered patients.

### MS prevalence and latitude

The prevalence of MS significantly increased for each degree of north latitude with 1.5% in men ( $p = 0.013$ ) and 1% in women ( $p = 0.015$ ). The gradient did



**Figure 1.** Age- and gender-specific prevalence of multiple sclerosis in Sweden on 31 December 2008. The overall nationwide prevalence was 188.9/100,000 population ( $n = 17,485$  MS patients).



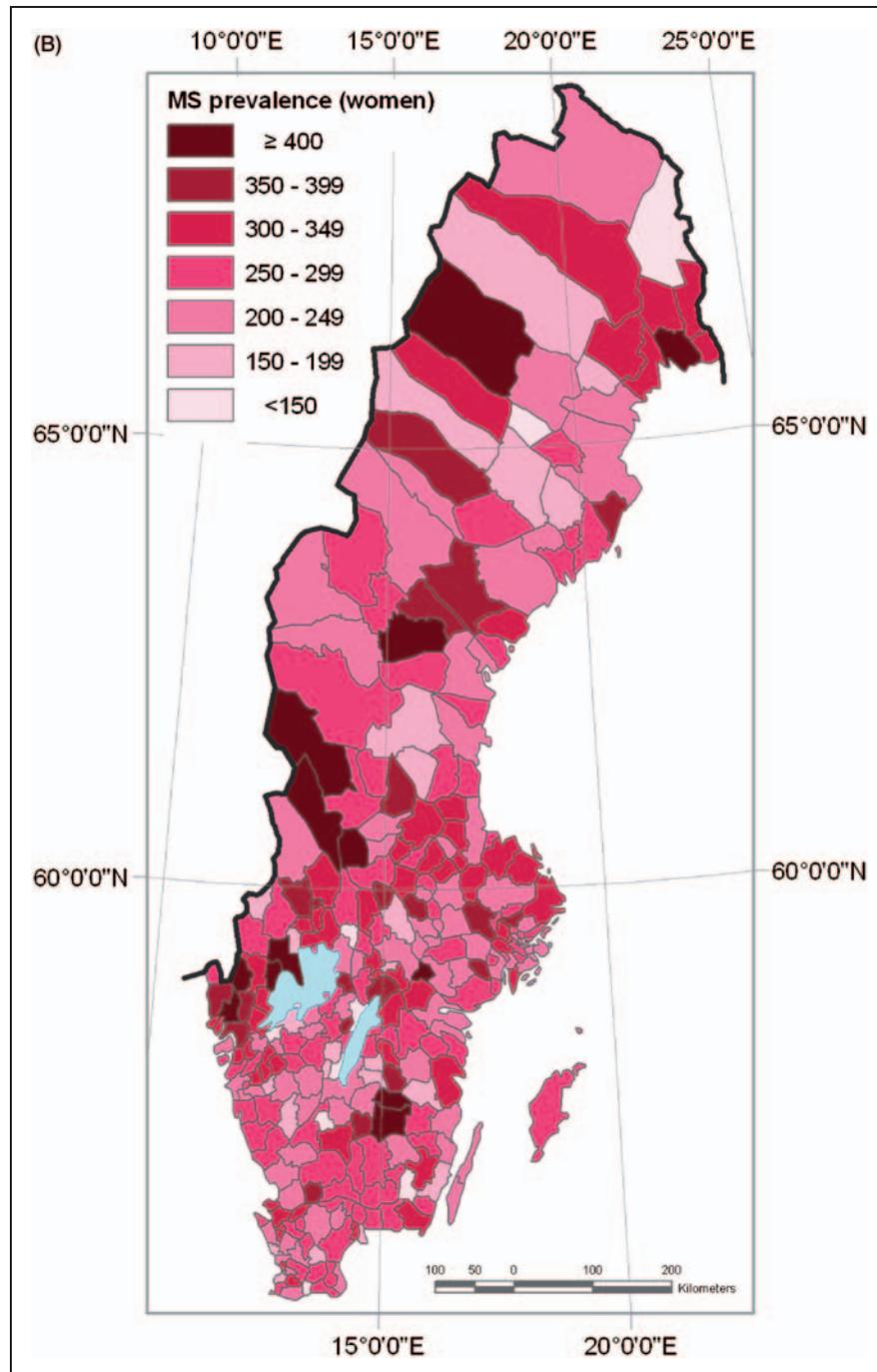
**Figure 2.** North latitude and gender-specific prevalence of multiple sclerosis in Sweden at municipality level. Sweden lies between latitudes 55° and 69° north. (A) Prevalence in men (blue) and (B) women (red). Darker colour indicates higher prevalence.

not significantly differ between men and women (Figure 2 A, B).

## Discussion

The nationwide prevalence of MS in Sweden was 188.9/100,000, based on 17,485 observed, registered patients.

This is among the highest nationwide MS prevalences reported, based on patients, registered in health and population registries. In Denmark, the prevalence was estimated at 173.3/100,000 in 2005, based on 9377 MS patients in the Danish MS registry. An advantage of that study was the high validity (94%) and completeness (> 90%) of the Danish MS registry.<sup>4</sup>



**Figure 2.** Continued.

Other nationwide MS prevalence surveys conducted in a similar manner have been much smaller. In Iceland, a relatively high prevalence of approximately 100/100,000 in 1990 was based on 252 MS patients.<sup>3</sup> In Israel, two MS populations were investigated separately. The nationwide prevalence of MS in relation to place of birth was 27.9–61.6/100,000 in the Jewish population ( $n = 3125$ ) and 10.9–35.3/100,000 in non-Jewish populations ( $n = 172$ ) in 2000.<sup>2</sup> In Kuwait, the MS

prevalence in 2000 was 14.8/100,000 based on 333 MS patients included in a high-coverage national MS registry.<sup>1</sup> By use of multiple sources, the MS diagnoses of almost all patients in New Zealand were validated. The MS prevalence in 2006 was 72.4/100,000 based on 2917 patients.<sup>5</sup> Recently, a large national MS study in France used a health insurance system that covered 87% of the French population as the source for case ascertainment. The MS prevalence of 94.7/100,000 in

2004 was based on 49,417 patients, classified in the database as having MS.<sup>6</sup>

Countries with no nationwide health or MS registries estimated the number of MS patients in the country from more or less representative population samples. For example, a generalization from the number of MS patients who had visited a random selection of hospitals in Japan yielded a prevalence of 7.7/100,000 in 2003.<sup>8</sup> A small statistical selection of the participants in a general health survey with self-reported MS diagnoses by 332 study participants was the basis for the overall weighted prevalence estimate of 240/100,000 in Canada<sup>7</sup> in 2000–2001. Another method was used in Austria, where the MS prevalence of 98.5/100,000 in 1998–1999 was estimated by means of questionnaire data and a model for extrapolation.<sup>22</sup>

The regional MS prevalence surveys which have been performed in Sweden used multiple sources, but not the NPR. The prevalence was 96/100,000 in Gothenburg on the Swedish west coast,<sup>10</sup> 154/100,000 in Västerbotten County in northern Sweden<sup>11</sup> and 170.1/100,000 further south in Värmland County in western Sweden.<sup>12</sup> No nationwide MS surveys have been performed in Norway or Finland. Regional population-based surveys in these countries have shown high or relatively high MS prevalence. In Norway, the MS prevalence varied between 73.0 and 163.6/100,000<sup>23–26</sup> and in Finland between 93 and 202/100,000<sup>27–30</sup>. The female to male MS ratio found in the present study was similar to that in the nationwide MS study from Denmark which, however, did not report the mean age of the MS patients.<sup>4</sup>

A north–south gradient of prevalence is a well-known feature of MS.<sup>5,13–15</sup> In a systematic review including studies from both Europe, the United States and Australia, the incidence of MS was higher at greater distance from the equator.<sup>16</sup> The latitude gradient of MS is particularly clear in Australia. This continent occupies a broad span of both tropical and temperate latitudes, and the prevalence of MS was more than six times higher in the south than in the north.<sup>14</sup> Interestingly, such a relationship may attenuate over time, as has been shown in the USA.<sup>16,31</sup>

The association between MS prevalence and latitude has recently been questioned in a large meta-analysis.<sup>17</sup> In that analysis, the latitudinal association in Western Europe vanished when prevalence was replaced by incidence. However, the included prevalence studies were performed during an extended period of time (1971–2006), and referred to widely scattered regions and populations of different age distributions.<sup>17</sup> Such meta-analyses may involve methodological drawbacks, lacking age-specific figures for different populations, diversities concerning ethnic and socio-economic conditions as well as health care availability in different

populations, case ascertainment and difficulties in determining latitudes. Our analysis of the existence of a latitude gradient was based on information concerning age with 1-year precision, gender, latitude of residence at municipality level (290 measure points) and whether or not a diagnosis of MS had been registered for each of the 9,256,347 inhabitants of Sweden on the prevalence date. Thus, the present analysis was performed with optimal and high precision. We found that the risk of MS in Sweden significantly increased for each degree of north latitude in both men and women. Sweden lies within one climate zone, despite the great distance of 14° of latitude between the southern and the northern extremities. The general conditions of Swedish health care, social–economic conditions and standard of living are homogenous. Case finding and case ascertainment are consistent throughout the country. These conditions resembled those of Norway, where a latitude gradient of MS, however, was absent.<sup>18</sup> Kampman and co-workers suggested that both climate and diet interact to influence the risk of MS, and this may explain the absence of a north–south gradient of MS in Norway. In northernmost Norway, a very high vitamin D intake through a high consumption of fish might compensate for the high latitude and low sunlight exposure.<sup>18</sup> The contrasting results of the present and the Norwegian study may also to some extent be explained by different methods. In Norway the prevalence was not estimated in all counties and not at the same point in time.<sup>18</sup> In our analysis, the prevalence was simultaneously estimated in all municipalities. Similarly, the prevalence of MS in six latitudinal regions of New Zealand was measured simultaneously, which revealed a strong latitudinal effect on MS prevalence.<sup>5</sup> Our finding of a latitude gradient of MS, although modest compared with the strong gradients of MS in Australia<sup>14</sup> and New Zealand,<sup>5</sup> supports that a latitude gradient of MS exists, even within the same climate zone.

An advantage of the present study was the unusual opportunity to utilize several nationwide registries. The TPR has been mandatory with complete coverage since 1947, the Inpatient NPR since 1987 and the Outpatient NPR since 2001. Consequently, mandatory registrations of diagnoses in Sweden most probably render an almost complete coverage of MS patients. The SMSreg is nationwide, with increasing coverage since the start in 1996. Swedish MS care is a system of spider nature, meaning that a patient with features suggestive of MS is generally referred to a department of neurology, which increases both the accuracy of the diagnosis and the probability of registration. An MS diagnosis is always determined by a neurologist, and only neurologists enter the diagnoses in the two registries. The present registry-based study was designed to preserve the integrity of the patients and did not allow access to the

patients' medical records for validation of the registered diagnoses of MS. When the NPR started in 1987, patients were diagnosed according to the Poser criteria<sup>21</sup> and at the start of the Outpatient NPR 2001 the McDonald criteria,<sup>19</sup> and thereafter the revised McDonald criteria<sup>20</sup> were introduced. This implies that similar diagnostic criteria have been used in the NPR and the SMSreg. Furthermore, the presence of oligoclonal bands and/or increased IgG index in the cerebrospinal fluid has long been used in the diagnostic investigation of MS in Sweden.<sup>32,33</sup> Thus, the risk of entering misdiagnosed MS patients into the registries should have been low even before the era of magnetic resonance imaging.

Out of 17,485 MS patients, 7001 were registered in the NPR only. There were three main reasons why these patients had not yet been included in the SMSreg. First, 4568 patients were included in the NPR before the start of the SMSreg. The mean age was about 10 years higher in the NPR than in the SMSreg. Among patients registered in the NPR only, 45% were older than 60 years, while only 22% of all registered patients in the SMSreg had reached that age. Second, patients were not captured by the SMSreg in counties where the registration rate in the SMSreg was low. The coverage of the SMSreg varied between counties, from 10–83% of the total number of registered patients. Thirdly, whereas the SMSreg from its start was primarily focused on patients who received immunomodulating therapy, the patients registered in the NPR only probably had more often a progressive course and/or had never been treated with immunomodulatory/immunosuppressive therapy. Diagnoses were most likely entered in the NPR and the web-based online SMSreg by the same neurology unit or even the same neurologist, which may explain the large overlap between the two registries.

The proportion of patients classified as Possible MS in the SMSreg on the prevalence date was 7%. These patients were included in this survey because the majority were registered also in the NPR. Moreover, a specified diagnosis of MS or Possible MS was lacking for 657 patients in the SMSreg. Again, these patients were most often registered also in the NPR. In fact, only 165 patients with Possible MS were registered in the SMSreg but not in the NPR, which is less than 1% of the total number of registered patients. Among these Possible MS patients, 40% were treated with immunomodulating/immunosuppressive agents and five patients were treated with natalizumab and/or mitoxantrone, which suggests that they had converted from Possible MS to MS. Thus, this difference between the registries may be explained, at least partly, by a delay of converting diagnoses of Possible MS to MS in the SMSreg. The contribution from Possible

MS patients to the estimated prevalence of MS was negligible.

The main value of this type of MS prevalence survey lies in providing the basis for health economic planning and future MS care development. We have used two separate sources for obtaining the number of observed, registered MS patients, and are approaching the real MS prevalence in Sweden. Nevertheless, we are aware that certain groups of MS patients were unregistered and therefore not included. Patients, who were registered neither in the NPR nor in the SMSreg, were most likely older or had a benign course of MS. In fact, patients diagnosed with MS before the start of the NPR remained unregistered, provided that they had no renewed contact with inpatient care after 1987 or outpatient care after 2001 and were never captured by the SMSreg. Taking this into account, future thorough MS prevalence surveys will probably show increasingly higher estimates.

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### Conflict of interest statement

The authors declare that they have no conflicts of interest.

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