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Multiple Sclerosis in Northern Ireland:

A historical and global perspective

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SUMMARY

The uneven worldwide distribution of multiple sclerosis has been of interest to epidemiologists, neurologists and statisticians for over a century, prevalence rates for the disease apparently being determined by variations in age, gender, geography, race and ethnic group. Northern Ireland has been recognised as an area of high MS prevalence since the truly seminal work of Allison and Millar almost 50 years ago.

The most recent study in Northern Ireland was undertaken in 1996 and involved the neighbouring districts of Coleraine, Ballymena, Ballymoney and Moyle (population, 151,000). Overall, 254 definite and probable cases were identified (prevalence: 168.2/100,000) with a further 34 suspected cases (overall prevalence: 190.7/100,000). Females predominated (ratio, 2.1: 1) and the average age at onset was 31.6 years. The highest age specific prevalence rate for females was in the 35-44 years old age group (519.6/100,000) and for males was in those aged 55-64 (292.3/100,000). The spectrum of disability was broad and 20% could be considered to have relatively "benign" disease. These figures sadly confirm that Northern Ireland has one of the highest and rising MS prevalence rates in the world and implies an enormous potential for societary costs.

MS EPIDEMIOLOGY – THE EARLY YEARS

Accumulated data over the last century indicates that multiple sclerosis (MS) is the commonest disabling neurological disease of young adults in developed countries. Although the earliest attempts to establish the frequency of MS involved the observation of the numbers of cases among hospital admissions with nervous diseases, in 1922 the study of the disease was taken a stage further by the reported distribution of MS in the United States based on diagnoses among army inductees in World War I.[1]

The first attempt to establish properly MS prevalence by identifying the total number of cases within a defined population was performed in Switzerland in 1918-22 and reported in 1926 (prevalence: 36.4/100,000).[2] The first such study in the British Isles was undertaken by an eminent Belfast neurologist, Sidney Allison, in Wales in 1929 (prevalence: 25.8/100,000).[3]

Although several hundred epidemiological surveys of MS have been undertaken worldwide, the credit for the first recognition that MS exhibited an uneven distribution must go to Charcot, who in 1868 commented that "even today I do not believe that disseminated sclerosis is known in England" and in 1877 continued to observe that although the disease was prevalent in France, it was little recognised in Germany and uncommon in England.[4,5] Although these observations are inapplicable today, other variations are now well established.

EVIDENCE FOR A LATITUDINAL GRADIENT?

The theory that the epidemiology of MS shows a latitudinal gradient in frequency probably originates from the demonstration in 1950 that MS death rates increased from south to north within North America.[6] Subsequent studies gradually developed the picture of a higher prevalence in temperate than in subtropical and

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tropical zones, with a suggestion of a decline in rates again towards the poles. Some of the most elegant supportive studies have come from Australia, where the prevalence declines gradually from tropical Queensland (12/100,000) in the north to Tasmania (76/100,000) in the south.[7,8]

Further evidence for geographic or environmental factors influencing the frequency of MS has come from migration studies. In South Africa, MS prevalence in immigrants from the UK and other European countries is about 36/100,000 population.[9] This rate is intermediate between those for the countries from which these people originated (50-100/100,000) and that for native born white South Africans (11/100,000). Further study of Europeans migrating to South Africa has also indicated that the risk of MS is related to the age of migration.[10] In the group migrating before age 15, the number developing the disease was only one-third of the number expected from rates in the European population generally.

The effects of latitude and changes in risk with migration are however only part of the picture. For example, in the US the significantly higher MS prevalence in the northern states has been shown to be better correlated with the extent of Scandinavian ancestry.[11] What is now clear is that what have previously been interpreted as geographical or environmental factors influencing disease prevalence are more likely to be racial and genetic. Generally, MS is most frequent in areas settled by individuals of predominantly Scandinavian descent.

CLUSTERS AND EPIDEMICS

Within these apparent trends along latitudinal gradients and across ethnic groups, the identification of apparent clusters and epidemics in, for example, the Faroes,[12] Iceland,[13] Florida,[14] Norway,[15] and Denmark[16] has caused much intense speculation regarding more specific possible aetiological factors, in particular, infectious agents. To date, despite intensive survey, no single infectious agent has been successfully incriminated.

POST-WAR SURVEYS IN GREAT BRITAIN

Since World War II there have been more than 30 epidemiological surveys in Great Britain (GB). The most intensively surveyed areas until recently have been the north-east of Scotland, Orkney and Shetland. Studies have involved numerators and denominators both large and small, used differing diagnostic criteria and employed varied epidemiological methods.

The Orkneys and Shetland have had the highest prevalence rates for MS in the world, prevalence in the former reaching a peak of 309/100,000 in 1974.[17] Interestingly, and in contrast to the pattern of earlier studies on these islands, both island groups have demonstrated a decline in MS prevalence in their most recent studies.[18,19] On the Scottish mainland, three studies have been conducted in the north-east, largely based on Grampian, the prevalence there reaching a peak of 178/100,000 in 1980.[20]

Such figures in Scotland, together with a perception that MS was much less common in the south of England, contributed to a belief that a north-south gradient for MS prevalence exists in GB. Over the past decade however there have been several well conducted studies in England and Wales which have challenged this hypothesis, with broadly similar prevalence rates for areas as far apart as Jersey (113/100,000),[21] Sussex (136/100,000),[22] North Cambridgeshire (118/100,000),[23] Glamorgan (120/100,000)[24] and Rochdale (122/100,000).[25] The absence of a latitudinal gradient within Scotland itself has also been confirmed by studies in south-east Scotland (prevalence: 187/100,000)[26] and Tayside (prevalence: 184/100,000)[27] which have found prevalence rates similar to those for Grampian, Shetland and Orkney.

THE HISTORY OF MS EPIDEMIOLOGY IN IRELAND

Northern Ireland has one of the most surveyed populations for MS in the world, previous studies having been undertaken in 1951, 1961 and 1987.[28-30] The original studies of Allison and Millar were among the most extensive ever completed, based as they were on the population of the province as a whole. They identified Northern Ireland as a high risk area for MS, observing prevalence rates of 51/100,000 in 1951 (population: 1,370,709) and 80 per 100,000 in 1961 (population: 1,484,775). More recently in 1987, a study of the contiguous Coleraine, Ballymoney and Moyle districts in the north-east of Northern Ireland (population: 86,500) produced a crude prevalence rate of 138/100,000.[30]

The 1951 study provided a template for all subsequent studies. All hospitals and doctors in the country were surveyed. A scheme of

classifying patients was established which is still widely applied. For this purpose patients were categorised as having "probable MS" (some physical disablement, usually a remitting quality in the history and on examination, physical signs explicable only by multiple lesions), "early MS" (patients showing few or no physical signs but having a recent history of remitting symptoms of the kind commonly associated with the onset of the disease) or "possible MS" (suggestive clinical findings but a progressive or static history and insufficient evidence of multiple lesions).

Remarkably, all 887 cases on the provisional register were individually assessed by Allison and Millar, the diagnosis being discarded in over 20%. Pains were also taken to establish an accurate incidence rate by personal questioning and checking statements with doctors, hospital records and relatives. The final overall incidence figure was 2.74/100,000. Allison and Millar's huge efforts were however undermined by at least two factors. Firstly, by the prevalence date replies had not been received from 25% of the doctors in Northern Ireland. Secondly, the incidence rate was calculated over a prolonged period and up to the prevalence date (1937-51) and may therefore have missed patients who had onset of disease during this period but who died before the survey was carried out, and also those who had onset during this period but had not yet been identified. One conclusion of the study also appears suspect. Although the authors state that there was no evidence to suggest that the disease was unevenly distributed, there is a considerable variation in prevalence rates across the region from 24/100,000 in Co. Londonderry to 63/100,000 in Co. Tyrone.

In the second study by Allison and Millar, 1,146 cases were identified in a population of 1,425,000. Again all of these patients were individually assessed. An unusually high proportion of "possible" cases were noted – 29% – rather more than the already high level seen in 1951 – 21%. However, even allowing for this increased recognition of "possible MS", the confidence limits for the 1961 prevalence figure (76-85/100,000) lie well above those from 1951 (47-55/100,000).

The 1987 study was the first in Northern Ireland to use the Poser criteria.[31] It was also the first to use the Kurtzke disability status scale [32] as a measure of neurological impairment in an MS population. The prevalence rate for probable disease by the Allison and Millar criteria was 104/100,000 and for definite/probable disease by Poser was 97/100,000.

Studies of MS prevalence elsewhere in Ireland have been less detailed, although one study reported in 1977 involved the whole population of the Republic of Ireland.[33] Covering almost three million people, it was subject to the problems of accurate case ascertainment inherent in a population of this size. Although many sources were used to identify cases and the existence of the study was advertised in the medical press, no data is provided by the authors on response rates to requests for information. Also patients who were identified to the researchers were not individually assessed, the opinion of the attending neurologist or physician being accepted. No diagnostic criteria were used, patients being designated as either probable or possible cases, and no measure of disability was applied. The overall prevalence rate for patients with probable or possible disease was 73/100,000. In a further study in the county of Wexford in 1984,[34] the criteria of McDonald and Halliday were used which make comparison with other surveys difficult. Although all patients were individually assessed, a remarkable 40% of this population were deemed to have benign disease, suggesting a bias in the case ascertainment against those with greater disability. It is also noteworthy that the quoted prevalence rate of 48.4/100,000 for clinically definite and progressive probable MS was actually less than that identified for the county 13 years earlier (54.5/100,000).[33]

CURRENT SITUATION IN NORTHERN IRELAND

In 1998 we first reported on a further prevalence study in Northern Ireland.[35] Our aims were to update the MS prevalence in the new era of magnetic resonance imaging and more sophisticated immunological investigation. A further purpose was to provide a database for immunological and genetic studies for which the relatively homogeneous conformation of this population is ideal.

METHODS

The survey populations were the neighbouring Ballymena, Coleraine, Ballymoney and Moyle districts, spanning the counties of Antrim and Derry. The total land area of 2,030km^2 lies between latitudes 54°7 N and 55°3 N. In the 1991

census, the population was 146,066, but by mid-year 1995 it had risen to an estimated 151,000 – Ballymena (57,500), Coleraine (54,100), Ballymoney (24,600), Moyle (14,800).

Primary sources for case identification were the records of the Northern Ireland Regional Neurology Service (NIRNS) at the Royal Victoria and City hospitals in Belfast and those held in outreach neurology clinics serving the study area at the Coleraine, Waveney, Moyle, Antrim and Mid-Ulster hospitals. Hospitals with inpatient diagnostic indices and computerised databases were further sources.

A postal survey of GPs in the area was performed. Those failing to respond were canvassed on a second and third occasion where necessary.

Local branches of the Multiple Sclerosis Society of Northern Ireland at Ballymena, Coleraine, Ballymoney, Antrim and Larne were approached for information. Another charity, Action MS, was also approached. The records of the MS Centre at the Dalriada Hospital in Ballycastle which provides a respite care facility were examined.

The hospital and/or GP records of all patients identified were studied. Potential MS patients were then invited for assessment. An invitation was not issued if felt by the GP to be inappropriate. Assessments occurred at a neurology clinic, in the patient's local health centre or own home and involved interview regarding date of onset, date of diagnosis, nature of the initial episode, subsequent clinical course and family history. Date of onset was obtained from the patient where possible, from the medical records if not. Date of diagnosis was obtained from the medical records.

Those satisfying the Poser criteria for clinically definite (CDMS), laboratory-supported definite (LSDMS), clinically probable (CPMS) or laboratory-supported probable (LSPMS) MS were accepted as prevalent cases. To enable comparison with previous studies a "suspected" group was included and the criteria of Allison and Millar were also employed.

A comparison of this study with the previous three in Northern Ireland was performed using the Allison and Millar criteria and calculating confidence intervals by a standard method.[36]

Patients were categorised as having relapsing-remitting (RRMS), secondary progressive (SPMS) or primary progressive (PPMS) MS. Those with an EDSS of ≤ 3.0, ≥ 10 years after onset were considered to have benign MS.

Patients were deemed prevalent if alive and resident in the study area on July 1st 1996. Addresses of patients were established as being within the study area using postcodes and maps obtained from HMSO and Ordnance Survey. Ethical approval was obtained from the Queen's University of Belfast Research Ethics Committee.

RESULTS

The provisional list of people with MS comprised 402 names. Many were identified by more than one source. Ninety-four of 97 (96.9%) GPs within the area responded positively to requests for information. Sources for the provisional cases and the proportion of the overall number notified were: GPs, 247 (61.4%); departmental records, NIRNS, 217 (54.0%); MS charities, 109 (27.1%); hospital database inpatient codings, 89 (22.1%); Dalriada MS Centre, 38 (9.5%).

Patients were excluded from the provisional register on the following grounds: residency outside the study area (47 cases); deceased (45 cases); not MS (22 cases). Therefore 288 patients remained alive and prevalent within the study area on 1st July 1996. The sources for these were: GPs, 230 (79.9%); departmental records, NIRNS, 158 (54.9%); MS charities, 74 (25.7%); hospital database inpatient codings, 69 (24.0%); Dalriada MS Centre, 33 (11.5%). Of the 288 prevalent patients, 116 (40.3%) were notified by a single source: GPs, 85 (29.5%); departmental records, NIRNS, 19 (6.6%); hospital database inpatient codings, 10 (3.5%); MS charities, 1 (0.3%); Dalriada MS Centre, 1 (0.3%).

Two hundred and fifty-one of the 288 patients (87.2%) were formally interviewed and examined. In a further eight cases (2.8%) an EDSS was calculated using information provided by the general practitioner or by other consultant neurologists during clinic attendance. The diagnostic classification of prevalent cases using the Poser criteria was as follows: CDMS – 185 (64.2%); LSDMS – 24 (8.3%); CPMS – 43 (14.9%); LSPMS – 2 (0.7%), and; suspected – 34 (11.8%). Applying the Allison and Millar criteria the classification was: probable MS – 186 (64.6%); early probable and latent MS – 60 (20.8%), and; possible – 42 (14.6%).

The prevalence rate based on all 288 patients is 190.7/100,000 (95% CI 168.7-212.7/100,000) whilst restricting to those with definite or probable disease by the Poser criteria gives a prevalence of 168.2/100,000 (95% CI 147.5-188.9/100,000).

The previously unsurveyed Ballymena population contained 110 patients [prevalence: 191.3/100,000 (95% CI 155.6-227.0/100,000)], 100 fulfilling the Poser criteria for definite or probable disease [prevalence: 173.9/100,000 (95% CI 139.9-208.0/100,000)].

There were 196 female and 92 male patients (ratio 2.1: 1). The mean age of prevalent patients was 49.3 (range 18-79, SD 13.3) years, the mean age for females and males being 48.3 (SD 13.4) and 51.5 (SD 13.0) years respectively. Mean age of onset was 31.6 (range 12-66, SD 10.1) years, the figures for females and males being 31.0 (SD 10.1) and 33.0 (SD 10.1) respectively. The age and sex specific prevalence rates are given in (Table 1). Both the peak age specific prevalence rate and modal age of prevalent female cases are in the 35-44 year age group. For males the peak prevalence rates are in the 45-54 and 55-64 year age groups whilst the modal age group for prevalent males is 45-54 years.

The homogeneity and stability of the population is emphasised by 90.9% of those with definite/probable disease being born either within the study area (184 patients) or elsewhere in Northern Ireland (47 patients). This figure reaches 95.1% upon exclusion of those cases whose place of birth was not ascertained, with just nine cases (3.5%) born elsewhere in the British Isles and three (1.2%) born overseas.

In those with definite or probable disease the mean interval between initial symptoms and diagnosis was 6.2 years. The mean duration of disease in definite/probable cases was 18.4 (range 0-52, SD 11.4) years. Using the technique of doubling the mean duration at prevalence day, the mean life expectancy was 36.8 years.[37]

The distribution of Kurtzke EDSS scores is shown in the figure. The mean EDSS score was 4.9 and the median 5.5. Clinical course from onset was established in 280 (97.2%) patients. Ninety-eight patients (35.0%) had RRMS, 36 (12.9%) had RR and benign disease, 111 (39.6%) had SPMS and 35 (12.5%) had PPMS. Of 180 patients undergoing an EDSS assessment and having disease duration of ≥10 years, 36 (20%) had a benign course.

Initial symptoms were established in 283 cases (98.3%). The commonest was sensory [95 (33.6%)] followed by motor [78 (27.6%)], brainstem/cerebellar [70 (24.7%)] and optic neuritis [57 (20.1%)]. Twenty-six (9.2%) had more than one of these symptoms initially and nine (3.2%) had another form of disturbance at

TABLE I

Prevalence of definite/probable MS in Coleraine, Ballymena, Ballymoney and Moyle per 100,000 by age and sex.

Age Group (years	*Male No.*	*Rate/10^5*	*Female No.*	*Rate/10^5*	*Total No.*	*Rate/10^5*
0-14	0	0	0	0	0	0
15-24	0	0	5	41.3	5	20.3
25-34	8	74.9	20	186.3	28	130.8
35-44	13	132.9	50	519.6	63	324.6
45-54	24	286.9	42	482.3	66	386.6
55-64	19	292.3	32	443.0	51	371.6
65-74	11	212.4	25	394.6	36	312.7
75+	2	68.3	3	56.0	5	60.4
TOTAL	77	104.1	177	229.9	254	168.2

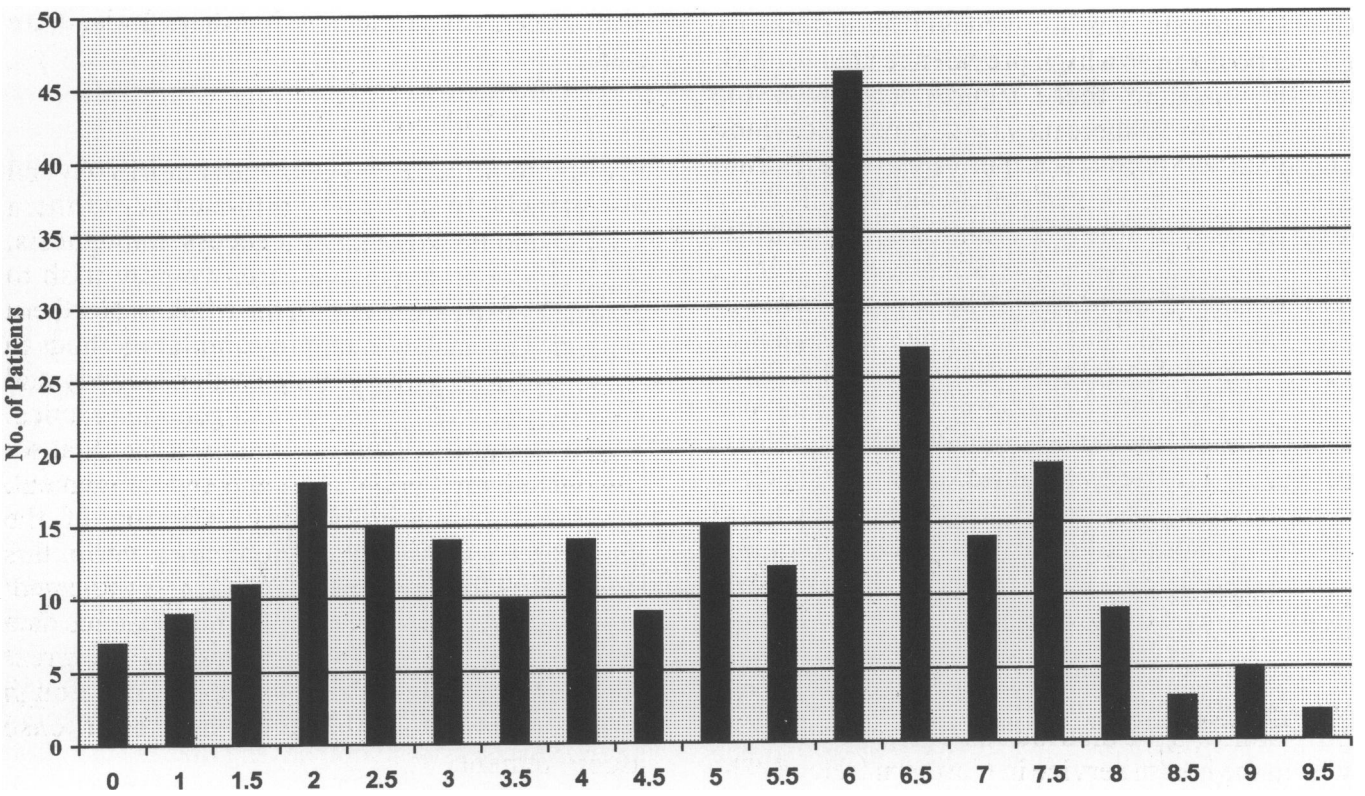

Fig. Kurtzke EDSS scores for prevalent patients.

onset (e.g. sphincter disturbance, sexual dysfunction). Sixty-five patients (22.6%) had a history of MS among first-, second- or third-degree relatives.

DISCUSSION

This study was the fourth completed in Northern Ireland in 50 years. We believe that, given the resources available, the population size in this study was optimal for accurate ascertainment of cases, not so small as to be subject to the quirks of clustering and not so large as to omit prevalent cases. The first two previous studies involved the entire population of the province [28, 29] and as such may be biased by incomplete ascertainment, while the third involved a rather smaller population.[30] The rising prevalence seen in the previous three has been emphasised.

The confidence intervals for the recent study lie entirely outside those of the previous studies, the differential being greater when restricting to those with probable or early probable and latent MS: 1951 – 41/100,000 (95%CI 37-44); 1961 – 57.100,000 (95% CI 53-61); 1987 – 104/100,000 (95% CI 85-128), 1996 – 163/100,000 (95% CI 144-185). This rising prevalence in serial studies, although not invariable,[24] has been demonstrated elsewhere[20] and attributed to several factors including prolonged survival of MS patients, improved recognition of cases, changes in survey methodology and the widening application of paraclinical tests in diagnosis. The prevalence rates for the Ballymena area, being similar to those for the more recently surveyed Coleraine, Ballymoney and Moyle districts, encourage our belief that the methods of case ascertainment have been thorough and evenly applied.

In the British Isles only Shetland, Orkney and Suffolk [38] have had higher prevalence rates. All of these involved significantly smaller populations with wide confidence limits and in Suffolk there was no neurological review. Other similarly populous areas studied in the British Isles (Sutton;[39] pop 169,600: Jersey & Guernsey,[21] pop 145,246) have had significantly lower prevalence rates. Although there is now little evidence for a latitudinal gradient within these islands, our figures, taken together with those in Scotland, appear to support the existence of a "step" between Northern Ireland/Scotland and England/Wales. This in turn may reflect the distinct profiles of the population bases, the genetic composition and ethnic origin being similar in Scotland and Northern Ireland.[40]

Overall, this study reinforced Northern Ireland's global position as a high prevalence area for MS. On the basis of these figures and, with the presumption that there may be an even distribution of the disease across Northern Ireland, we could extrapolate that almost 3,000 individuals have definite or probable MS and there are a further 400 suspected cases in the region as a whole. A comparison of *standardised* prevalence rates for probable and definite MS in the UK, that is prevalence calculated on the basis of the 1961 census population of Northern Ireland,[29] is shown in Table II. The list is limited to those studies providing sufficient information for such a comparison to be made.

In light of the new and costly disease modifying therapies becoming available for the disease [42-43] and the standards being established for the management of many of its symptoms, these figures have major implications for health care provision and the distribution of resources to and within the health service in Northern Ireland. The long and unacceptable delay identified in our recent study between onset of symptoms and diagnosis of MS (6.2yrs) partially reflects the long waiting lists for clinical assessment and prolonged waiting times for supportive investigations. Again, given that the newer disease-modifying agents may be at their most effective early in the course of the disease, the imperatives for adequate funding and provision of neurological services in Northern Ireland are clear.

FUTURE STUDY

In order to broaden the awareness of MS beyond the intensively surveyed north-east of Northern Ireland and improve patient access to diagnosis, treatment and supportive care, we now wish to establish an MS database for the whole of Northern Ireland. This task will employ similar methods to those outlined in the 1996 prevalence study and will involve every hospital and general practice. The recent study detailed here indicates that we can depend on their support and encouragement. In addition, continuing investigation of the immunogenetic predisposing factors within this stable and homogeneous population is indicated; there remains a need for updated prevalence data in the Republic of Ireland, based on current diagnostic criteria and employing more thorough and now well established means of case ascertainment.

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TABLE II

Standardised prevalence rates (SPR) for probable and definite MS in the UK (based on 1961 Northern Ireland census population)

Survey	*Male Population*	*SPR/10⁵*	*Female Population*	*SPR/10⁵*
N. Ireland 1996[35]	74,000	100	77,000	226
Tayside 1996[27]	190,715	85	204,885	236
Jersey 1991[21]	40,620	46	43,462	140
Guernsey 1991[21]	29,836	37	31,328	98
Sussex 1991[22]	289,129	58	307,214	142
S. Cambs 1990[41]	143,252	66	152,816	171
Rochdale 1989[25]	98,978	75	104,365	156
SE Wales 1985[37]	191,302	73	203,044	142
Sutton 1985[39]	81,518	64	89,483	137

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