

Further considerations on the distribution of multiple sclerosis in Sweden

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Objectives – The geographic distribution of multiple sclerosis (MS) in Sweden over time was compared in order to analyze homogeneity.

Methods – The distribution of MS was compared among three nationwide resources: 1301 hospital cases 1925–1934; 5425 deaths 1952–1992; and 11,371 disability pension recipients 1971–1994.

Results – Distributions by county (län) were markedly non-homogenous, with greatest variations in the early prevalence series (16–232% of the national mean), less within the death data (75–170%), and least for the disability series (87–128%). Maximal rates for MS in the early prevalence series were found for the cluster of seven counties surrounding the two major lakes of south central Sweden, as well as for one region on the northern shore of the Bay of Bothnia, and another also off the Bay north of Stockholm. **Conclusion** – Though the epidemiologic sources are quite different, they are internally consistent and thus provide three consecutive cross-sectional views of the distribution over time. When considered together the data may be compatible with a thesis of the origin and spread of MS within Sweden from the south-central inland lake regions of the country. Such spread within a half century is too rapid for a genetic cause, including HLA patterns.

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Recently a paper in *Neuroepidemiology* described the distribution of multiple sclerosis (MS) from mortality and disability compensation data from Sweden, and compared these with similar data on amyotrophic lateral sclerosis and Parkinson's disease (1). There was a strong linear correlation between the MS death rates (median year 1972) and those for disability rates (median year 1983) by county of residence: the intercept for $y = 0$ (deaths) was at almost 80% for x (disability). This results from a variation in the disability rates that was smaller than that of the death rates, and suggests considerable geographic diffusion of the disease over time. Were the rates proportionately stable by region, the regression line would have gone through 0 on both x and y . To explore further this important point, we chose this opportunity to compare both of these MS distributions directly with those for the earliest nationwide assessment of MS in Sweden, that of Sällström (2). Other than these works there are prevalence studies from two Swedish areas: Gothenburg at 96 per 100,000

population in 1990 (3); and Västerbotten county at 154 per 100,000 in 1997 (4, 5). These figures are not included in our analysis.

Some important features affecting the prevalence should be mentioned: duration of illness, time to disability, and time to mortality. Sällström (2) used 9 years for prevalence duration. In a previous study by some of us (1) disability pension correlated well with mortality 10 years later. Median survival time in a recent study was 43 years for white females, 30 years for black males and 34 years for white males (6). Mean change in Expanded Disability Status Scale (EDSS) over a 10-year period was 1 point and only 20% worsened by 2 points or more (7).

Materials and methods

As described previously (1), all deaths coded to MS, whether underlying or contributory cause, for the years 1952–1992 were collected, together with demographic data (age, sex, residence) and

population distributions from the Swedish national statistics office (Statistics Sweden). Similarly all Swedish residents with MS who received disability pension in the years 1971–1994 were ascertained from the national social insurance board records.

Sällström's monograph (2) described MS from all patients hospitalized in 87 cited hospitals covering all of Sweden during the 10 years 1925–1934. After his review he recorded 2100 (unduplicated) cases of which he classified 1365 as certain MS and 735 as doubtful. In his Table 20 were listed the numbers of MS and 1931 populations for each of the 24 counties (län). These were the data used in prior assessments of the distribution of MS in Sweden (8, 9). In addition to calculating prevalence rates for each county, the variation between the counties was tested using a modified chi-squared 'goodness-of-fit' test. Each unit's contribution to the total χ^2 , that is $(O - E)^2/E$ (where O is the observed value and E the expected value for the number of MS cases within each area, with expectations $[E]$ calculated from the unit's population times the national total of cases/population), was taken as an approximate chi-squared value (χ_a^2) for that unit vs the mean. Values of χ_a^2 for each unit over 4.0 were considered statistically significantly different from the mean for that unit; those with χ_a^2 2.0–4.0 of dubious significance; and those with $\chi_a^2 < 2.0$ insignificantly different from the mean (10). In mapping out the data, only regions at or above the mean were plotted, whether by percentile ranges or levels of statistical significance (8, 9).

In preparation for another paper on this material to detail the distribution more fully than the large counties provided, Sällström's data had been reassessed (11). In the same table with the county data, he had listed cases and populations for 400 smaller regions (härad, skeppslag, tingslag, individual towns and cities) subsumed within the 24 counties. These regions were combined from contiguous areas within each county for a new total of 106 small units. An example for one county is given below (Table 3). Combinations were based on a minimum population of 23,500 persons per unit, which was the number required for an expectation of five cases of MS, as needed for the chi-squared test to be valid. It was then found that there were some discrepancies for county totals as published (2) and the sums from the small units; cases and populations summed to 1301 MS in 6,130,228 residents. This reassessment of MS in the 106 units of the 24 counties had been presented as a part of a paper entitled 'On the fine structure of the distribution of multiple sclerosis' (11). This title was a totally unrecognized pun on the status of electron

microscopy, a highly regarded scientific method of study of diseases, in comparison with epidemiology, not often considered in the same light.

Distributions by county for the two series of Landtblom et al. (1) were also recalculated and presented as average annual incident disability rates or death rates per 100,000 population. The sum of incident hospitalized cases in the 10 years of Sällström's study was taken as an estimate of the point prevalence rate per 100,000 population, as duration of illness had been cited as 9 years (2). The rates for each unit of the three respective series were again expressed as proportions or percentages of the respective national mean rates; the former approximating the standard odds ratios. Tests of homogeneity were carried out for all as noted above. Age adjustments were not performed, as they are not necessary in lands like Scandinavia for studies of distributions among the native population for incidence or prevalence rates, and also probably for death rates (8, 10).

Results

Prevalence rates per 100,000 population for Sweden in 1933 are presented in Table 1. They ranged from three per 100,000 in Gotland (no. 8) to 49 in Uppsala (now Uppland, no. 2). As percentages of the national rate of 21.22 per 100,000 these counties ranged from 16% to 232%. In formal testing, the distribution by county was markedly non-homogenous, with χ_{23}^2 of 151.21 ($P = 0.00001$ at χ_{23}^2 of 63.97).

The rates by county are shown in Fig. 1, expressed as percentile ranges of the national rate. Most of the high rates, aside from that in Uppsala (no. 2), tend to cluster about the southern inland lake region around Lake Vänern, south of Värmland (no. 16), and Lake Vättern, east of Skaraborg (no. 15). Rates otherwise were generally low along the coastlines, west, south, and east. The elevated rate in the large county of Västerbotten (no. 23) in the north reflects excess of cases near the Bay of Bothnia. This is more clearly seen when small unit distributions are considered. Fig. 2 describes the distribution as percentile ranges of the national mean for the 106 units of Sweden (11). Homogeneity is again rejected with very high statistical significance: $\chi_{105}^2 = 239.0$, $t = 9.74$ ($P = 0.001$ at $t_{120} = 3.37$). In Västerbotten the highest units were for the coastal city and subunits of Umeå and its surrounding areas near the sea, while the large western expanse of the county was low (Fig. 2). From the small unit distribution, rates in the southern part of Sweden tended to reflect those for the counties, but with some notable differences.

Table 1 Prevalence rates per 100,000 population for MS in Sweden 1933, from hospital cases 1925–1934; data of Sällström (2), average annual death rates per 100,000 population for MS in Sweden, 1952–1992; data of Landtblom et al. (1) and average annual disability incidence rates per 100,000 population for MS in Sweden, 1971–1994; data of Landtblom et al. (1)

No.	County (län)	Prevalence rates per 100,000 population for MS in Sweden 1933, from hospital cases 1925–1934; data of Sallstrom (2)				Average annual death rates per 100,000 population for MS in Sweden, 1952–1992; data of Landtblom et al. (1)				Average annual disability incidence rates per 100,000 population for MS in Sweden, 1971–1994; data of Landtblom et al. (1)			
		Pop. (k)	No. MS	Prevalence	% total	Pop.(k)	No. MS	Death rate	% total	Pop. (k)	No. MS	Disability rate	% Total
1. (1a)	(Greater) Stockholm	741.9	132	17.79	83.8	1433.8	749	1.274	76.6	1574.2	2018	5.341	94.8
2.	Uppsala (Uppland)	138.1	68	49.24	231.7	214.0	129	1.470	88.4	250.1	325	5.415	96.2
3.	Södermanland	189.2	35	18.50	87.2	242.0	198	1.995	120.0	252.8	330	5.439	96.6
4.	Östergötland	309.9	69	22.26	104.9	377.4	227	1.613	88.2	395.9	503	5.293	94.0
5.	Jönköping	231.6	63	27.20	128.2	295.2	224	1.851	111.3	318.7	426	5.570	98.9
6.	Kronoberg	155.5	41	26.37	124.2	166.9	108	1.578	94.9	173.7	215	5.158	91.6
7.	Kalmar	231.5	26	11.23	52.9	237.8	141	1.446	87.0	241.0	297	5.135	91.2
8.	Gotland	57.4	2	3.48	16.4	54.9	35	1.555	93.5	55.8	61	4.554	80.9
9.	Blekinge	144.8	22	15.19	71.6	149.7	114	1.857	116.6	152.8	207	5.645	100.2
10.	Kristianstad	245.9	46	18.71	88.1	268.8	179	1.624	97.6	280.1	330	4.908	87.2
11.	Malmöhus	510.7	122	23.89	112.6	699.2	433	1.510	90.8	758.1	1036	5.694	101.1
12.	Halland	150.1	29	19.32	91.0	205.9	135	1.599	96.1	235.8	361	6.379	113.3
13.	Göteborg (-Bohus)	456.2	85	18.63	87.8	680.7	503	1.802	108.4	727.9	1055	6.039	107.2
14.	Älvsborg	313.2	81	25.86	121.9	403.3	346	2.093	125.8	427.4	653	6.366	113.0
15.	Skaraborg	232.6	74	31.33	147.6	250.2	211	2.057	123.7	269.6	454	7.018	124.6
16.	Värmland	269.9	75	27.78	130.9	283.9	329	2.826	169.9	283.2	491	7.224	128.3
17.	Örebro	219.2	64	29.20	137.6	267.7	244	2.223	133.7	273.8	303	4.861	86.3
18.	Västmanland	180.0	33	18.33	86.4	248.0	145	1.426	85.7	259.2	357	5.738	101.9
19.	Kopparberg	249.6	50	20.03	94.4	281.5	190	1.646	99.0	284.7	362	5.298	94.1
20.	Gävleborg	279.6	45	16.09	75.8	290.9	210	1.761	105.9	291.5	375	5.361	95.2
21.	Väster-norrland	281.2	29	10.31	48.6	270.9	142	1.279	76.9	264.2	310	4.889	86.8
22.	Jämtland	134.5	25	18.59	87.6	134.8	113	2.044	122.9	134.2	177	5.496	97.6
23.	Västerbotten	204.0	63	30.88	145.5	238.6	187	1.911	114.9	245.2	290	4.928	87.5
24.	Norrbottnen	199.8	22	11.01	51.9	259.5	133	1.250	75.2	263.1	435	6.888	122.3
Total Sweden		6130.2	1301	21.22	100.0	7955.8	5425	1.663	100.0	8413.1	11371	5.632	100.0

Average annual death rates for MS, all causes, for the years 1952–1992 are provided by county in Table 1, together with their percentages of the national rate of 1.66 per 100,000 population. These data have been presented in more detail by Landtblom et al. (1). Distributions were once again markedly non-homogenous with the 5425 cases providing χ^2_{23} of 257.04 ($P < 0.00001$).

Incident disability cases for MS in 1971–1994 were also provided by Landtblom et al. (1). With corrections, average annual disability rates per 100,000 population were calculated by county of residence (Table 1). The 11,371 pensioners provided an average annual rate of 5.63 per 100,000. Again, the distribution was statistically non-homogenous, with a highly significant χ^2_{23} value of 139.60. In Fig. 3 are the distributions by county for both the death rates and the disability rates again expressed in percentile ranges of the mean values.

Fig. 4 indicates the correlation by county of the death rates on the x -axis vs, on y , the hospital prevalence rates, all as percentages of their mean values. There is a significant relationship with a Spearman rank-order coefficient of correlation of

0.55 ($t = 3.07$, $P < 0.01$). The y intercept is at about 60% on the x -axis, indicating marked diffusion of the disease over these intervals. If we accept a 9-year duration for the early hospital series, and a 25-year duration of illness for the death rates, this suggests an average interval between these two points from disease onset of only some 25 years or so (1933–1939 = 1924; 1972–1925 = 1947).

Comparison of the hospital series (y -axis) with the disability incidence material (x -axis) also shows an apparent correlation with a y intercept at some 80% on the x -axis (Fig. 5). Similar comparison with the deaths (y -axis) vs disability (x -axis) indicates (Fig. 6) an intercept for y near 60% on x , quite similar to that for the (old) prevalence series vs the (new) death data noted above. Both of these last two correlations, however, lacked statistical significance for the respective Spearman coefficients of 0.24 ($t = 1.15$) and 0.23 ($t = 1.09$; both with P -value between 0.30 and 0.20). These low coefficients may be reflecting the very small range for the most recent series (see below).

Table 2 summarizes the results of the distribution for these three data sets. It is obvious that the

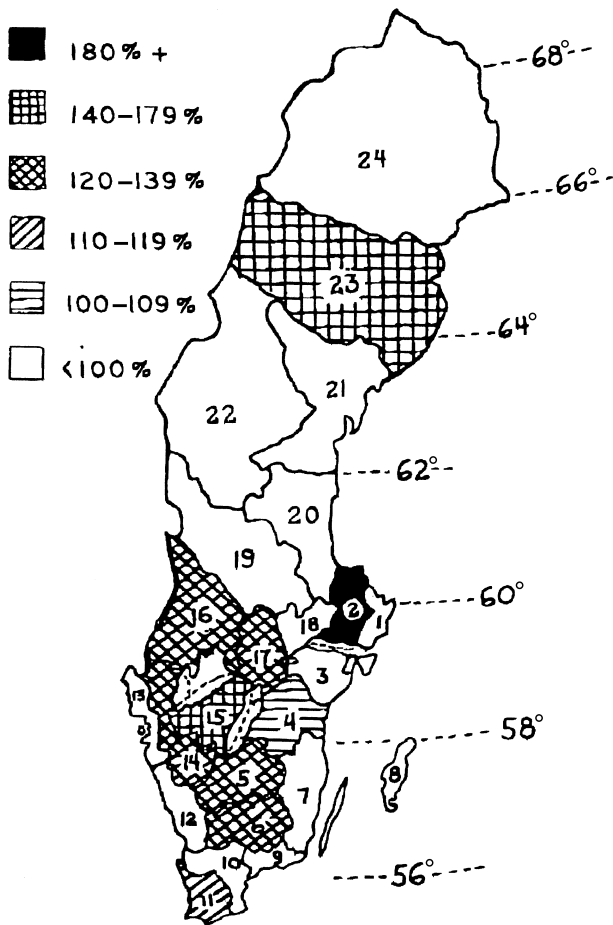


Figure 1. Multiple sclerosis in Sweden. Prevalence rates per 100,000 population (1933) for hospitalized patients, 1925-1934, by county (län) of residence, expressed as percentile ranges of the national rate of 21.22 per 100,000. Data of Sällström 1942 (2) and Kurtzke 1966 (3). Modified from Kurtzke 1966 (4).

range has been contracting markedly, and, while each one is still formally highly significant in the statistical sense, the chi-squared value for the most recent series is only half that for the death rates, even though numbers are twice as large. In fact, if we use exactly the same percentages by county as given in Table 1, but apply them to a total of 1306 cases, the most recent series does not even approach significance: $\chi^2_{23} = 15.9$, $P > 0.80$. Thus, the distribution of MS by county in Sweden has apparently become essentially homogenous – if we accept as valid the maneuver of decreasing the number of disability cases by more than 90%. However, the original publication on the method noted:

This method of testing has limitations. It should not be used when the expected numbers of cases in any area is less than five* (* notes exceptions)... More difficult to settle is the maximum number of cases for an area. The method works well with up to 500 or so cases within a few parts in a survey. If, however, there are thousands of

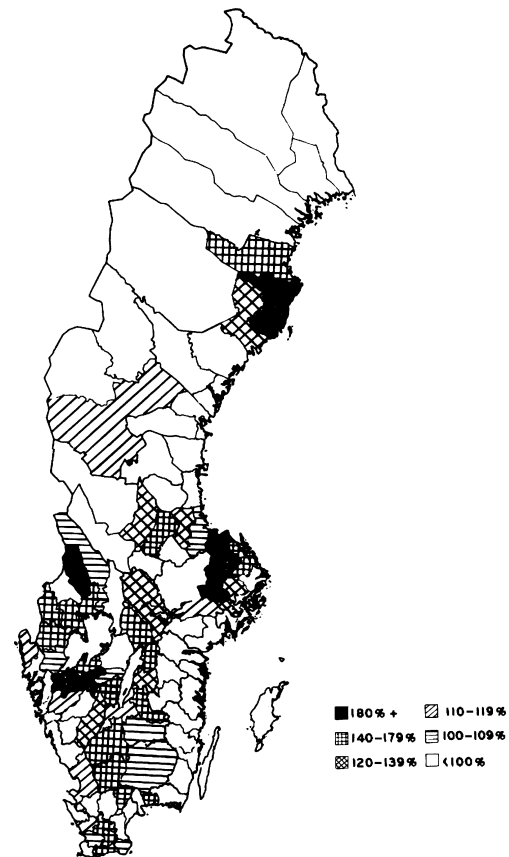


Figure 2. Multiple sclerosis in Sweden. Prevalence rates per 100,000 population as in Fig. 1 for residence within 106 small geographic units, expressed as percentile ranges of the national mean for each unit. Data of Sällström 1942 (2) and Kurtzke 1967 (11).

cases in each area, as might be found with vascular disease or diabetes, a distribution might be properly considered as non-homogenous with statistical significance while the actual variation is quite small. This is analogous to a 'significant difference' between means of 45.0 and 45.4, a possibility with very large samples, but usually inconsequential in medical work. Arbitrarily, I think little weight should ordinarily be attached to statistically significant variations among areas unless several areas at least are some 25% beyond the mean prevalence (75-125 percent of the mean) (10; p. 915)...

It may be seen (Table 1) that only one area exceeded 125% (value 129%), and none were <80% of the mean. These are the reasons why we focus on the possibility that the disorder now – at the county level – may be more homogenous. And, if we wish to compare the three distributions directly, the only valid method would seem to be equate the total numbers in each, as we have performed. Thus we believe the data do indicate a marked change in the distribution of MS within half a century from one strongly clustered to one of

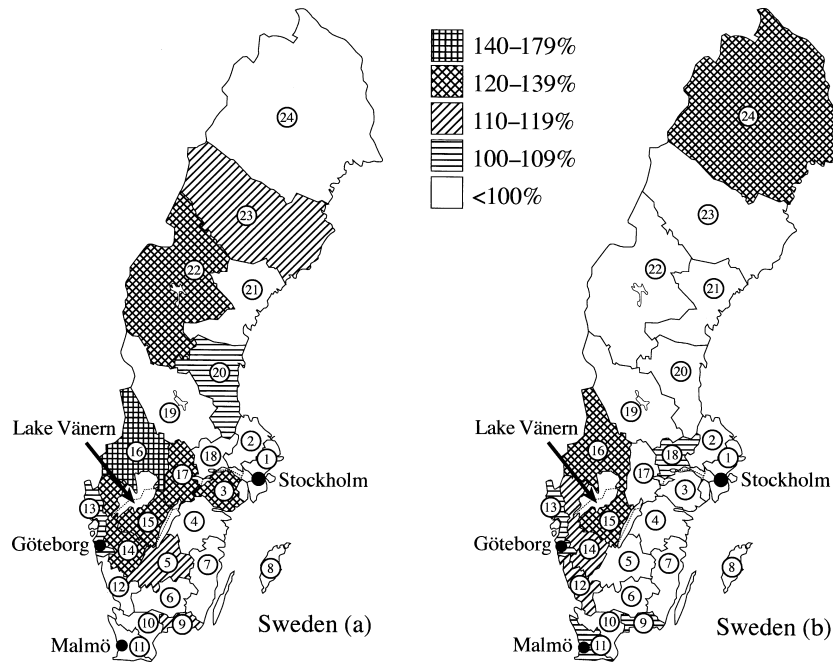


Figure 3. Multiple sclerosis in Sweden. Average annual rates per 100,000 population by county (län) of residence expressed as percentile ranges of the respective national mean rates: (a) death rates 1952–1992; (b) disability incidence rates 1971–1994. Data of Landtblom et al. (1).

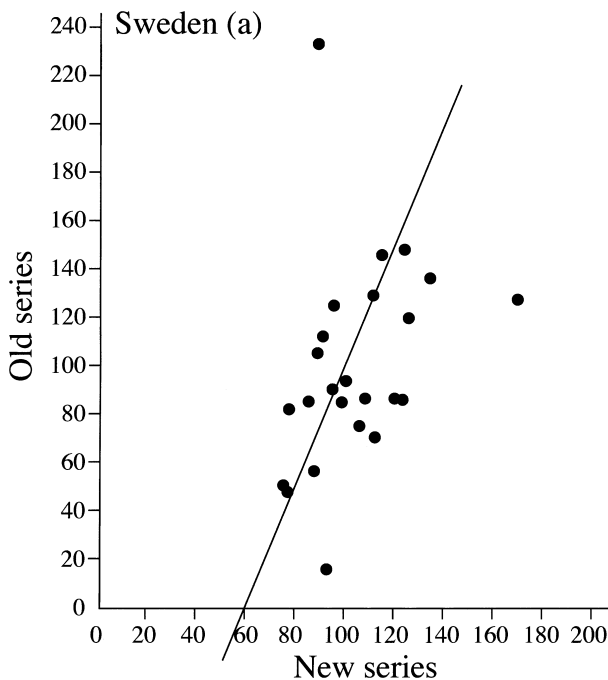


Figure 4. Multiple sclerosis in Sweden. Correlation of percentages of national rates by county for prevalence rates 1933 (old series; y-axis) and death rates 1952–1992 [new series: Sweden (a); x-axis]. Data of Table 1.

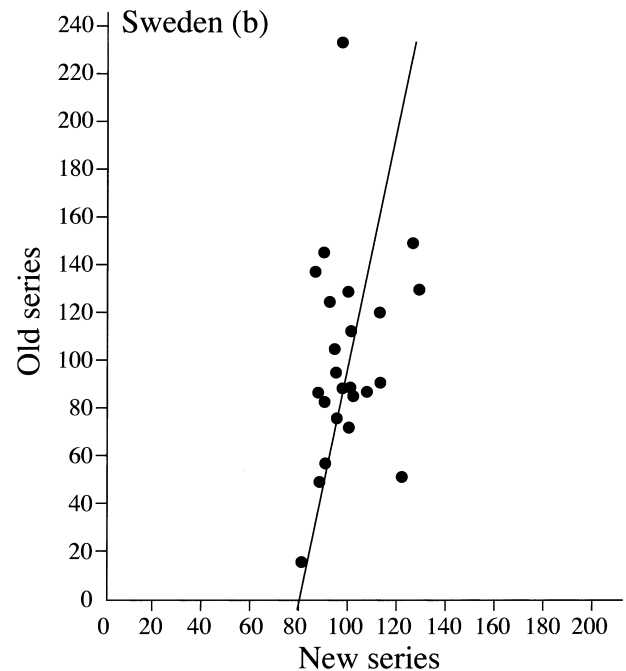


Figure 5. Multiple sclerosis in Sweden. Correlation of percentages of national rates by county for prevalence rates 1933 (old series; y-axis) and disability incidence rates 1971–1994 (new series: Sweden (b); x-axis). Data of Table 1.

equivalence. There is no basis to believe this was other than a gradual change over this interval.

However, the death rate data still showed significant differences, and thus worth a closer

look. The county with the highest death rate, Värmland (no. 16), had been subdivided into 16 municipalities which demonstrated statistically significant differences among them, while 14 of 16

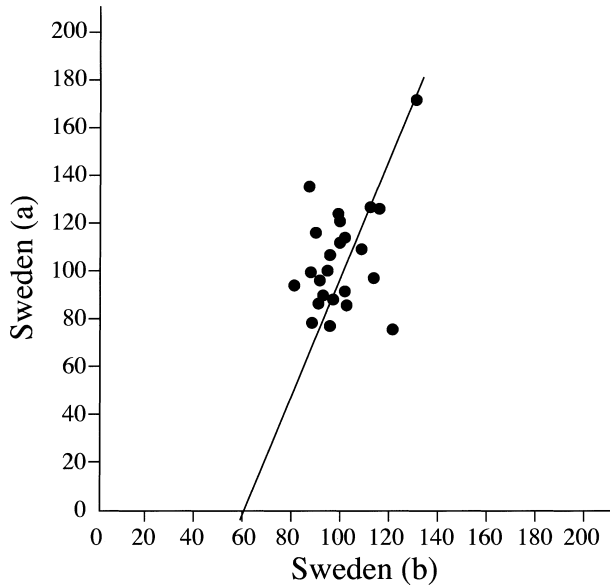


Figure 6. Multiple sclerosis in Sweden. Correlation of percentages of national rates by county for prevalence rates between the two new series: (a) death rates 1952–92 (y-axis); (b) incidence rates 1971–94 (x-axis). Data of Table 1.

Table 2 MS in Sweden. Range of rates by source and time. Number of counties within specified percentile ranges of respective national mean rates

Percentage total approximate year: (range of years)/ estimated onset/	Prevalence 1933 (1925–1934)/ 1924/	Death incidence 1972 (1952–92)/ 1947/	Disability incidence 1983 (1971–94)/ 1968/
180+	1	—	—
160–179	—	1	—
140–159	2	—	—
130–139	2	1	—
125–129	1	1	1
120–124	2	3	2
115–119	—	1	—
110–114	1	2	2
105–109	—	2	1
100–104	1	—	3
100+	10	11	9
95–99	—	3	5
90–94	2	3	5
85–89	5	4	4
80–84	1	—	1
75–79	1	3	—
70–74	1	—	—
60–69	—	—	—
50–59	2	—	—
<50	2	—	—
<100	14	13	15
<i>n</i>	1301	5425	11371
χ^2_{23}	151.2	257.0	139.6
<i>P</i>	<0.00001	<0.00001	<0.00001
<i>N'</i>	1306	1306	1306
χ^2_{23}	151.3	61.7	15.9
<i>P</i>	<0.00001	<0.0001	0.90 > <i>P</i> > 0.80

also exceed the national mean death rate in prior analysis (see Fig. 7) (1). The municipalities differed from those presented by Sällström (2), which had

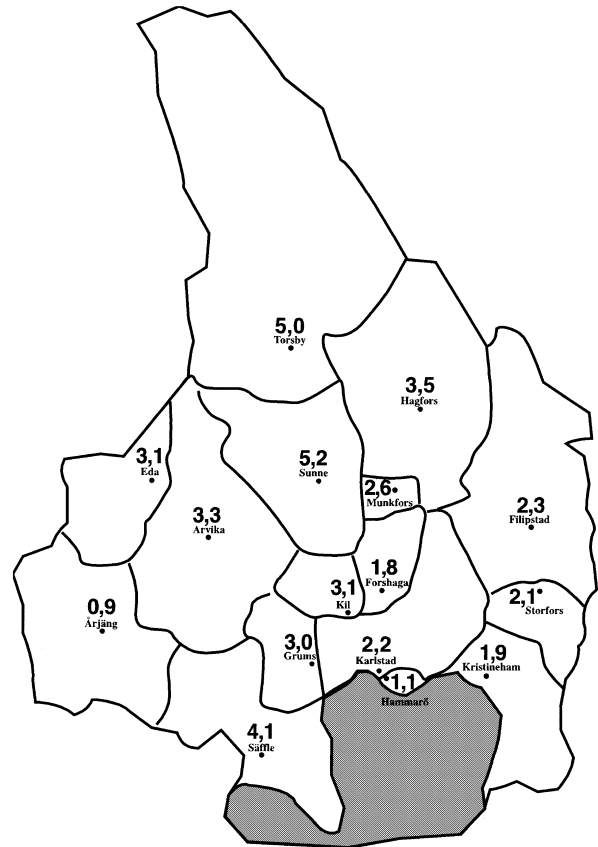


Figure 7. Multiple sclerosis death rates within 16 municipalities of the county of Värmland (no. 16). From Landtblom et al. (1). Reproduced with permission by *Neuroepidemiology*.

been combined by Kurtzke (11) as indicated in Table 3.

In agreement with the later death data, some, but not all, of Värmland (no. 16) was indeed high in this earliest distribution, but it does appear that this was really only a part of a clustering of high frequency MS in the regions surrounding both Lake Vänern and Lake Vättern. This includes, aside from Värmland, much of the counties of Älvsborg (no. 14), Jönköping (no. 5), Kronoberg (no. 6), westernmost Östergötland (no. 4), and all of Örebro (no. 17) to complete the circle around the lakes. Included too is most of Skaraborg (no. 15) between the lakes. This does then seem to support earlier interpretations of the main focus of MS in Sweden occupying the south-central inland lake regions, with two ‘metastases’: Uppland (no. 2) to the east, and Umeå region of Västerbotten (no. 23) to the north (11, 12).

In Table 4 is a summation of the distribution of MS in Sweden for each of these three data sets by county, listed in numerical order and subdivided according to their status in the earliest nationwide distribution available. First are the seven counties

Table 3 Prevalence rates per 100,000 population for MS by small units of one county of Sweden, 1925–1934 (Sällström 1942, Kurtzke 1967)

No.	Area	Population	MS	Prevalence	χ^2_a
16	Värmlands län	269,944*	75	27.78	5.48†
16.1	Östersysslet	51,778	9	17.37	0.36
	Färnebo härad	16,845	3	18	
	Visums härad	6517	2	31	
	Ölme härad	4175	2	48	
	Väse härad	7175	2	28	
	Kristinehamn†	12,434	0	–	
	Filipstad‡	4632	0	–	
16.2	Älvdal and Nyed	37,150	8	21.51	0.00
	Älvdals härad	31,407	7	22	
	Nyeds härad	5743	1	18	
16.3	Mellansysslet	66,255	23	34.69	5.68
	Karlstads härad‡	15,899	6	38	
	Kils härad‡	18,938	7	37	
	Grums härad‡	10,507	4	38	
	Karlstad‡	20,911	6	28	
16.4 + 5	Södersysslet/4/, Nordmark/5/	45,839	15	32.75	2.86
	Näs härad/4/	13,709	4	29	
	Gillberga härad/4/	13,352	8	60	
	Nordmarks härad/5/	18,778	3	16	
16.6	Jösse	35,252	6	17.00	0.29
	Jösse härad	27,273	3	11	
	Arvika‡	7979	3	38	
16.7	Fryksdalen	33,670	14	41.54	6.57
	Fryksdals härads övre	13,040	6	46	
	Fryksdals härads nedre	20,630	8	39	
Total	Sweden (106 units)	6,130,228*	1301*	21.223	239.0

* Corrected from published figures in Sällström (2).

† From Table 1.

‡ Units named in Landtblom (1) (Fig. 7); borders may differ there for those above.

which define the main focus of high frequency of MS: nos 4–6, 14–17, which surround the two main inland lakes and extend southward. Next are the three which were also high in 1933: Västerbotten (no. 23), probably constituting a separate high-risk area, Uppsala (no. 2), probably an effect of special interest in neurology (2; p. 97) and Malmö (no. 11). Then come the eight counties which had rates above their respective mean values at any time: nos 3, 9, 12, 13, 18, 20, 22, and 24; and lastly the six (nos 1, 7, 8, 10, 19, and 21) that were never high.

Discussion

The geographic distribution of MS has been an area of increasing interest – and controversy – for much of the past century. The long-held thesis of ‘high north, low south’ has needed considerable modification, as it has become increasingly evident that this is not a disease with a fixed distribution, but rather one with marked changes over periods far too short to be accounted for by genetics or HLA patterns. Southern Europe is now an area of high frequency MS with little difference from the north. Intrnational diffusion of the disorder was

Table 4 Summary of county distributions of MS in Sweden

No.	County	Percentage of national mean		
		Prevalence (1933)	Deaths (1972)	Disability Incidence (1983)
Main focus of high frequency				
4.	Östergötland	105	88	94
5.	Jönköping	128	111	99
6.	Kronoberg	124	95	92
14.	Älvsborg	122	126	113
15.	Skaraborg	148	124	125
16.	Värmland	131	170	128
17.	Örebro	138	134	86
Other high-risk zone				
23.	Västerbotten	146	115	88
Others high in 1933				
2.	Uppland	232	88	96
11.	Malmöhus	113	91	101
Others high at any period				
3.	Södermanland	87	120	97
9.	Blekinge	72	117	100
12.	Halland	91	96	113
13.	Göteborg	88	108	107
18.	Västmanland	86	86	102
20.	Gävleborg	76	106	95
22.	Jämtland	88	123	98
24.	Norrbottn	52	75	122
Never high				
1.	Stockholm	84	77	95
7.	Kalmar	53	87	91
8.	Gotland	16	93	81
10.	Kristianstad	88	98	87
19.	Kopparberg	94	99	94
21.	Västernorrland	49	77	87
Total	Sweden (estimated onset)	100 (1924)	100 (1947)	100 (1968)

described earlier for Norway, Denmark, and Switzerland, and more recently for the United States as well (13).

It is important to note that universal medical care in Sweden has been a function of the state since the 1920s, and is uniformly available throughout the country with negligible private facilities. It is not likely that there would be appreciable differences among counties for seeking medical care or disability pension. These aspects speak to the validity of the three data sources. The first series from hospital would include all known cases of MS, and there was careful review of all suspected case records by the author.

Our results can be interpreted as evidence of dispersion of MS cases over the last 50 years. However, there are some methodological weaknesses. The data are collected not only from different epochs but also with different methodology, some of which is ordinarily considered weak from a scientific point of view (mortality data). However, death data for MS in Sweden are largely based on the prior disability pensions,

which in turn require reliable evidence as to diagnosis. Residence near health care facilities because of disability or migration because of other factors are possible sources of bias, but the former have been considered for all three series with no evidence this was the case, with no correlation between MS distributions of neurologic or hospital facilities. Results from the last study (1) included some observations regarding the character of the high-risk zone Värmland and the counties around lake Vänern. These areas did not have extensive neurologic facilities in the time period of the study and the population has been rather stable for many years with almost no migration. However, the 'metastasis' of Uppland in the earliest study may be explained by the University facilities as well as an old medical center. The finding was not reproduced in the later studies.

Another argument against that the geographical distribution of MS might be biased towards areas with presence of neurologic expertise is that also the first series was based on residence of the patients and not locations of clinics and specialists. Further, a lessening variance was also seen between the last two series, the death rates and the disability rates, where such biases are even less likely to have occurred. However, the pattern indicating diffusion is not fully clear, as regions of high prevalence in the old study, to a certain extent remain high. The communities of Värmland still show a variance, (see Fig. 7) which to some extent resembles the data from Sällström/Kurtzke. There is no doubt regarding the high-risk zone Fryksdalen (Torsby and Sunne communities), where a cluster (Lysvik) recently has been described (14).

This study provides further evidence indicating that the genetic background of MS cannot solely explain the origin of the disease. The diffusion over time seen in this study is compatible with the hypothesis that one single infectious agent could be the cause of MS. Also a more complex etiology with interplay between genetics and several exogenous factors, possibly interacting, would fit our results. Such possible factors include radiation (15) and occupational exposures (16–18), nutritional factors (19), smoking (20), and exposure to organic solvents (18). Further, an activation of latent viruses through exposure to other environmental factors is an example of a possible interaction between exogenous factors (21). Also, a genetic makeup predisposing for an atypical behavior when encountering infectious agents should be considered, i.e. for example the tendency of MS patients to contract childhood diseases late in life (22). Hypothetically, such genetic aberrations may build the basis upon

which infectious agents can operate – an example of genetic/environmental interaction.

It is indeed the earliest distribution which may suggest an origin for MS within Sweden for the seven counties surrounding the two lakes of the south-central part of the country. Whether this seems likely beyond Sweden is currently under investigation (J. F. Kurtzke. On the origin and spread of multiple sclerosis; in preparation). However, to one of us, this topic has long been tantalizing, as stated in 1977:

Where within Europe the disease originated is sheer conjecture, even should one accept the above. Were I forced to speculate (and not to document), I might hazard the guess that MS could have originated in Scandinavia, possibly in southern Norway; when however, is even more tenuous (23; p. 136).

A later expression of this view in 1993 was that MS 'may have originated in central Norway and the south-central Swedish lake region near the center of the Fennoscandian focus, possibly at about the 17th or the beginning of the 18th century... (24; p. 418).' Aside from the action of a single agent to explain these findings, another interpretation is that a combination of several risk factors, genetic as well as environmental, had come together in this area.

More studies on the diffusion of MS are encouraged to shed more light on these issues.

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