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Birth Cohort Effects in Multiple Sclerosis

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PURPOSE: To identify potential birth cohort effects in multiple sclerosis in Sweden and particularly in Stockholm county.
METHODS: Data on multiple causes of death from multiple sclerosis during 1962 to 1995 in Sweden and 1968 to 1995 in Stockholm county were analyzed using age-period-cohort models and curvature.
RESULTS: Mortality from multiple sclerosis was higher in Sweden than in Stockholm county, with stable time trends, slight period effects and marked age effects. Cohorts born before or after a central period, from 1910 through 1930, registered lower mortality. A periodic wave-form mortality pattern was identified, following a 5-to-6-year cycle for cohorts born before 1925 both in and outside Stockholm county, and changing to longer or irregular cycles for cohorts born after 1930.
CONCLUSIONS: Although methodological constraints inducing the saw-tooth pattern cannot be excluded, these results are consistent with etiologic hypotheses claiming a role for environmental factors in multiple sclerosis.
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KEY WORDS: Cohort Studies; Epidemiology; Etiology; Multiple Sclerosis; Mortality.

INTRODUCTION

Although the etiology of multiple sclerosis (MS) is unclear, accumulating evidence strongly suggests that MS is the result of gene-environment interactions and that environmental factors are of primary importance in initiating the disease process (1). Results of migrant studies indicated that susceptibility to MS was acquired during childhood or before puberty (2, 3). However, studies focusing on simultaneous exposure early-in-life to agents potentially related to MS failed to demonstrate evidence of space-time clustering of MS patients, whether by date and place of birth (4, 5), by residence at ages under 15 years (6), or by contact at school (7). Some authors claimed that it might perhaps be better for some of these negative results (4, 6, 7) to be deemed inconclusive, due to lack of data specificity (8), an inappropriately specified clustering model (6) or low statistical power. Later studies found clustering of MS cases after birth: 21 years prior to MS onset and close to MS onset in the Orkney Islands (8), and at age 13 through 20 years in Hordaland, Norway (9).

Birth-cohort analysis, a method capable of indirectly revealing space-time aggregated risk factor activity close to birth, have been sparsely explored in MS (10). In Norway, Gronning et al (11), found a low risk in cohorts born during the period 1946 to 1950 in Hordaland whereas Midgard et al, failed to find such effects in More and Romsdal (12). In the UK, Li et al (13) reported declining MS mortalities in recent birth cohorts. Kurtzke and Hyllested (14) reported four small MS epidemics in the Faroe Islands, with approximately 13-year intervals, which, in our view, correspond to a birth-cohort pattern.

Bimodality in age-specific incidence, which may result from birth-cohort effects (15), was frequently (16–22), though not systematically (23–32), observed.

Monosymptomatic optic neuritis (MON) is an entity closely related to MS. In a recent study in Stockholm County (SC), we found a bimodal distribution of MON incidences consistent with the presence of a pseudo-periodic birth-cohort effect, which was also observable in patients in whom MON had converted to MS, differentially affecting birth cohorts in an approximately 6-to-7-year cycle (33). The purpose of this study was to describe and analyze potential birth-cohort effects in MS in the Swedish population, and particularly in the population in SC, using death

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Selected Abbreviations and Acronyms
ICD = international classification of disease
MON = monosymptomatic optic neuritis
MS = multiple sclerosis
RR = rate ratio
SC = Stockholm County
SD = standard deviation

records. An important reason to report results for Sweden and SC in parallel was the nature of findings and its possible interpretations.

MATERIALS AND METHODS

Mortality and population data

Statistics Sweden furnished data on individual death records for residents in Sweden. Records featuring MS as underlying or contributing cause of death from 1962 through 1995 in Sweden and SC were identified and collected. During this period, three versions of the International Classification of Diseases (ICD) were used to classify causes of death in Sweden. The code for MS was: 345 under ICD-7 for the interval, 1962 to 1968; and 340 under ICD-8 and -9 for the periods, 1969 to 1986 and 1987 to 1995, respectively. Information was obtained on date of birth, date of death, residence at death, underlying cause of death, and contributing cause of death, up to the 6th level for ICD-7 and -8, and the 12th level for ICD-9. Age at death was generated from year of birth and year of death.

TABLE 1. Summary of modeling strategies

Study population	Duration in years: Cohort period of birth	Age interval	Period of death
Sweden	10 (overlapped)	5	5
	5	5	10 (overlapped)
	1	5	5 (overlapped)
	1	8	8 (overlapped)
SC	10 (overlapped)	5	5
	5	5	10 (overlapped)
	1	5	5 (overlapped)
	1	8	8 (overlapped)
Sweden except SC	1	5	5 (overlapped)
	1	8	8 (overlapped)

Data on the annual resident population at December 31, from 1961 through 1995 in Sweden, broken down in 1-year age groups, were obtained from Statistics Sweden. For SC, similar data on annual resident population were only available as from 1967 onwards. Accordingly, the study period for SC was shorter. Based on these data, we calculated the average annual population in 1-year, 5-year, and 8-year age groups for the corresponding study periods, namely, 1962 to 1995 for Sweden and 1968 to 1995 for SC.

Modeling strategies

The number of MS-related deaths in the population was assumed to follow a Poisson distribution. A log-linear Poisson regression model was used to assess the effect of age, period and birth cohort. The Poisson deviance table and the max-

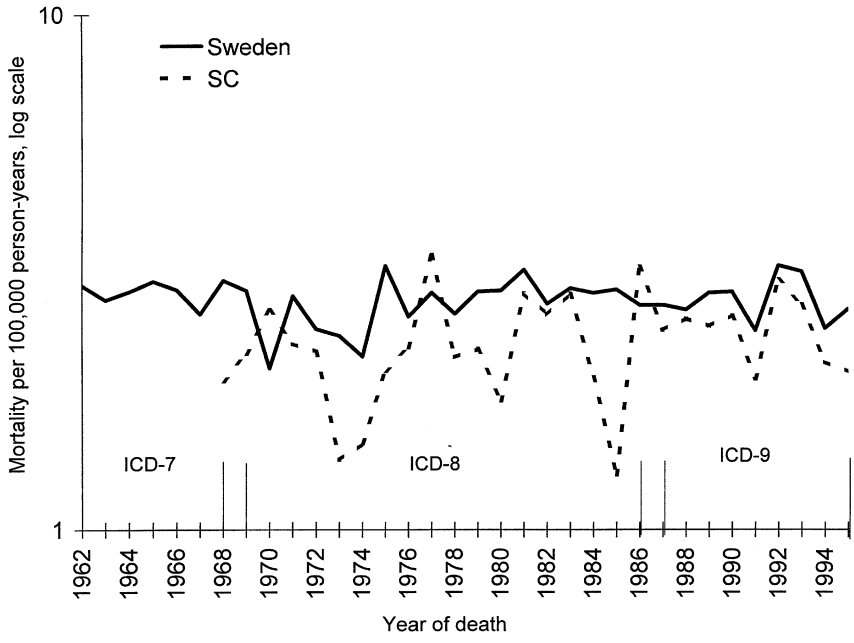

FIGURE 1. Annual age-adjusted MS mortality in Sweden and SC, 1962 to 1965.

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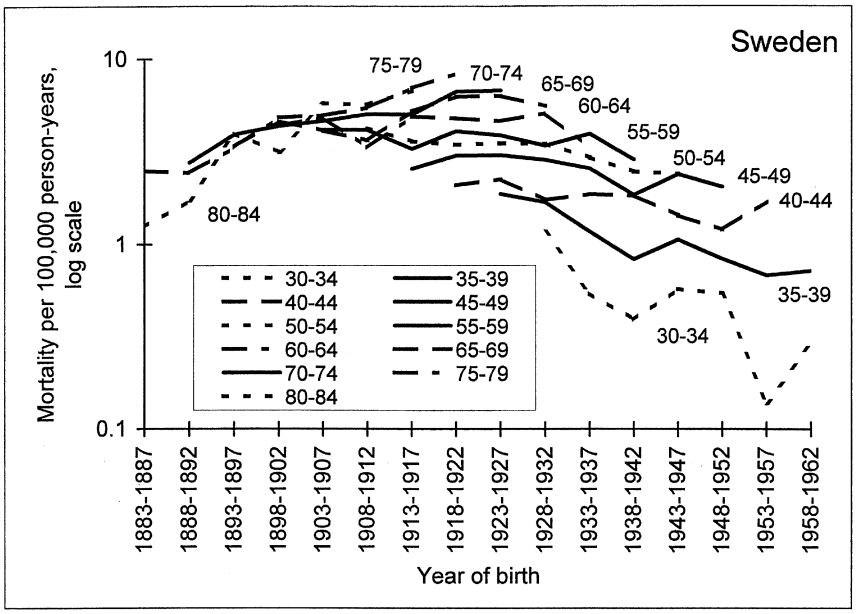
imum likelihood estimates of regression parameters were ascertained. Goodness-of-fit of models was evaluated from the deviance and determination coefficient, R^2 values (34). Extra-Poisson variation was assessed by the departure of the deviance from the number of degrees of freedom. Bearing in mind the non-identifiability issue, which arises in this type of analysis when the three factors -age, period and cohort- are simultaneously introduced into the model, we used curvature analysis as proposed by Holford (15) to evaluate trends in data. Following Holford's paper, we defined the cohort (or period) effects as a linear slope term (β_c or β_p) and a curvature term. The curvature term is an invariant set of estimates regardless of the parameterization used, and is an estimable function of the parameters (15). Cohort effect curvature was calculated as the deviation exhibited by the estimated versus the predicted value for any given cohort, taking into account the general slope of the cohort effect. We use the term "drift" to describe the variation in time, which could be predicted either by age-period or age-cohort model (35).

Using a data array structured in columns for 5-year periods of death, broken down into 5-year age groups, with



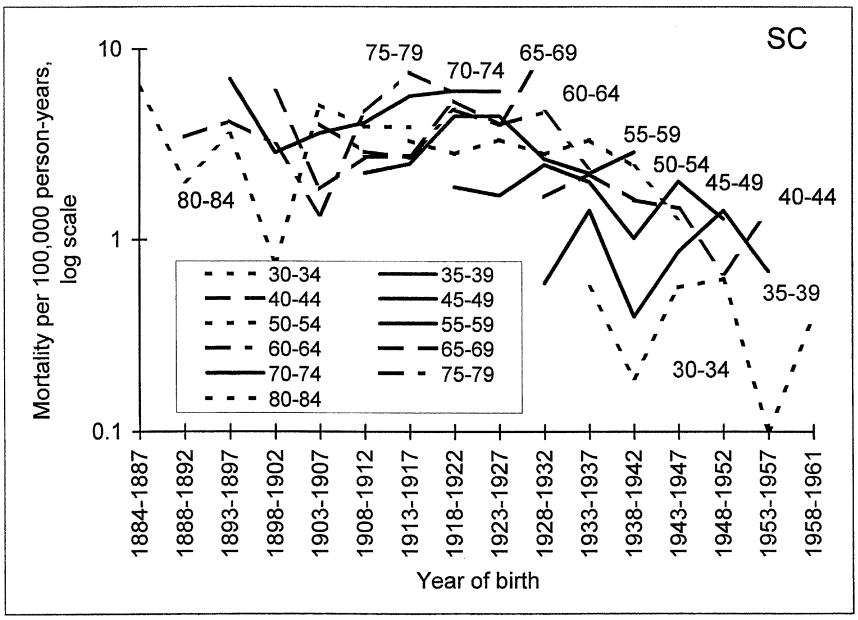


FIGURE 2. MS mortality by year of birth in Sweden and SC: period of death, 1962 to 1995.

TABLE 2. Goodness of fit in different models

Region	Model	5-year age-groups 5-year birth-cohorts			5-year age-groups 1-year birth-cohorts			8-year age-groups 1-year birth-cohorts		
		Deviance	df	R^2 (%)	Deviance	df	R^2 (%)	Deviance	df	R^2 (%)
Sweden	Intercept	1816.7	85		2132.4	407		1959.2	275	
	Age alone	256.9	75	85.9	614.6	397	71.2	471.4	269	75.9
	Age + drift	251.4	74	86.2	609.8	396	71.4	469.4	268	76.0
	Age + period	239.2	68	86.8	553.0	360	74.1	417.9	229	78.7
	Age + cohort	79.9	60	95.6	378.4	320	82.3	229.2	192	88.3
	Age + period + cohort	47.7	54	97.4	312.7	288	85.3	171.1	160	91.3
SC	Intercept	310.7	75		527.2	323		418.4	221	
	Age alone	82.6	65	73.4	347.1	313	34.2	240.6	215	42.5
	Age + drift	80.3	64	74.2	343.3	312	34.9	237.7	214	43.2
	Age + period	77.4	59	75.1	320.8	283	39.2	202.9	181	51.5
	Age + cohort	56.0	50	82.0	282.6	250	46.4	174.9	152	58.2
	Age + period + cohort	53.4	45	82.8	260.7	224	50.6	148.2	126	64.6

R^2 : determination coefficient; df: degrees of freedom.

each cell corresponding to 10-year overlapping periods of birth (36), classical age-period-cohort analysis was conducted solely for the study of period effects. Since our main interest lay in birth cohort rather than period-of-death analysis, and the study of birth cohort effects at an approximately 6- to 7-year cycle requires detailed differentiation of birth cohort effects in MS mortality, we included 5-year and 1-year periods of birth in our study and built matrices arranged by birth cohort columns, broken down by age, where overlaps only affected periods of death. To explore the possible effects of population concentration or arbitrary choice of age-interval, we replicated details of the analysis for the SC and the Swedish population resident outside SC, using 5-year as well as 8-year age-groups. A summary of the most relevant models used in the birth-cohort effect study is shown in Table 1.

RESULTS

During the period 1962 to 1995, there were 4854 MS-related deaths among the 30 to 84 age group in Sweden, while in SC this number was 596 for the period 1968 to 1995. Proportionately, MS diagnosis as underlying cause of death was 61 percent for both populations (2978/4854 for Sweden and 366/596 for SC). In Sweden, mean age at death increased from 56 years (SD 11.23 years) during the 1960s to 64 years (SD 12.41 years) during the 1990s. A similar increase in age at death, from 59 to 63 years, was likewise seen in SC. The female-to-male ratio was 1.14 for Sweden versus 1.51 for SC.

Age-specific and age-adjusted mortality for both sexes during the corresponding study periods, for Sweden and SC, was tabulated but is not shown here. Mortality in Sweden and SC rose from 0.35 and 0.46 per 100,000 person-years at ages 30 to 34 years to 4.75 and 4.94 at ages 70 to 74 years, respectively.

The annual age-adjusted mortality rates for the whole Swedish population and for the SC population in the study periods are shown in Figure 1. Annual age-truncated mortality held stable in Sweden and fluctuated even less in SC, with a mean of 2.79 (SD 0.28) per 100,000 person–years for Sweden, and 2.32 (SD 0.53) for SC. No impact was observed when new ICD versions were introduced in 1969 and 1987.

Age-specific mortality for consecutive 5-year birth cohorts is plotted in Figure 2. Patterns for all-Sweden and SC data though similar, were more stable on a nationwide basis. Mortality increased with recent birth at ages over 40 years in generations born up to the early 1920s, and, decreased with recent birth at ages below 40 years in Sweden and below 45 years in SC for cohorts born ca. 1930 onwards.

The goodness-of-fit of the age-period-cohort models is shown in Table 2. In general, models with nationwide data registered the best fit. Age alone explains most of the variation observable from R^2 values. The temporal variation independent of period or cohort influences is small, seen from the sparse fit improvement of the age-drift models, which is in agreement with the observation in Figure 1. Cohort effects were more marked than period effects. The small differences between df and deviance values in the age-period-cohort models point to the absence of substantial extra-Poisson dispersion.

The period effects obtained from the traditional age-period model measured as RR, reference 1977 to 1981 (data not shown), ranged from 0.88 (95% CI 0.79–0.98) in 1972 to 1976 to 1.08 (95% CI 0.98–1.20) in 1992 to 1995 for Sweden, and from 0.74 (95% CI 0.55–0.99) to 1.01 (95% CI 0.81–1.40) for SC in the same periods.

The cohort-effects, as seen from the 5-year birth-cohort and age-interval data (reference cohorts born 1918 to

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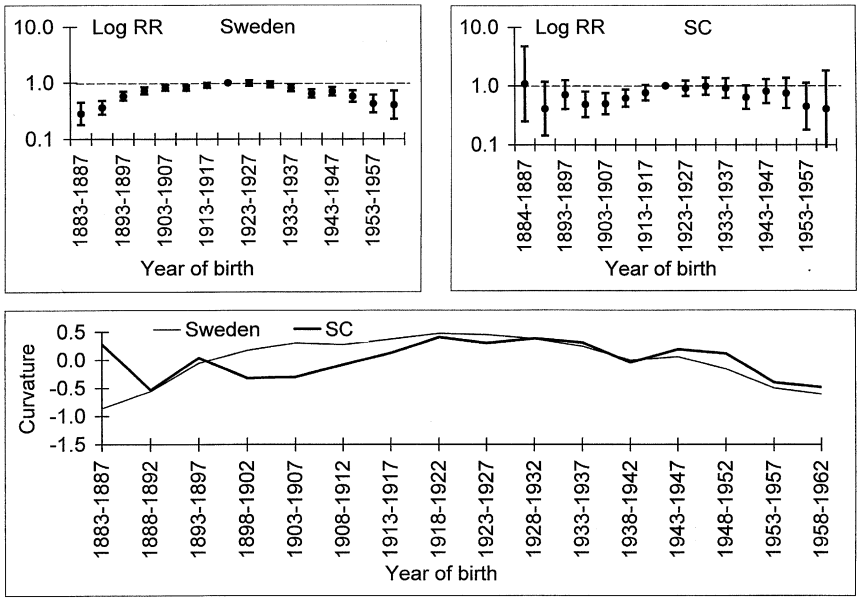

FIGURE 3. Rates ratios from an age-cohort model, and cohort-effect curvature from the age-period-cohort model using 5-year age groups and 5-year birth cohorts in Sweden and SC.

1922), are depicted in Figure 3. The curve for mortality ratios in Sweden and SC displayed an inverted U-shape, which proved less stable for SC, with lowest ratios of 0.28 (95% CI 0.18 to 0.44) and 0.40 (95% CI 0.23–0.72) for the earliest and most recent cohorts in Sweden. In SC, these ratios were 0.41 (95% CI 0.14–1.17) and 0.41 (95% CI 0.09–1.80). The shape of the cohort curvatures for the two populations follows the same pattern especially for generations born after 1918, including coincidence of small local changes for cohorts born in 1938 to 1942. This suggests similar cohort effects over time in SC and Sweden.

The cohort-effects observable from mortality ratios for Sweden and SC, when 1-year birth cohorts were studied in 5-year age groups, are shown in Figure 4. For Sweden, a pseudo-periodic, inverted U-shaped pattern was suggested, with lowest ratios for cohorts born in 1900, 1903, 1909, 1910, 1917, 1924,

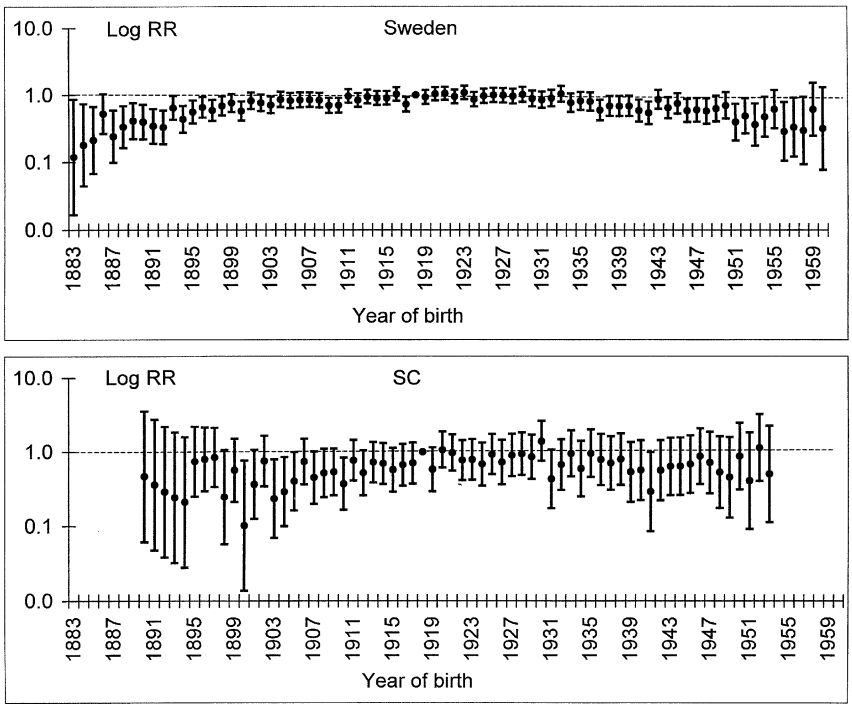

FIGURE 4. Rates ratios from an age-cohort model using data sets for 5-year age groups and 1-year birth cohorts in Sweden and SC.

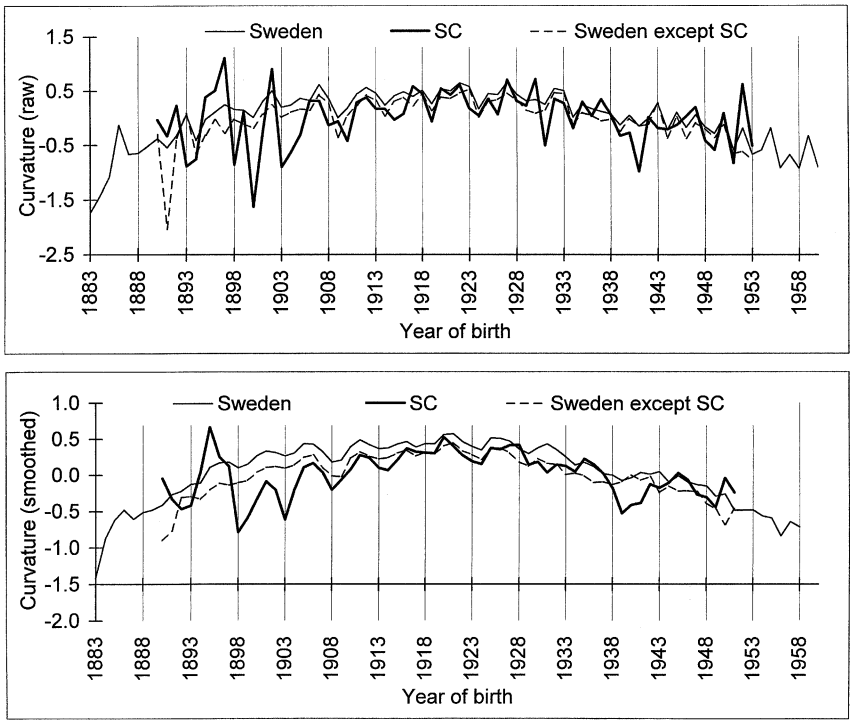

FIGURE 5. Cohort-effect curvature (upper, raw and low, smoothed) from age-period-cohort models using data sets for 5-year age groups and 1-year birth cohorts in Sweden, SC, and Sweden except SC.

1934, 1937 and 1941 to 1942. For SC a similar pattern was in evidence for 1900, 1903 and 1910, with wider confidence intervals and few statistically significant differences.

Cohort-effect curvatures in 1-year birth cohorts for the Swedish population resident within SC, outside SC and in the country as a whole, as well as smoothed curvatures for such populations using triennial, centered one-step-ahead moving averages, are shown in Figure 5. The graphs for raw data display curves similar to those for age-cohort models, but no discernible patterns were present. From the smoothed curves, synchronous pseudo-periodic patterns in 5- to 6-year cycles (of low amplitude in the case of the country as a whole and areas outside SC, and more clearly apparent in the case of SC) were suggested, though solely for cohorts born before 1925.

The smoothed curvatures for 5-year and 8-year age-group analyses for SC are depicted in Figure 6. They show that: (i) the birth cohort patterns for 5- and 8-year duration of age-intervals were similar, but the saw-tooth pattern was more clearly observed in the 8-year age-interval analysis; (ii) for cohorts born since 1907 onwards, the average length of the cycle in the 8-year age-interval analysis is almost 8 years; (iii) in the 5-year age-interval analysis there was a 5- to 6-year cyclic pattern, for cohorts born in the 1890 to 1925 period, shifting to an 8-year or longer, irregular cycle for cohorts born after 1930; (iv) cohort effects for generations contributing data to our reported SC-based MON survey (33), namely, those born post-1935 (see also Figure 5 for raw curvatures), were suggested as being negative for the late-1930 and -1940 birth cohorts.

DISCUSSION

The present study suggests that birth cohorts evince different risks for MS, as seen from mortality records in Sweden. Such variation comprises: (i) lower risk in recent and early cohorts; (ii) an inverted U-shaped pattern evenly changing with time; and (iii) minor period effects. The pseudo-periodic pattern found here deserves a particularly cautious interpretation.

MS underdiagnosis, MS underreporting and disease misdiagnosed and reported as MS in the death certificate may well have been present in Sweden and, indeed, changed with time. However, we are unaware of any validation study comparing MS diagnosis in death certification as against that in clinical data in Sweden. Studies in Norway (37) demonstrated a 0.98 positive predictive value for MS diagnosis recorded on the death certificate. Nevertheless, death certificates failed to show MS diagnosis in 24% and 19% of patients diagnosed with MS in Norway (37) and the USA (38), respectively. In the latter study, of patients with MS as a diagnosis officially filed on the death certificate, 65% corresponded to underlying and 35% to contributory causes. We believe that the probability of such information biases selectively affecting consecutive birth cohorts or inducing lower mortality in recent generations is low, yet we cannot exclude the fact that this phenomenon may underlie the negative effect in old birth cohorts.

The lower mortality observed in our young cohorts, which may reflect the decline in mortality at young ages, is

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difficult to reconcile with improved survival, since the period in question was marked neither by the introduction of any new effective therapies nor by any change in mortality among the young general Swedish population. In England and Wales, increasing MS mortality with recent birth was reported in cohorts born in the period, 1885 to 1910 (13), much along the same lines as descriptions for Parkinson's disease in Italy (39, 40) and malignant tumors of the nervous system in Spain (41), diseases in which the rising trend was most likely due to more accurate case-ascertainment (39, 41). We believe that a decrease in MS incidence in recent times, akin to that reported in Denmark (20, 27), Orkney and the Shetland Islands (42, 43), and Gothenburg (31) —linked in-part to migration of young lower-risk populations from southern Europe—might be the most plausible phenomenon capable of explaining such an effect in Sweden. Our fairly stable time trends contrasted to a reported progressive increase in crude general MS mortality in Sweden for the 1965 to 1982 period (44), in a study examining underlying causes of death only.

A considerable contribution of our results is based on the interpretability of curvatures. In general it could be said that curvature provides a pattern of the deviation of observed effects from the linear component of the trend. Although expected from a prior study (33), the pseudo-periodic curvature observed in 1-year birth cohorts is difficult to explain. First, the similar pattern, particularly for cohorts born prior to 1925, observed for SC and Sweden except SC, two populations considerably different in population size, might be a strong argument against random variation as a plausible explanation of such pattern. Second, sources of systematic bias such as cohort-selective MS under- or misdiagnosis, MS severity or MS-related fatality, reporting at death, or migration are all unlikely explanations for the suggested birth-cohort pattern. Despite that, the proportions of immigrant population from medium-MS-risk geographical areas (Turkey and southern Europe) and of Swedish population born outside the study area are higher in SC, and these high proportions may have acted as a diluent of traits. Third, periodic changes in MS incidence similar to those observed in Germany (45), if due to the differential impact of birth cohorts predominantly contributing to incidence and prevalence counts in different study periods, may not be excluded as an explanation of the pseudo-periodic birth cohort pattern. This would reinforce the role of environmental factors in determining incidence and prevalence of MS in birth cohorts in our study. Unfortunately, neither MS surveys have been conducted in SC, nor has birth cohort incidence been studied in Swedish populations. Fourth, Holford (46) pointed out that part of the effect due to the use of unequal intervals for age and period, in our case age and cohort, is to induce a saw-tooth pattern with periodicity equal to the ratio of the interval widths. Such pattern had to be expected only when the interval width of the second factor, period, is wider (46). While this is not exactly our case, because the wider intervals correspond to age, the observed 5- and 8-year cycle still closely corresponds to the age/cohort intervals width ratio. We point here methodological insufficiencies of the age-period-cohort analysis, which may require targeted development. In consequence, we believe that our curvature findings in Figure 6, the first results of a relatively unexplored field, should therefore be cautiously interpreted, suggesting either the effect of environmental factors or the presence of a methodological limitation.

To conclude, this study reports high MS-related mortality in SC and Sweden, accompanied by stable time trends, slight

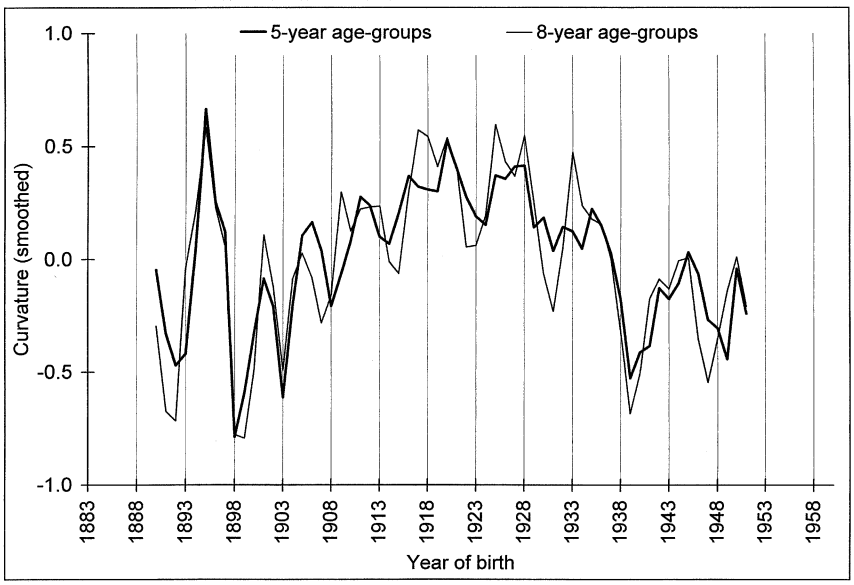

FIGURE 6. Smoothed cohort-effect curvatures observed from age-period-cohort models using data sets for 5-year and 8-year age group intervals and 1-year birth cohorts in SC.

period effects, and negative effects in cohorts born in the distant and recent past.

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REFERENCES

1. Waksman BH. Multiple sclerosis. Curr Opin Immunol. 1989;1:733–739.
2. Alter M, Okihiro M. When is multiple sclerosis acquired? Neurology. 1971;21:1030–1036.
3. Dean G, Elian M. Age at immigration to England of Asian and Caribbean immigrants and the risk of developing multiple sclerosis. J Neurol Neurosurg Psychiatry. 1997;63:565–568.
4. Ashitey GA, Mackenzie G. "Clustering" of multiple sclerosis cases by date and place of birth. Br J Prev Soc Med. 1970;24:163–168.
5. van Buuren S, Zaadstra BM, Zwanikken CP, Buljevac D, van Noort JM. Space-time clustering of multiple sclerosis cases around birth. Acta Neurol Scand. 1998;97:351–358.
6. Neutel CI, Walter SD, Mousseau G. Clustering during childhood of multiple sclerosis patients. J Chron Dis. 1977;30:217–224.
7. Isager H, Larsen S, Hyllested K. School contact between patients with multiple sclerosis. Int J Epidemiol. 1980;9:145–147.
8. Poskanzer DC, Walker AM, Prenney LB, Sheridan JL. The etiology of multiple sclerosis: temporal-spatial clustering indicating two environmental exposures before onset. Neurology. 1981;31:708–713.
9. Riise T, Gronning M, Klauber MR, Barrett-Connor E, Nyland H, Albrektsen G. Clustering of residence of multiple sclerosis patients at age 13 to 20 years in Hordaland. Norway. Am J Epidemiol. 1991; 133:932–939.
10. Weinshenker BG, Rodriguez M. Epidemiology of multiple sclerosis. In: Gorelick PB, Alter M, eds. Handbook of Neuroepidemiology. New York: Marcel Dekker Inc.; 1994:533–567.
11. Gronning M, Riise T, Kvale G, Nyland H, Larsen JP, Aarli JA. Incidence of multiple sclerosis in Hordaland, Western Norway: A fluctuating pattern. Neuroepidemiology. 1991;10:53–61.
12. Midgard R, Riise T, Svanes C, Kvale G, Nyland H. Incidence of multiple sclerosis in More and Romsdal, Norway from 1950 to 1991: An age-period-cohort analysis. Brain. 1996;119:203–211.
13. Li TM, Swash M, Alberman E. Morbidity and mortality in motor neuron disease: comparison with multiple sclerosis and Parkinson's disease: age- and sex-specific rates and cohort analyses. J Neurol Neurosurg Psychiatry. 1985;48:320–327.
14. Kurtzke JF, Hyllested K, Heltberg A. Multiple sclerosis in the Faroe Islands: transmission across four epidemics. Acta Neurol Scand. 1995; 91:321–325.
15. Holford TR. Understanding the effects of age, period, and cohort on incidence and mortality rates. Annu Rev Public Health. 1991;12:425–457.
16. Fischman HR. Multiple sclerosis: a two-stage process? Am J Epidemiol. 1981;114:244–252.
17. Fischman HR. Multiple sclerosis: a new perspective on epidemiologic patterns. Neurology. 1982;32:864–870.
18. Alter M. Multiple sclerosis in the Negro. Arch Neurol. 1962;7:83–91.
19. Dean G, Kurtzke JF. On the risk of multiple sclerosis according to age at immigration to South Africa. BMJ. 1971;3:725–729.
20. Koch-Henriksen N, Bronnum-Hansen H, Hyllested K. Incidence of multiple sclerosis in Denmark 1948–1982: A descriptive nationwide study. Neuroepidemiology. 1992;11:1–10.
21. Morariu MA, Linden M. Multiple sclerosis in American blacks. Acta Neurol Scandinav. 1980;62:180–187.
22. Poskanzer DC, Schapira K, Miller H. Epidemiology of multiple sclerosis in the counties of Northumberland and Durham. J Neurol Neurosurg Psychiatry. 1963;26:368–376.
23. Baum HM, Rothschild BB. The incidence and prevalence of reported multiple sclerosis. Ann Neurol. 1981;10:420–428.
24. Cavalletti S, Merelli E, Cavazzuti M, Guidetti D. Frequency of MS in the province of Modena, 1970–1990. Acta Neurol Scand. 1994;90: 377–381.
25. Guidetti D, Cavalletti S, Merelli E, Zanoni P, Simonazzi P, Sola P, et al. Epidemiological survey of multiple sclerosis in the province of Reggio Emilia and Modena. Italy. Neuroepidemiology. 1995;14:7–13.
26. Kinnunen E. Multiple sclerosis in Finland: Evidence of increasing frequency and uneven geographic distribution. Neurology. 1984;34: 457–461.
27. Koch-Henriksen N, Hyllested K. Epidemiology of multiple sclerosis: incidence and prevalence rates in Denmark 1948–64 based on the Danish Multiple Sclerosis Registry. Acta Neurol Scand. 1988;78: 369–380.
28. Kuroiwa Y, Igata A, Itahara K, Koshijima S, Tsubaki T. Nationwide survey of multiple sclerosis in Japan. Neurology. 1975;25:845–851.
29. Larsen JP, Kvaale G, Riise T, Nyland H, Aarli JA. An increase in the incidence of multiple sclerosis in Western Norway. Acta Neurol Scand. 1984;69:96–103.
30. Larsen JP, Kvaale G, Riise T, Nyland H, Aarli JA. Multiple sclerosis — more than one disease? Acta Neurol Scand. 1985;72:145–150.
31. Svenningsson A, Runmarker B, Lycke J, Andersen O. Incidence of MS during two fifteen-year periods in the Gothenburg region of Sweden. Acta Neurol Scand. 1990;82:161–168.
32. Visscher BR, Clark VA, Detels R, Malmgren RM, Valdiviezo NL, Dudley JP. Two populations with multiple sclerosis. J Neurol. 1981; 225:237–249.
33. Jin YP, de Pedro-Cuesta J, Söderström M, Stawiarz L, Link H. Incidence of optic neuritis in Stockholm, Sweden 1990–1995: I. Age, sex, birth and ethnic-group related patterns. J Neurol Sci. 1998;159:107–114.
34. Frome EL, Checkoway H. Epidemiologic programs for computers and calculators. Use of Poisson regression models in estimating incidence rates and ratios. Am J Epidemiol. 1985;121:309–323.
35. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: Age-period and age-cohort models. Stat Med. 1987;6:449–467.
36. Robertson C, Boyle P. Age-period-cohort analysis of chronic disease rates. I: Modelling approach. Stat Med. 1998;17:1305–1323.
37. Midgard R, Riise T, Kvale G, Nyland H. Disability and mortality in multiple sclerosis in western Norway. Acta Neurol Scand. 1996; 93:307–314.
38. Malmgren RM, Valdiviezo NL, Visscher BR, Clark VA, Detels R, Fukumoto M, et al. Underlying cause of death as recorded for multiple sclerosis patients: associated factors. J Chronic Dis. 1983;36:699–705.
39. Chio A, Magnani C, Tolardo G, Schiffer D. Parkinson's disease mortality in Italy, 1951 through 1987. Analysis of an increasing trend. Arch Neurol. 1993;50:149–153.
40. Chio A, Magnani C, Schiffer D. The increase of Parkinson's disease mortality could be due to a cohort effect. Acta Neurol Scand. 1995; 92:113–115.
41. Ruiz-Tovar M, de Pedro-Cuesta J, Pollan-Santamaria M, Lopez-Abente G. Time-trend analysis of mortality from malignant tumors of the nervous system in Spain, 1952–1986. J Neurol Sci. 1995;131:15–20.
42. Cook SD, Cromarty JI, Tapp W, Poskanzer D, Walker JD, Dowling PC. Declining incidence of multiple sclerosis in the Orkney Islands. Neurology. 1985;35:545–551.

43. Cook SD, MacDonald J, Tapp W, Poskanzer D, Dowling PC. Multiple sclerosis in the Shetland Islands: an update. Acta Neurol Scand. 1988;77:148–151.

44. Lai SM, Zhang ZX, Alter M, Sobel E. World-wide trends in multiple sclerosis mortality. Neuroepidemiology. 1989;8:56–67.

45. Meyer-Rienecker H, Buddenhagen F. Incidence of multiple sclerosis: a periodic or stable phenomenon. J Neurol. 1988;235:241–244.

46. Holford TR. The estimation of age, period and cohort effects for vital rates. Biometrics. 1983;39:311–324.