PAPER

# The epidemiology of multiple sclerosis in Devon: a comparison of the new and old classification criteria

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**Objectives:** To determine the prevalence of multiple sclerosis in Devon and compare the new McDonald classification guidelines with the Poser criteria currently used.
**Methods:** All patients known to have multiple sclerosis and alive and resident within the chosen area on 1 June 2001 were included in the study. Seven sources of case ascertainment were used and each patient was classified according to both the Poser criteria and the McDonald guidelines.
**Results:** The prevalence of multiple sclerosis in Devon was 118 per 100 000 (definite and probable cases, Poser criteria) in a population of 341 796, on the prevalence day. The prevalence of definite and possible cases, as classified by the new McDonald guidelines, was slightly lower at 117 per 100 000. Clinical demographics of the prevalent population were similar to those of other studies in the United Kingdom.
**Conclusions:** This is first survey to use the new recommended guidelines and compare these criteria with the Poser classification. The difficulties encountered with applying the new criteria in research are highlighted, as are the differences between the new and old criteria. This study reports one of the highest prevalences in the south of the UK, adding support for a north-south divide being a step effect rather than a latitudinal gradient.

Multiple sclerosis is the most common cause of neurological disability in young adults in the United Kingdom. Following Limburg's use of mortality statistics to report a distinct geographical distribution in multiple sclerosis prevalence in the USA in 1950,[1] numerous studies have supported a significant variation in the world-wide distribution of this disease, with prevalence increasing with latitude north and south of the equator.[2 3]

Because surveys of Scotland and Northern Ireland have consistently reported the highest prevalence of multiple sclerosis in the world,[4–11] and similar rates have not been reproduced by studies in England and Wales, it has been suggested that a latitudinal gradient exists within the United Kingdom.[12] However, there have only been a handful of epidemiological studies of multiple sclerosis in the south of the UK over the past 20 years, and it remains debatable whether there is a latitudinal gradient within the UK.[13 14] Comparison of data is made difficult because of inconsistencies in methodology and diagnostic criteria. One of the biggest outstanding issues, despite advances in laboratory investigations, is the certainty with which one can make a diagnosis of the disease.

The diagnostic classification suggested by Allison and Millar[15] was used most often until the mid-1980s, when it was replaced by the Poser criteria.[16] Studies comparing the two criteria have shown that the earlier classification system overestimated prevalence, thus accounting for the higher rates reported in older studies.[8 14] The Poser criteria have recently been replaced by new diagnostic guidelines,[17] which take into account improved diagnostic methods and progress in technology. While they are expected to supersede the Poser criteria, as yet no study has reported prevalence using this classification system. It is to be hoped that the change in diagnostic criteria will result in more precise case ascertainment; however, improved diagnostic methods also mean that earlier epidemiological studies become less comparable.

The prevalence of multiple sclerosis in Devon has not been reported previously. At its low latitude and with relatively low migration rates, it is an ideal region to be studied and compared with the north of the United Kingdom. This study provides the first prevalence figure for this part of Britain, as well as being the first study to use the new diagnostic guidelines. We present prevalence rates using the new guidelines and the Poser criteria, as well as age and sex specific prevalence rates to allow for the demographic structure of the population.

## METHODS

### Study area

Devon is situated between latitudes 50° and 51° north of the equator. The region chosen for the study was limited to Plymouth and its surrounding area. The specific area was determined by post code address and gave a denominator population of 341 796 for April 2001. These population figures were obtained from the South and West Devon Health Authority and show a difference of only 5937 from the 1991 census. A point prevalence date of 1 June 2001 was chosen. The study area is served by four neurology consultants at Derriford hospital and 63 general practices.

### Sources of ascertainment

A provisional list of patients with definite or probable/possible multiple sclerosis, resident within the chosen area, was compiled from the following sources:

- Pre-existing databases, clinic letters, and discharge letters (over the past decade)
- Hospital episode statistics
- Records and case files compiled by the multiple sclerosis specialist nurse
- Visual evoked potential data (dating back to 1980s)
- Multiple sclerosis support groups for the south west region
- Regional community therapy services
- General practitioners—through letters, follow up phone calls, and visits to the practices.

Confirmation of residence, and whether the patient was still alive on the prevalence day, 1 June 2001, was then obtained using the Office of National Statistics search engine.[18] Cases not successfully traced were checked through the regional Patient and Practitioner Services Agency (PPSA). All those who had moved out of the area, could not be traced, or had died before the prevalence day were excluded from the study.

### Diagnostic criteria

This left a provisional register of patients known to be alive and resident on 1 June 2001. The diagnosis was confirmed and classified retrospectively in each case by CF, using hospital notes or general practitioner records. All cases had been assessed by a neurologist at some stage. Patients were classified according to the Poser criteria (clinically definite multiple sclerosis, laboratory supported definite multiple sclerosis, clinically probable multiple sclerosis, and laboratory probable multiple sclerosis). As with other studies, patients with age of onset older than 59 years were included. Other cases were recorded as ''classification unknown'' and ''suspected multiple sclerosis.'' The suspected group included clinically isolated syndromes (CIS) and clinically determined primary progressive cases that did not fulfil the Poser criteria. Cases with two attacks but no objective clinical evidence of a lesion were excluded. In addition, disease course was determined for each patient as relapsing-remitting (with no distinction made for a benign course), secondary progressive, or primary progressive.

All cases were also classified according to the recent recommended diagnostic criteria for multiple sclerosis by the international panel in multiple sclerosis diagnosis (the McDonald criteria),[17] and compared with the Poser criteria. These new criteria contain three broad groups: ''definite multiple sclerosis,'' ''possible multiple sclerosis,'' and ''not multiple sclerosis.'' Those patients with insufficient investigations to fulfil the definite multiple sclerosis criteria were classified as ''possible multiple sclerosis.''

### Statistical methods

Age and sex specific prevalence rates were calculated with the denominator of our own specific population data. Standard methods for proportions were used to calculate 95% confidence intervals. A two source capture-recapture method was used to estimate the number of missed cases, and coverage was expressed as a percentage of observed over expected cases.[19] Mean duration was calculated, with duration of disease taken from the first episode. Results were compared with similar published data from throughout the British Isles.

This study was approved by the local research ethics committee and conformed to the Data Protection Act.

## RESULTS

The two source capture-recapture calculations (based on the three sources with case ascertainment >10) suggests that the true number of cases is between 467 and 477, implying a coverage of 93.7% to 95.5%.

The provisional list of prevalent cases gave 510 names. This list only included cases known to be resident within the boundaries of the study area. From this provisional database, 64 patients were excluded (13%)—six died before the prevalence day, 13 were not resident in the chosen area on prevalence day, four could not be traced, and 41 were excluded because a different diagnosis had been made. This left us with 446 prevalent patients.

Of the prevalent patients, the largest source of ascertainment was from the hospital, identifying 352 patients (79%). The second largest source (largest sole source) was from general practitioners, with 328 patients (74%). No cases within our region replied to the survey sent through the multiple sclerosis society (table 1). Of 63 general practices, only 25% responded to the initial letter. Eventually, 97% of general practices replied to the survey (of these, 13% refused to provide information). Despite repeated phone call requests, 3% of practices did not respond. Forty nursing homes (40/45, 89%) responded to our survey, but only one case was notified solely from this source.

**Table 1** Case ascertainment from each source

| Source | All, n (%) | Sole source, n (%) |
|---|---|---|
| General practitioners | 328 (74%) | 67 (15%) |
| Hospital (neurology dept, hospital activity, MS specialist nurse) | 352 (79%) | 65 (14.6%) |
| Evoked potential data | 149 (33%) | 14 (3%) |
| Nursing homes | 10 (2%) | 1 (0.2%) |

MS, multiple sclerosis.

The prevalence of multiple sclerosis including only definite and probable cases, was 402/341 796 (117.6 per 100 000, 95% confidence interval (CI), 106.1 to 129.1). This is compared with the new criteria (breakdown shown in table 2), where the prevalence of definite and probable cases was 399/341 796 (116.7 per 100 000, 95% CI, 105.3 to 128.2). The reason for this difference is largely attributable to 1% of cases (n = 4) becoming ''Not multiple sclerosis'' under the new classification. The clinical characteristics of these four patients are shown in table 3.

Age and sex specific prevalence rates per 100 000 population were calculated (Poser criteria). The highest prevalence rate for women was 370 per 100 000 in the 45 to 54 age group, and for men, 207 per 100 000 in the 55 to 64 age group. The age range of prevalent cases was 23 to 89 years, with a mean of 52.0 (13.2) years. Mean age at disease onset was 34.6 (10.7) years. Mean duration from first episode was 17.3 (11.2) years, and the female to male ratio was 2.65:1. Ten patients had disease onset over the age of 59. Magnetic resonance imaging (MRI) was undertaken in 84% of cases and a lumbar puncture in 59%. According to the new criteria, MRI was required to confirm 32 cases as definite multiple sclerosis.

The percentage of prevalent patients within each course classification is similar to other studies: relapsing-remitting (46%), secondary progressive (30%), primary progressive (12%), clinically isolated syndrome (9%), unknown (3%). The most common symptom at first episode was sensory, followed by optic neuritis and then motor disturbance. The summation of our results, with 95% confidence intervals, is shown in table 4 and compared with other studies within the United Kingdom.

## DISCUSSION

### Prevalence rate and comparison with other UK studies

This is the first prevalence study of multiple sclerosis in Devon, as well as the first to calculate prevalence rates using the new diagnostic classification system. We report a prevalence rate of 118 per 100 000 (95% CI, 106.1 to 129.1) for patients with definite or probable disease according to the Poser criteria. The prevalence of definite and possible disease according to the McDonald criteria was slightly lower, at 117 per 100 000 (105.3 to 128.2). Our coverage, as calculated using the capture-recapture method, is good at 93.7–95.5% within the limits of this methodology.[19]

This prevalence rate is amongst the highest reported in England and Wales, adding further support for a step effect between the north and the south of the UK, rather than a

**Table 2** Prevalence of multiple sclerosis according to Poser classification

| Category | n | % | Prevalence per 100 000 | 95% CI |
|---|---|---|---|---|
| *Poser classification* | | | | |
| CDMS | 303 | 68.9 | 88.6 | (78.7 to 98.6) |
| LSDMS | 32 | 7.3 | 9.4 | (6.1 to 12.6) |
| CPMS | 50 | 11.4 | 14.6 | (10.6 to 18.7) |
| LPMS | 2 | 0.5 | 0.6 | (0.0 to 1.4) |
| Classification unknown | 15 | 3.4 | 4.4 | (2.2 to 6.6) |
| Suspected MS *(CIS)* | 44 *(39)* | 10 *(8.9)* | 12.9 *(11.4)* | (9.1 to 16.7) *(7.8 to 15.0)* |
| Total | 446 | 100.0 | 130.5 | (118.4 to 142.6) |
| *McDonald classification* | | | | |
| Not MS | 4 | 0.9 | 1.2 | (0.0 to 2.3) |
| Definite MS | 323 | 72.4 | 94.5 | (84.2 to 104.8) |
| Possible MS | 61 | 13.7 | 17.8 | (13.4 to 22.3) |
| Classification unknown | 15 | 3.4 | 4.4 | (2.2 to 6.6) |
| Suspected MS *(CIS)* | 43 *(39)* | 9.8 *(8.9)* | 12.6 *(11.4)* | (8.8 to 16.3) *(7.8 to 15.0)* |
| Total | 446 | 100.0 | 130.5 | (118.4 to 142.6) |

CDMS, clinically definite MS; CI, confidence interval; CIS, clinically isolated syndrome; CPMS, clinically probable MS; LPMS, laboratory probable MS; LSDMS, laboratory supported definite MS; MS, multiple sclerosis.

simple prevalence-latitudinal gradient, possibly reflecting underlying differences in genetic susceptibility.

## Problems with the new criteria

The prevalence rate for definite and possible multiple sclerosis patients using the McDonald criteria was calculated at 117 per 100 000. This slightly lower figure reflects the exclusion of four cases that were included with the Poser criteria. All these cases had negative investigations and only one objective clinical lesion (table 3). It is well recognised that a minority of patients have normal MRI results and that an abnormal investigation—whether of CSF, evoked potentials, or MRI—may be dependent upon the timing with respect to the onset of symptoms. Whether to label cases with negative investigations as ''Not multiple sclerosis'' under the new guidelines, even when there is a high index of suspicion clinically, is unclear. Invariably this group of patients with negative investigations will always be a difficult subset to include in epidemiological studies.

Several groups have commented on the difficulties with diagnostic criteria in multiple sclerosis.[20 21] As pointed out by Ebers,[21] the new criteria have not been compared with the Poser classification, which itself has not been formally validated with respect to diagnostic accuracy. In using these criteria it is difficult to see how they are superior to the current Poser criteria. The difficulties encountered in incorporating the various presentations of multiple sclerosis remain. In addition, the suggestion that a degree of individual interpretation is allowed within the diagnostic scheme will inevitably lead to interobserver variability, limiting its use as a research tool. If the new guidelines are to be used, there needs to be a change in clinical practice by increasing the number of investigations requested, particularly lumbar puncture, as well as improving and standardising the reporting of MRI, with increased use of gadolinium. Currently however, gadolinium enhancement is not routine, and many NHS radiologists lack both time and facilities to report to the detail suggested by Barkhof *et al*.[22]

## Methodological difficulties

Our methodology was similar to that of other multiple sclerosis surveys done in the United Kingdom over the past 10 years.[14 23–30] Although it is debated whether type A studies (where each prevalent case is interviewed to confirm multiple sclerosis and its course) are superior and more accurate than type B studies (using case notes alone to diagnose and classify patients), the overall percentage of excluded patients does not seem to differ significantly between the two types of

**Table 3** Clinical characteristics of ''Not MS'' patients according to McDonald classification

| Patient | Age at onset (years) | First episode | Second episode | Course | Investigation results | Poser criteria |
|---|---|---|---|---|---|---|
| 1 | 46 | Spinal cord syndrome (onset 1996) | – | PP | 2001: delayed VEP; CSF normal; MRI (head+spinal cord) normal | CPMS |
| 2 | 61 | Leg weakness (onset 2000) | – | PP | 2000: delayed SSEP; CSF normal; MRI: a few lesions in brain +1 lesion in spinal cord | CPMS |
| 3 | 23 | Myelitis (onset 1998) | Myelitis (2001) | RR | 2001: delayed SSEP; pos CSF; MRI (head+spinal cord) normal | LSDMS |
| 4 | 41 | Difficulty in walking, fatigue (1996) | Multiple symptoms, fatigue, walking difficulties | RR | 1996: pos CSF; MRI (head+spinal cord) normal | LPMS |

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; pos CSF, multiple oligoclonal bands present in CSF but not in serum; PP, primary progressive; RR, relapsing remitting; SSEP, somatosensory evoked potentials; VEP, visual evoked potentials.

**Table 4** Comparison of surveys throughout the United Kingdom (Poser criteria)

| | Devon 2001 | Cambridge (N Cambs) 1993 | Southampton 1987 | Sussex 1991 | Leeds 1996 | SE Wales 1985 | Tayside Scotland 1996 | Northern Ireland 1996 |
|---|---|---|---|---|---|---|---|---|
| Population | 341 796 | 378 959 | 411 000 | 596 394 | 732 061 | 376 718 | 395 600 | 151 000 |
| Number of cases | 446 | 449 | 411 | 665 | 712 | 441 | 727 | 288 |
| Crude prevalence (/100 000) | 131 (118 to 143) | 118 (108 to 130) | 99 (89 to 109) | 136 | 97 | 117 (106 to 128) | – | 191 (169 to 213) |
| Prevalence of definite and probable (/100 000) | 118 (106 to 129) | 107 (98 to 118) | 95 (88 to 107) | 111 (103 to 120) | 85 | 101 | 184 (171 to 198) | 168 (148 to 189) |
| Prevalence of clinically definite cases only (/100 000) | 89 | 75 | 76 | 89 | 44 | 79 | 114 | 123 |
| Mean age (years) | 52 | 50 | 48.6 | 48.6 | 51 | 48.7 | 49.5 | 49.3 |
| Mean age of onset (years) | 34.6 | 33.8 | 33 | 33.1 | 34 | 32 | – | 32 |
| Mean duration (years) | 17.3 | 16.5 | 15.7 | 15.5 | 16 | 16.5 | 15 | 18.4 |
| Sex ratio F:M | 2.65 | 2.2 | 2.1 | 2.5 | 2.8 | 2 | 2.8 | 2.1 |

Values in brackets are 95% confidence intervals.

study.[9 23–27] For this reason, we do not feel that our prevalence rate is an overestimation, but a true reflection of its population.

The problems with overestimating prevalence by including a suspected group have been alluded to before.[1 13 25] Despite this, many studies still report a crude prevalence rate that incorporates the subcategories of the Poser criteria plus a suspected group, which itself may contain patients with clinically isolated syndromes. However, the precise definition of the suspected group is often unclear. Table 4 shows that the prevalence rate for definite and probable cases only is much more comparable between studies than the crude prevalence. The Tayside group[8] goes one step further, suggesting that it is the clinically definite prevalence that should be compared between regions as this is a much more robust statistic with less interobserver variability. Again, we would agree that it is this figure that should ideally be quoted and compared with prevalence rates throughout the United Kingdom.

We have not standardised our population to the Northern Ireland 1961 population. Although this has been used in nearly all papers to compare the prevalence between areas with different demographics, the use of a Northern Ireland population is somewhat arbitrary. In addition, the initial study from which those data were obtained used the Allison and Millar classification which is now redundant. More specifically the demographics of the population have changed over the past four decades. We therefore feel that it is more accurate to compare specific age-sex prevalence rates between regions and so we have not standardised our population to any denominator other than our specific age and sex matched population rates.

Prevalence studies provide important information about the disease and its relation to the environment. Dissecting the complex interaction between genetic susceptibility and environmental triggers is made more difficult when methodological inconsistencies occur between studies. A multicentre survey, such as that carried out in Australia,[31 32] would eliminate any differences in regions caused by demographic movements over the years, as well as providing comparable data with precise methodology and diagnostic criteria. This is the only definitive way of confirming or refuting the suggestion of a north-south divide within the United Kingdom, as well as providing more accurate data for aetiological hypotheses based on the distribution of multiple sclerosis and its relation to the environment. In addition, we conclude that more studies need to be undertaken to assess the discrepancy between the new and old criteria, how different groups interpret and use them, and which is more reflective of the true prevalence, so that these guidelines can be successfully incorporated into epidemiological studies of multiple sclerosis.


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# ECHO

## Stress may increase the risk of an exacerbation in people with relapsing remitting multiple sclerosis

Please visit the *Journal of Neurology, Neurosurgery, and Psychiatry* website [www.jnnp.com] for a link to the full text of this article.

Neurologists and patients have long suspected that stress can trigger exacerbations of multiple sclerosis. Circumstantial evidence has suggested it since Charcot first described the disease. New, more robust, prospective data from the Netherlands now confirm a clear link between stressful life events and clinically defined exacerbations. The risk of an exacerbation seems to double in the four weeks following a stressful life event including a death in family, marriage problems, holiday stress, or even the death of pet. The researchers, who recruited a cohort of 73 patients from a single Dutch outpatient clinic, found that the link between stress and worsening disease is independent of any reported infections, ruling out confounding by this well known trigger.

Patients, who were all between 15 and 55 with relapsing remitting multiple sclerosis, kept weekly diaries recording stressful events for an average of 1.4 years. They were all examined regularly by a neurologist, and had extra appointments after self reported neurological deterioration, or an infection. Compliance with the diaries was good, covering 84% of follow up. Patients were considered high risk for an exacerbation for four weeks after a stressful event. At the end of follow up, the researchers compared the rate of clinically proven exacerbations in high risk weeks, with the rate in low risk weeks. The rate was 2.2 times higher in high risk weeks, a significant increase. The next step, they say, is to find out why. Measuring the neuroendocrine response to stress in these patients might be a good place to start.

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