

Latitudinal variation in the prevalence of multiple sclerosis in Ireland, an effect of genetic diversity

C McGuigan, A McCarthy, C Quigley, L Bannan, S A Hawkins, M Hutchinson

J Neurol Neurosurg Psychiatry 2004;**75**:572–576. doi: 10.1136/jnnp.2003.012666

See end of article for authors' affiliations

Correspondence to:
Dr C McGuigan,
Department of Neurology,
St Vincent's University
Hospital, Elm Park, Dublin
4, Republic of Ireland;
cmcguigan@
doctors.org.uk

Received 17 February 2003
In revised form
20 August 2003
Accepted 20 August 2003

Background: Northern Ireland has a high and rising prevalence rate of multiple sclerosis (MS). The most recent survey in 1996 found a rate of 168.7/100 000. Recorded prevalence rates for the south of Ireland, including County Wexford, have been markedly lower and seemed to suggest the existence of a prevalence gradient within the island.

Objectives: To compare the prevalence of multiple sclerosis in Co. Wexford in the south east of Ireland and Co. Donegal in the north west, and to establish whether a variation in prevalence of MS exists within Ireland.

Methods: Patients were referred from multiple sources. Review of clinical case records and/or patient examination confirmed the diagnosis.

Results: In Co. Wexford, 126 patients were found to have clinically definite or probable multiple sclerosis with a prevalence rate of 120.7/100 000 (95% confidence intervals (CI) 100.6 to 143.8), which is similar to other areas of similar latitude within the British Isles. In Co. Donegal, 240 people had clinically definite or probable MS with a prevalence rate of 184.6/100 000 (95% CI 162.0 to 209.5). The difference in prevalence rates is statistically significant ($Z = 3.94$, $p = <0.001$).

Conclusion: There is a latitudinal variation in the prevalence rate of MS between the north and the south of Ireland. The increased prevalence of MS seen in Co. Wexford is likely to represent better case ascertainment and improved diagnostic accuracy rather than an actual increase in prevalence. The north/south variation in prevalence may represent a variation in the genetic predisposition to MS between the background populations of the two counties.

Ireland has been recognised as a high risk area for multiple sclerosis (MS) since the pioneering work of Allison and Millar in the 1950s.¹ Their initial study, conducted on the entire population of Northern Ireland, identified a prevalence rate for possible or probable MS of 51/100 000. Further studies in the same population showed high and rising prevalence rates.^{2–4} The most recent study, conducted in the north east of the island reported a prevalence rate for clinically definite and probable MS (Poser criteria)⁵ of 168.2/100 000,³ one of the highest prevalence figures within western Europe.

In contrast, the Republic of Ireland has been less extensively studied. Brady ascertained the prevalence rate of MS in the country as a whole as 77/100 000 in 1977.⁶ In a population of 3.5 million, case ascertainment was likely to have been sub-optimal. County Wexford in the south east of Ireland has been studied on two occasions; in 1971, Brady and Dean reported a prevalence rate of 54.5/100 000⁶ and in 1984 the prevalence rate was estimated to be 48.4/100 000.⁷

The north/south differences in prevalence rates within the island of Ireland have suggested a gradient, but in the absence of a modern study in the Republic of Ireland, this was uncertain.

Variations in the prevalence of MS based on latitude have previously been reported within other regions of the British Isles⁸ and worldwide.^{9–10} In recent years some doubt has been cast on the validity of these observations within England and Wales,¹¹ although an increase in prevalence from England up to Scotland seems to be reinforced with further scrutiny of the methods, including capture–recapture adjustment of prevalence rates.¹² This step in prevalence between England and Scotland remains unexplained.

In order to address the question of the low prevalence rate of MS in the south east of Ireland in relation to the north of

the island, this study of Co. Wexford and Co. Donegal was devised.

METHODS

Study areas

Co. Wexford is a maritime and farming county in the south east of Ireland lying between 52°20' and 52°44' latitude north with a land area of 1454 km² and a population of 104 372.¹³ Co. Donegal is located on the Atlantic coast in the north west of Ireland. It lies between 54°30' and 55°43' latitude north (fig 1), and has a land area of 1876 km² and a population of 129 994.¹³ Both counties have a general teaching hospital located in the main county town, and neurological services are provided by the teaching hospitals in Dublin.

Case ascertainment

Ethical approval for the study was obtained from the ethics committee of St. Vincent's University Hospital, Dublin.

Patients with the diagnosis of multiple sclerosis were ascertained from the following sources: general practitioners in Co. Wexford and Co. Donegal, consultant neurologists throughout Ireland, and county physicians in Wexford and Donegal; hospital coding lists, the local and national MS societies, respite care facilities, and interferon prescription lists.

Definition of prevalence

Individuals were considered prevalent if they had clinically definite or probable MS as defined by the Poser diagnostic

Abbreviations: MS, multiple sclerosis

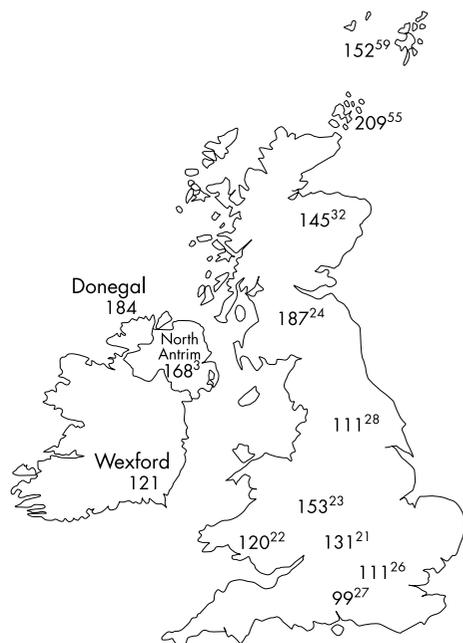


Figure 1 Map of the British Isles indicating the location of the study areas and the prevalence rates. The prevalence rate is the figure stated per 100 000 population, and the superscript figure is the study reference.

criteria⁵ and were resident within the county borders on 1 January 2001.

Patient assessment methods

All prevalent cases were invited to interview in Wexford General Hospital or Letterkenny General Hospital, Donegal. If this was not possible, a home visit was arranged. At interview, all cases had their demographic information recorded and historical notes assessed. The diagnosis of MS was confirmed by review of clinical case records and neurological examination. The Kurtzke Expanded Disability Status Scale¹⁴ and the Multiple Sclerosis Functional Composite¹⁵ scores were recorded.

If a general practitioner felt it was inappropriate to supply a patient’s name or contact details he or she was requested to provide sufficient information to ensure the case had not already been ascertained and to confirm the diagnosis.

Statistical methods

Ninety-five percent confidence intervals (CI) were calculated using a standard formula.¹¹ The prevalence rates for Co.

Wexford and Co. Donegal were compared using a Z value, where Z is a standard normal deviate. The correlation between Wexford, Donegal, and other studies within the British Isles compared with latitude was assessed using Spearman’s rank coefficient (r). A two source capture–recapture method¹⁶ was used as a measure of the likely number of missed cases. Survey completeness or “coverage” was expressed as a percentage of observed over expected cases.¹⁷ Standardised prevalence rates were calculated using the population of Northern Ireland from the 1996 study by McDonnell and Hawkins to allow direct comparison.³

RESULTS
County Wexford

The total number of cases ascertained from all sources was 161; 96 of these were referred from multiple sources. The number referred from each source included 46 from general practitioners, 51 from consultant neurologists, 94 from general physicians and hospital coding lists, and 33 from the MS society. Respite facilities and interferon prescription lists accounted for a further 27 referrals. Neither of these two latter sources contributed any unique cases. Twenty two patients were excluded from the study because the diagnosis was incorrect (7), or the patient was not resident within the study area (8) or was deceased prior to our defined prevalence day (7). Of the remaining patients 126 had clinically definite or probable MS, resulting in a prevalence rate for MS in Co. Wexford of 120.7/100 000 (95% CI 100.6 to 143.8). Age/sex specific prevalence rates for the county are displayed in table 1. The highest prevalence rates for men and women were in the 45–54 year age range. A further 13 cases had clinically possible disease. Applying two source capture–recapture adjustments to our data indicated that the likelihood estimate of missed cases for each source was between 4 (consultant physicians, neurologists and hospital coding lists) and 12 (general practitioners) missed cases. The range of adjusted prevalence rates when the estimated number of missed cases are included is 124.6–132.2/100 000. The estimated coverage of the study is 91.3–96.9%. (table 2) Disease characteristics for the prevalent population are given in table 3.

County Donegal

The total number of cases ascertained from all sources was 280; 128 were referred from multiple sources. The number referred from each source included 96 from general practitioners, 76 from consultant neurologists, general physicians and hospital coding lists, and 174 from the MS society. Respite facilities and interferon prescription lists accounted for a further 30 referrals; once again, neither of these two sources contributed any unique cases. Thirty one patients

Table 1 Prevalence of MS in Counties Wexford and Donegal per 100 000 population by age and sex

Age range (years)	Co. Wexford						Co. Donegal					
	Women		Men		Total		Women		Men		Total	
	No.	Prev.	No.	Prev.	No.	Prev.	No.	Prev.	No.	Prev.	No.	Prev.
0–14	0	0	0	0	0	0	0	0	0	0	0	0
15–24	4	49	1	11	5	29.2	4	36	1	9	5	22.9
25–34	8	113	5	69	13	90.8	23	254	7	78	30	167.0
35–44	22	318	9	128	31	222.3	53	715	12	164	65	442.3
45–54	24	407	14	226	38	305.6	44	647	15	218	59	426.1
55–64	16	364	10	221	26	291.1	36	630	9	160	45	397.2
65–74	5	135	6	178	11	155.0	18	377	8	170	26	274.9
75+	1	33	1	53	2	40.1	7	179	3	78	10	129.2
Total	80	154	46	88	126	120.7	185	282	55	85	240	184.6

Table 2 Two source capture–recapture adjustments applied to the main sources of case ascertainment (general practitioners, hospital coding lists/physicians/neurologists, and the MS society) by county.

	Co. Wexford			Co. Donegal		
	GPs	Hospital coding lists/physicians/neurologists	MS society	GPs	Hospital coding lists/physicians/neurologists	MS society
Total in source (a+b)	46	108	33	96	76	174
Unique to source (b)	6	20	3	8	11	38
Common to all sources (a)	40	88	30	88	65	136
Not in source (c)	80	18	93	144	164	66
Unobserved (bc/a)	12	4	9	13	27	18
Estimated size of population a+b+c+(bc/a)	138	130	135	253	267	258
Coverage (%)	91.3	96.9	93.3	94.9	89.9	93.0
Ascertainment adjusted prevalence (per 100 000)	132.2	124.6	129.3	194.6	205.4	198.5

GPs, general practitioners.

were excluded from the study because the diagnosis was incorrect (11), or the patient was not resident within the study area (5) or was deceased prior to our defined prevalence day (15). Of the remaining 249 cases, 240 had clinically definite or probable disease, resulting in a prevalence rate for MS in Co. Donegal of 184.6/100 000 (95% CI 162.0 to 209.5). Age/sex specific prevalence rates are given in table 1. A further nine cases had clinically possible MS, resulting in a crude prevalence rate of 191.5/100 000 (95% CI 168.5 to 216.9). Applying two source capture–recapture adjustments to our data indicated that the likely number of missed cases was 13 (general practitioners) to 27 (consultant physicians, neurologists and hospital coding lists). Including the number of missed cases adjusted the prevalence rate to Donegal from 194.6–205.4/100 000. The estimated coverage of the study was 89.9–94.9% (table 2). Disease characteristics for the prevalent population are shown in table 3.

Comparison between the two counties

The prevalence rate for Co. Wexford was significantly lower than that for Co. Donegal ($Z = 3.94$, $p = <0.001$). The difference in the prevalence rates is 63.9/100 000 (95% CI 49.3 to 82.7).

Age standardisation of the prevalence rate for both counties against the population from the 1996 study in the north east of Ireland³ adjusted the prevalence rates to 121.2/

100 000 for Co. Wexford and 194.6/100 000 for Co. Donegal, further strengthening the north/south gradient.

DISCUSSION

This study confirms the presence of a prevalence difference for MS between the north west and south east of Ireland. The incidence rates for the two counties studied are surprisingly similar, given the large variation in prevalence rates. This study is underpowered to perform a direct comparison of incidence rates. Difficulties in the accuracy of recording onset of first symptom, especially when only patient recall was available, may explain the lower than expected incidence rate for Co. Donegal.

The two source capture–recapture methods indicate excellent coverage (90%–94%) of the populations in both counties. The estimated number of missed cases compares favourably to many recent British studies in which the likely number of missed cases have ranged from 0 to 125 and percentage coverage varied from 78.2% to 99.6%.¹² In the 1996³ Northern Ireland study, the likely number of missed cases was 18

Table 3 Disease characteristics for the prevalent population for both Co. Wexford and Co. Donegal

Disease characteristic	Co. Wexford	Co. Donegal
Average age, years (range)	47.2 (19–73)	48.9 (24–78)
Mean age at onset, years (range)	33.4 (14–57)	32.8 (14–56)
Average duration of MS, years	13.4	16.1
Female : male ratio	1.7:1	3.4:1
Mean annualized incidence rate/ 100 000/year (95% CI)	4.47 (0.27 to 8.67)	5.12 (1.6 to 11.7)
Clinical course (%)		
Primary progressive	12.5	10.7
Relapsing/remitting	48.9	51.1
Secondary progressive	38.6	38.2
Mean Kurtzke EDSS score (range)	4.36 (0–9.5)	4.78 (0–0.5)
Mean MSFC – Z score* (range)	–1.28 (–6.55–0.77)	–1.28 (–6.55–0.77)

*Calculated using the task force database control.¹⁵ EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite.

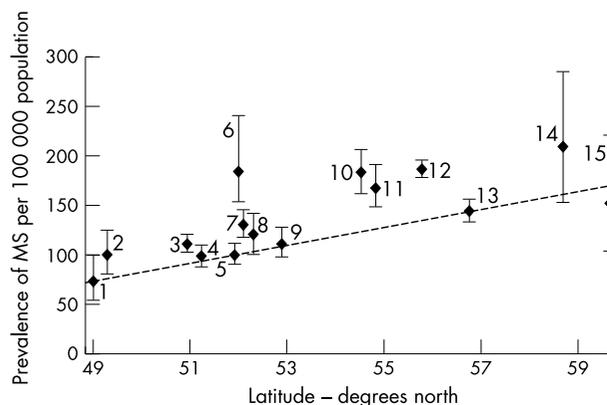


Figure 2 Graph of MS prevalence rates expressed as means (95% confidence limits) against latitude for 14 studies in the British Isles. The dashed line represents the correlation between latitude and prevalence of MS, correlation coefficient ($r = 0.65$). The numbers beside each data point indicate the following studies: (1) Guernsey 1991,³¹ (2) Jersey 1991,³¹ (3) Sussex 1991,²⁶ (4) Southampton 1987,²⁷ (5) south east Wales 1988,²² (6) Suffolk 1988*,²³ (7) Cambridge 1993,²¹ (8) Wexford 2001, (9) Rochdale 1986,²⁸ (10) Donegal 2001, (11) N Ireland 1996,³ (12) Lothian 1995,²⁴ (13) Aberdeen 1980*,³² (14) Orkneys 1983*,³³ (15) Shetland 1974*,³⁴ Poser criteria⁵ of probable/definite MS used for all studies unless marked with an asterisk (*) in which case the Allison and Millar¹ criteria were applied. (Adapted from Robertson and Compston.¹¹)

(coverage 94%) resulting in an adjusted prevalence rate of 180.1/100 000.¹⁸

The prevalence rate from Co. Wexford was similar to rates from areas of similar latitude within the British Isles (fig 2). In 1993, a study in the Cambridge district of East Anglia, the first such population based study in the south east of England, found a prevalence rate of 130/100 000¹⁹ (updated in 1996 to 152/100 000),²⁰ and a similar study in north Cambridgeshire reported a prevalence rate of MS of 119/100 000.²¹ South east Wales had a prevalence rate for MS of 120/100 000 in 1990.²² A study conducted in Suffolk in 1988 produced the highest figure for the prevalence of MS in England of 153/100 000 clinically probable or definite cases of MS.²³ However, this study was based on general practitioner notes only with no confirmation of the diagnosis by a neurologist. Additionally, the population size was small (31 379) and the under 35 age group was over-represented. Thus, the reported prevalence may not reliably reflect the actual prevalence rate for the Suffolk region.

The prevalence rate in Donegal is strikingly similar to that of north Co. Antrim from the 1996 study by McDonnell *et al.*³ It is also comparable to areas of similar latitude in the British Isles such as Lothian.²⁴

A plot of prevalence rates of MS within the British Isles, including Wexford and Donegal, against latitude shows a moderate correlation, $r = 0.65$, indicating the presence of a latitudinal variation in the prevalence of MS for the British Isles (fig 2).

Wexford has been surveyed on two previous occasions.^{6,7} Our prevalence figure is much higher than either of the previously reported figures, with no overlapping of the confidence intervals. The most recent study in 1984 by Hutchinson employed the diagnostic criteria of McDonald and Halliday,²⁵ making direct comparison with the current study difficult. In that study, all patients were also individually examined, but 40% were deemed as having benign disease. A bias against the more severely disabled may have accounted for the lower prevalence rate. It is our opinion that the increase in prevalence rates is likely to represent better case ascertainment in the current study. Prolonged patient survival, improved diagnostic accuracy, and earlier diagnosis with the widespread use of MRI will also have contributed to the higher prevalence rate.

The revised prevalence rate for Co. Wexford is significantly lower than the rate from the 1996 survey of northeast Ireland³ and the study performed simultaneously on Co. Donegal, despite employing similar methods of case ascertainment. Thus, the evidence is that there is a latitudinal gradient within Ireland. The existence of a latitudinal gradient within England has been challenged by the prevalence rates published from several well conducted surveys over the past 20 years.^{19–21, 26–28} Closer analysis of methodology, diagnostic criteria used, and the inclusion of possible missed cases have all tended to bring most prevalence rates within England and Wales to a similar level.^{11, 29} However, the increased prevalence of MS in Scotland compared with England and Wales remains.¹² This is likely to represent a differing rate of MS susceptibility gene prevalence, in particular HLA DR15 (formerly HLA DR2) in the background populations. HLA DR15 is known to be more prevalent in the Scottish population compared with the south of England.⁸

The population in the north of Ireland has close historical and cultural links with the Scots, both deriving from Gaelic ancestry, whereas that of Wexford and the south east of Ireland has a strong Norman and English influence. The postulated background genetic north/south differences probably relate to population movements such as the 17th century settlement of Ulster by people from the Scottish lowlands and the 13th century Norman invasion of the south east of

Ireland, and they also correspond to well recognised trade and migration routes between Ireland and mainland Britain. A crude test of this hypothesis is to measure the prevalence of surnames beginning with “Mc” or “Mac” as surrogate markers of northern European (Scots/Nordic) ancestry, a method previously employed in other studies.^{10, 24} In the Co. Wexford telephone directory there are 670/100 000 such surnames, whereas in Co. Donegal in the northwest of Ireland there are 6174/100 000. We hypothesise therefore that the variation in the prevalence of MS within the island of Ireland is due to differences in the prevalence of MS susceptibility genes in the background populations of the two regions rather than a true latitudinal/environmental factor, a theory supported by the reduction in prevalence rate differences at varying latitudes with the application of age standardisation to previously reported studies.³⁰ A study of the HLA status of the background populations in both Co. Wexford and Co. Donegal is currently in progress to test this hypothesis.

ACKNOWLEDGEMENTS

This study was supported by a Serono Fellowship from the Irish Brain Research Foundation. The authors gratefully acknowledge the contribution of Drs G Dean, G McDonnell, and R Forbes for their advice in planning this study. We thank the general practitioners, consultant physicians and neurologists for their support and the patients with MS who agreed to participate in this study.

Authors' affiliations

C McGuigan, A McCarthy, M Hutchinson, St Vincent's University Hospital, Elm Park, Dublin 4, Republic of Ireland

C Quigley, Wexford General Hospital, Wexford, Republic of Ireland

S A Hawkins, The Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, UK

L Bannan, Letterkenny General Hospital, Letterkenny, Republic of Ireland

Competing interests: none declared

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