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Prevalence of multiple sclerosis in Denmark 1950–2005

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Abstract

Multiple sclerosis is an inflammatory disease of the central nervous system of unknown aetiology. Its prevalence varies by ethnicity and place: persons of northern European descent are at increased risk while persons living at lower latitudes appear to be protected against the disease.

The Danish Multiple Sclerosis Registry is a national registry established in 1956 after a population-based survey which receives information from numerous sources. It is considered to be more than 90% complete, with a validity of 94%. Using data from the Registry, we calculated prevalences per 100,000 inhabitants.

The standardized prevalence of multiple sclerosis increased from 58.8 (95% confidence interval: 54.9–62.7) in 1950 to 154.5 per 100,000 (95% confidence interval: 148.8–160.2) in 2005, and the female to male ratio increased from 1.31 in 1950 to 2.02 in 2005. The increase in prevalence is due to both increased survival of multiple sclerosis patients and an increased incidence rate.

The rise in prevalence in the past 50 years is probably due more to environmental factors than to genetic changes in the Danish population. Among women, environmental changes could include older age at first birth, use of oral contraceptives, or changes in sun behaviour and/or vitamin D status.

Keywords

multiple sclerosis, registry, Denmark, sex, age, prevalence

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Introduction

Estimates of disease prevalence are important for forward planning in the healthcare system. The cost of a multiple sclerosis (MS) patient in Denmark was estimated to €40,000 in 2005, including: direct costs for medicines, hospitals, and domestic help; indirect costs for loss of productivity and informal care.[1] Higher disability scores were associated with higher cost.[1] As patients grow older, their illness becomes progressive and they are dependent on care from professionals or peers. Older patients are more severely affected by their disease, have higher disability scores and need more care than younger patients, demanding more resources from, e.g. healthcare facilities.[2] Therefore, the increase in patient numbers as wells as in patients above a certain age (e.g. 60 years) is interesting for healthcare professionals and society also from an economical point of view.

Denmark, situated at 54–57° latitude, is a high-risk area for MS. We present point prevalence estimates from the Danish Multiple Sclerosis Registry on 1 January for 1950–2005.

Materials and methods

The Danish Multiple Sclerosis Registry has been described in detail previously.[3] It was established in 1956 after a population-based survey in Denmark. It receives information from all departments of neurology, the National Hospital Discharge Register, the MS rehabilitation centres, practising neurologists, and pathologists. All patient records were evaluated by the same three neurologists according to the criteria of

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Allison and Millar[4] (for cases with onset before 1994) or of Poser[5] (for cases with onset from 1994 onwards), who classified patients as having clinically definite, laboratory-supported definite, clinically probable, or laboratory-supported probable MS. We had kept an additional category: possible MS, e.g. cases which did not fulfil the Poser criteria, but in which no other disease could be detected. Possible cases were not included in the prevalence calculations. The Registry is considered to have a validity of 94% and to be more than 90% complete.[6]

Prevalence was calculated as the number of people with definite and probable MS cases in the Registry who were alive and resident in Denmark at the prevalence date, divided by the number of residents of Denmark on the same date, as stated by Statistics Denmark. Prevalence is given per 10^5 inhabitants. Confidence intervals (CIs) were calculated on the assumption of a Poisson distribution.

Prevalence was calculated separately for males and females and for persons younger and older than 60 years, reported in 5-year intervals starting in 1950 (data from all years is available from the authors on request). In addition to the crude prevalence rate, prevalence standardized to the European Standard Population (as described by the European Union Public Health Information System at http://www.euphix.org/) calculated by the direct method is presented.

Results

By the end of 2004, 11,236 patients had been recorded in the Danish MS Registry with an approved diagnosis of MS according to the diagnostic criteria used and were alive on prevalence day with a previous onset of MS. Of these, 1859 had been evaluated as possible cases and hence not included in the analyses. The remaining 9377 cases (3095 men and 6282 women) were accepted as definite or probable cases. The crude prevalence rate for women was 229.8 (95% CI: 224.1–235.4), for men 115.6 (95% CI: 111.5–119.7), and for both sexes 173.3 (95% CI: 169.9–176.7). The age-adjusted prevalence rate for women was 201.6 (95% CI: 192.4–210.8), for men 107.0 (95% CI: 100.2–113.7), and for both sexes 154.5 (95% CI: 148.8–160.2).

The Danish population grew from approximately 4.25 million in 1950 to 5.41 million in 2005, a 27% increase. The female to male ratio of the population was 1.02 in both 1950 and 2005. In 1980, the first year in which ethnicity was recorded, 1% of Danes were of non-western origin; in 2005 the proportion was 6%. In the MS Registry, 2% of persons with definite or probable MS were born outside Denmark, 0.05% were born in Greenland, and 0.1% in the Faroe Islands.

The number of patients in all age groups increased during the study period. The number of patients who were 60 years or older increased from 217 in 1950 (corresponding to 9% of the total patient population) to 2466 in 2005 (26% of all patients), while there was only a small increase in patients younger than 24 years, from 81 (3.4% of all patients) in 1950 to 153 in 2005 (1.6% of all patients) (Figure 1). The prevalence of MS among men and women and among persons younger and older than 60 years is presented in Table 1.

The number of male patients with MS almost tripled during the study period (from 1035 in 1950 to 3095 in 2005), while the number of female patients was nearly 5 times higher in 2005 than in 1950 (1353 in 1950 and 6282 in 2005) (Figure 2). Hence, the female to male ratio increased from 1.31 in 1950 to 2.02 in 2005.

The prevalence standardized to the European Standard Population (Table 1) also increased in the study period. It was higher than the crude prevalence until 1990 and lower thereafter. Especially for women, the crude prevalence rate was remarkably higher than the standardized rate in both 2000 and 2005.

Discussion

We found that the prevalence of MS in Denmark increased steadily between 1950 and 2005. The number of MS patients was highest in 2005, when more than 9300 people had the disease, corresponding to a prevalence of 173.3 per 10^5 inhabitants. From around 1960 to 1985, the number of prevalent cases increased only modestly, due to a decrease in incidence up to circa 1965, a subsequent rise in incidence, particularly in women, and a decline in mortality.[7,8] The retrospective disease duration from death and back to onset in patients dying in a specific year almost doubled from 1950 to 2000 (source: the Danish Multiple Sclerosis Registry).

The rise in prevalence during the study period can be attributed to the longer survival of MS patients, resulting in a marked increase in prevalence in the group aged $\geq$60, especially in the later part of the study period, as well as to increased incidence. MS is ultimately a progressive disease, but treatment may slow down progression and hence increase longevity. With today's knowledge, however, the progressive phase will evolve if the patient lives long enough. Also the increased life expectancy in the general population will probably rub off on MS patients. This indeed positive development will have implications on the cost of the disease.

An increased incidence among women was observed from 1950 to 2000,[9] and we have no reason to expect this increase to have stopped in the past 10 years. The increase in newly diagnosed cases could be due partly to

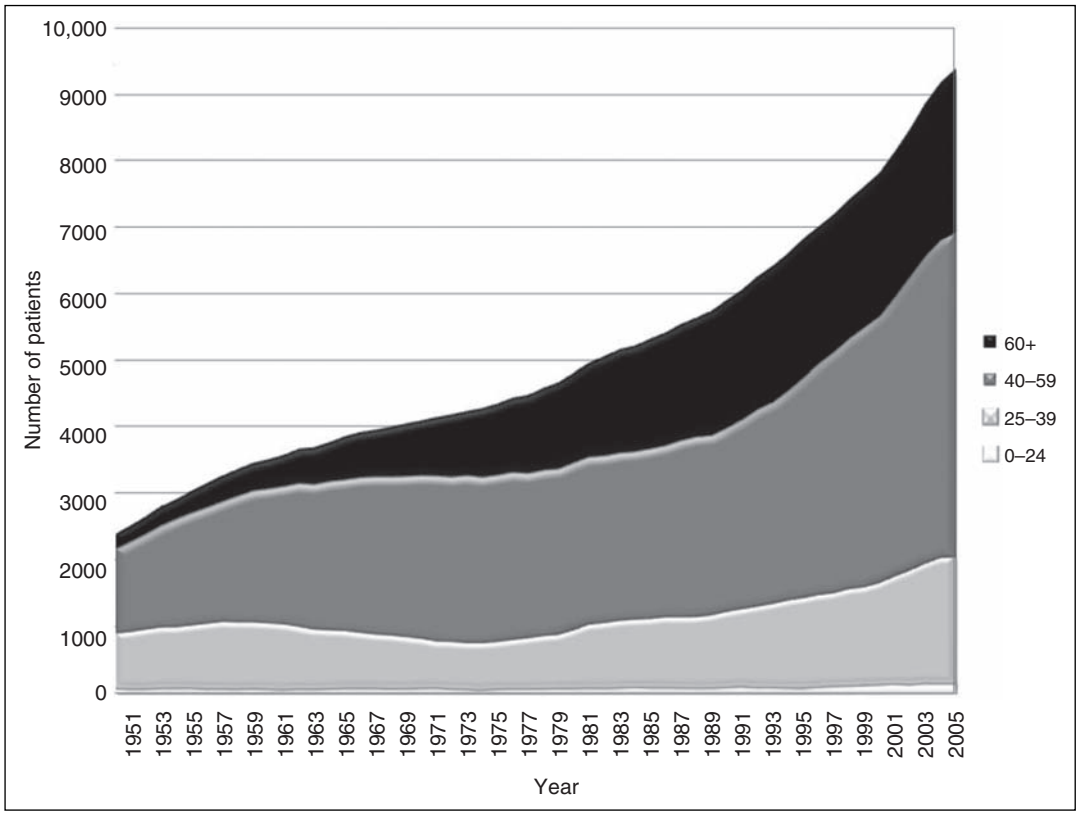

Figure 1. Number of patients in four age groups with multiple sclerosis in the Danish population on 1 January.

improved diagnosis. If this was the main reason for the increase in prevalence, however, the disease would have affected men and women to the same extent. This is clearly not the case, as the prevalence among women has increased more than that among men. The increased prevalence is also unlikely to be due to a change in population composition. Denmark had an influx of migrant workers of non-western origin (mainly from Turkey, Pakistan, and the former Republic of Yugoslavia) in the 1970s and refugees from countries like Iran, Iraq, and Somalia in the 1980s and 1990s; however, they and their offspring still constitute only a small minority of the population. The immigrants originate predominantly from areas with low risks for MS[10–12] and their risk of disease will probably increase because of their immigration to a high-risk area, but the risk would not likely be higher than that of the native Danish population.[13] Other western countries have experienced increases in MS prevalence similar to that which we report. In Oslo, Norway, the prevalence increased from 120 per 10^5 inhabitants in 1995[14] to 148 in 2005,[15] with a female to male ratio of about 2 in both studies. These studies were also registry-based and the numbers are in gross accordance with those we report. A Finnish study also showed an increase in MS prevalence between 1980 and 2000, from 39 to 105 per 10^5 inhabitants, with a female to male ratio of 2.5 in 2000.[16] This study was, however, hospital-based, which probably led to underestimation of the true prevalence, as benign cases were not necessarily included. In the Croatian region of Gorski kotar, the prevalence of MS rose from 85.1 in 1971 to 151.9 per 10^5 inhabitants in 1999,[17,18] a prevalence similar to that found in this study. The population of that region is of Germanic descent, which would explain the high occurrence of the disease in an otherwise lower risk area. None of these studies, however, was based on the population of an entire country followed systematically by the same neurologists for more than 50 years, which makes our study unique.

The increase in MS prevalence over the past 50 years is most likely not attributable to a change in the genetic composition of the population. However, our study did not specifically investigate this. The rapid growth in the number of patients is therefore in all probability, leaving aside the improved survival, due to the environment or perhaps gene–environment interactions. Women especially have experienced a large increase in the prevalence of MS, as shown by us and others,[19,20] which implies that factors affecting the environment, lifestyle, or life course of women are risk factors or risk markers of MS. Hormonal factors related to (delayed) childbirth

Table 1. Prevalence rates (95% confidence intervals) per 10^5 inhabitants on 1 January in Denmark, stratified on sex and age group and standardized to the European Standard Population

Year	Age <60	Age ≥60	Women	Men	All	Standardized		All
						Women	Men	
2005	160.5 (157.8–165.2)	217.9 (209.9–225.9)	229.8 (224.1–235.4)	115.6 (111.5–119.7)	173.3 (169.9–176.7)	201.6 (192.4–210.8)	107.0 (100.2–113.7)	154.5 (148.8–160.2)
2000	132.2 (128.5–135.9)	204.7 (196.7–212.7)	190.4 (185.2–195.6)	101.6 (97.7–105.4)	146.5 (143.1–149.8)	179.2 (170.5–187.9)	95.8 (89.2–102.3)	137.6 (132.1–143.0)
1995	113.5 (109.7–117.2)	200.0 (192.0–208.0)	164.4 (159.5–169.1)	96.0 (92.2–99.8)	130.7 (127.3–134.0)	156.9 (148.7–165.2)	92.8 (86.4–99.3)	125.1 (119.8–130.3)
1990	97.6 (94.6–100.7)	181.1 (173.7–190.1)	141.5 (136.9–146.0)	87.4 (83.7–91.0)	114.8 (111.9–117.7)	138.1 (130.3–145.9)	87.4 (81.0–93.7)	113.0 (109.0–118.1)
1985	90.3 (87.4–93.2)	157.9 (150.2–165.5)	126.9 (122.5–131.2)	80.4 (76.9–83.9)	104.0 (101.2–106.8)	128.9 (121.4–136.5)	83.5 (77.3–89.7)	106.6 (101.7–111.5)
1980	84.0 (81.2–86.8)	135.2 (128.0–142.5)	112.1 (108.0–116.1)	75.3 (71.9–78.7)	93.9 (91.3–96.6)	118.4 (111.0–125.7)	81.7 (75.5–87.9)	100.3 (95.5–105.1)
1975	79.9 (77.1–82.6)	113.0 (106.2–119.8)	100.5 (96.7–104.4)	71.2 (67.9–74.5)	86.0 (83.5–88.6)	107.3 (100.4–114.2)	77.9 (71.8–83.9)	92.8 (88.2–97.4)
1970	81.0 (78.2–83.8)	94.9 (88.4–101.5)	97.4 (93.6–101.3)	69.2 (65.9–72.5)	83.4 (80.9–86.0)	105.1 (98.2–112.0)	76.5 (70.4–82.6)	91.0 (86.4–95.7)
1965	81.0 (78.2–83.8)	82.9 (76.5–89.3)	93.6 (89.7–97.5)	68.9 (65.6–72.3)	81.4 (78.8–83.5)	99.7 (92.8–106.6)	75.1 (69.0–81.1)	87.5 (82.9–92.2)
1960	79.6 (76.8–82.4)	61.9 (56.0–67.7)	86.5 (82.7–90.3)	67.2 (63.9–70.5)	76.9 (74.4–79.4)	91.1 (84.5–97.7)	72.3 (66.3–78.3)	81.9 (77.4–86.4)
1955	71.5 (68.8–74.2)	51.8 (46.1–57.4)	77.3 (73.6–80.9)	60.0 (56.8–63.3)	68.7 (66.3–71.2)	80.5 (74.2–86.9)	64.3 (58.5–70.2)	72.6 (68.2–76.9)
1950	58.8 (56.4–51.3)	38.6 (33.5–43.7)	63.2 (59.8–66.5)	49.1 (46.1–52.1)	56.2 (53.9–58.4)	65.1 (59.3–70.8)	52.4 (47.1–57.6)	58.8 (54.9–62.7)

Source: data from the Danish Multiple Sclerosis Registry.

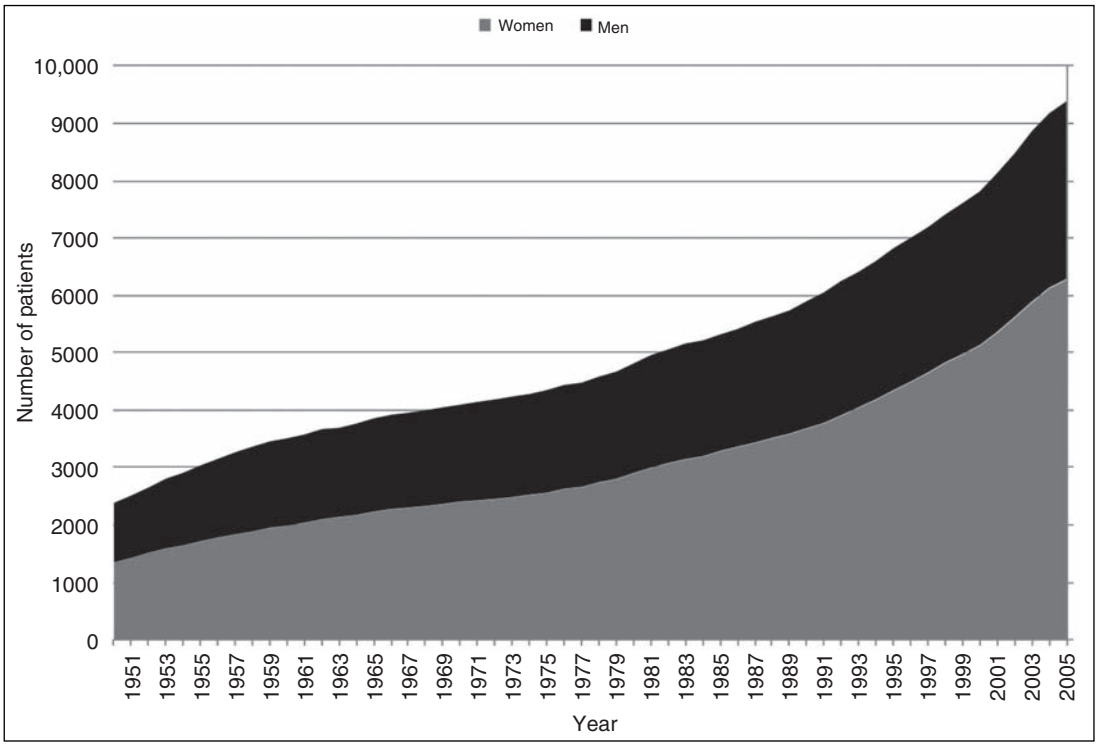

Figure 2. Number of patients (male and female) with multiple sclerosis in the Danish population on 1 January.

and contraception could be crucial.[21] Lower levels of serum vitamin D or decreased sun exposure might also influence the prevalence of MS. The finding that women have vitamin D insufficiency more often than men could explain the skewed gender distribution of MS.[22,23]The strength of this study is most certainly the use of a nationwide, complete registry that allows us to systematically follow a population for more than 50 years. Unfortunately, the registry does not systematically collect information about disability. It would have been interesting to monitor the development in disability among patients. The McDonald criteria were not applied, which could mean that a few cases were categorized as possible instead of definite. This would tend to lower our prevalence estimate.

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