RESEARCH PAPER

A new prevalence study of multiple sclerosis in Orkney, Shetland and Aberdeen city

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ABSTRACT

Background 30 years ago very high multiple sclerosis (MS) prevalence rates were recorded in northern Scotland. A prevalence study was repeated in Aberdeen, Orkney and Shetland to see if prevalence rates had changed, assess which factors affect prevalence and record disability status.

Methods Hospital, general practice and laboratory records were searched to identify prevalent MS patients (alive and registered with a participating general practice on 24 September 2009). Records were reviewed to confirm diagnoses applying Poser definite and probable and McDonald diagnostic criteria. Disability status (Expanded Disability Status Scale) was recorded from records and questionnaires. Rates were standardised to the Scottish population.

Results 590 patients were found (Aberdeen 442, Orkney 82, Shetland 66). Mean age and disease duration were 53 and 19.4 years, respectively. The standardised prevalence rates for Poser probable/definite MS per 100 000 were: combined area 248 (95% CI 229 to 269), Orkney 402 (95% CI 319 to 500), Shetland 295 (95% CI 229 to 375) and Aberdeen 229 (95% CI 208 to 250). McDonald diagnostic criteria gave a lower prevalence (202, 95% CI 198 to 206). Prevalence was highest in women (2.55:1, 95% CI 2.26 to 2.89) with about 1 in 170 women in Orkney affected. Prevalence was lowest in the most deprived socioeconomic group. 45% had significant disability (Expanded Disability Status Scale ≥6).

Conclusion The prevalence of MS has increased in the overall area, most markedly in Orkney, then Shetland, over the past 30 years. This increase could be due to a number of factors, but rising incidence as reflected by a rising sex ratio, influenced by gene—environment interaction, is the most likely. Orkney has the highest prevalence rate recorded worldwide.

INTRODUCTION

Much has been written about the epidemiology of multiple sclerosis (MS) in the north of Scotland. Between the 1950s and the 1980s, studies in Orkney and Shetland[1–6] showed a steady rise in the prevalence to about 190/100 000 (95% CI 150 to 280). Studies in the 1970s and 1980s found a similar increase in the prevalence in Aberdeen and north east Scotland, from 127/100 000 (95% CI 116 to 137) to 178/100 000 (95% CI 162 to 185)[7–10] (figure 1). More recent studies in lowland Scotland revealed crude prevalence rates of 145/100 000 (95% CI 127 to 163) in Fife and Glasgow,[11 12] 187/100 000 (95% CI 178 to 195) in Borders and Lothian[13] and 222/100 000 (95% CI 210 to 240) in Tayside.[14]

There have been no prevalence studies of MS in northern Scotland since the early 1980s despite this area having one of the highest rates in the world. This study, therefore, aimed to measure the age—gender specific prevalence of MS in Aberdeen, Orkney and Shetland to assess whether it had changed over time and to determine which factors might influence prevalence (socioeconomic status, diagnostic criteria, migration). We also recorded disability status, which has not previously been reported in this area.

METHODS

Ethics approval was obtained from the North of Scotland Research Ethics Committee.

Geographical area

The surveyed populations were that of Aberdeen city (latitude 57°9′N) and the islands of Orkney (latitude 58°41′N-59°24′N) and Shetland (latitude 59°50′N-60°88′N). The neurology department of Aberdeen Royal Infirmary (ARI) supplies all specialist neurological services in these areas, including the only access to MRI, neurophysiology tests such as visual evoked responses and biochemical analysis of CSF for oligoclonal bands. In Shetland, there are general physicians based at Gilbert Bain hospital who have access to a CT scanner and in Orkney the Balfour Hospital is managed by general practitioners and visiting general physicians with no brain imaging available.

Patients were eligible if alive, resident in the study area and registered with a participating general practice (GP) on the prevalence day of 24 September 2009. All GPs in Aberdeen (n=32), Orkney (n=14) and Shetland (n=10) were approached. The baseline populations were calculated from GP data held by Information Service Division, Scotland.[15] All neurology and rehabilitation consultants in Aberdeen, general medical physicians in Shetland, the visiting consultants to Orkney and MS specialist nurses involved in the care of MS patients were informed about the project by letter.

Case ascertainment

Prevalent cases were identified by: (1) searching electronic GP databases for patients registered on the prevalence day with a specified MS diagnostic code (READ code F20); (2) searching hospital discharge data (ICD-10 code for MS G35) from 1999 for ARI, Woodend Hospital (a large rehabilitation facility), Gilbert Bain Hospital (Shetland) and the Balfour Hospital (Orkney), as well as the MS specialist nurse databases in Aberdeen and Shetland; and (3) searching the ARI laboratory
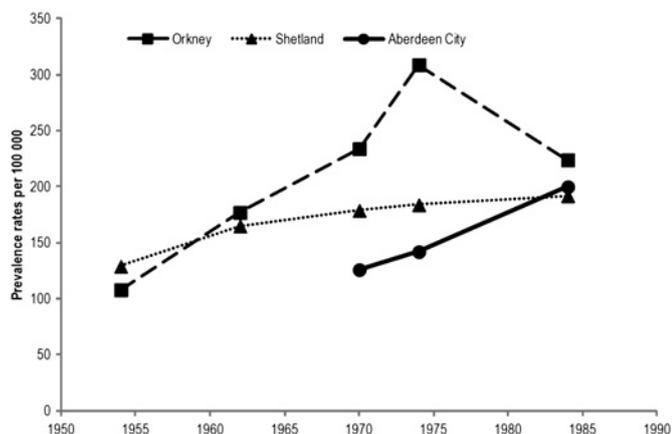
Figure 1 Prevalence in Orkney, Shetland and Aberdeen over time.

results for positive CSF oligoclonal bands from 1999 and neurophysiology for abnormal visual evoked responses from 1973. Radiology records were not accessible for case ascertainment. Independent MS patient organisations supported the study in an advisory capacity and helped advertise the project.

Case definition

A neurology research fellow and a supervised medical student reviewed the hospital records, GP records and laboratory data of all patients identified by the searches to confirm the diagnosis according to internationally accepted diagnostic criteria. Patients were included if they satisfied Poser criteria for clinically definite, laboratory supported definite, clinically probable or laboratory supported probable criteria or McDonald 2001 or the revised McDonald 2005 criteria.[16–18] Patients with clinically isolated syndromes were excluded unless they met McDonald 2005 criteria for MS. In cases of doubt, a senior neurologist made the final decision. Some patients (n=81) taking part in a parallel genetics study[19] were examined by the research fellow. We recorded the subtype of MS (relapse–remitting, secondary progressive and primary progressive), and disability status was scored using a modified Expanded Disability Status Scale (EDSS)[20] (mild 0–2.5, mild to moderate 3–5.5, moderate to severe 6–7.5 and severe 8–9.5) estimated from the patient records.

The Scottish Index of Multiple Deprivation (SIMD)[15] was used to analyse socioeconomic status. This index uses data from 31 indicators in different domains (income, employment, housing, health, education and access) and scores are allocated to postcode sectors in quintiles, the first quintile being the most deprived group and the fifth quintile the least.

Questionnaire

A subsequent postal questionnaire asked about: (1) level of disability using the modified EDSS; (2) place and date of diagnosis to identify patients who migrated into the study area after diagnosis; and (3) employment status (see figure S1; supplementary figure S1 is available online only). We worked with the GPs to identify all MS patients from the prevalent population suitable for invitation to complete the questionnaire such that patients who were unaware of their diagnoses or disputed it were not sent the questionnaire. Non-responders were sent a second questionnaire after 4 weeks.

Sample size

Based on the previous prevalence of about 190 per 100 000 from the 1980s, we expected to find 480 MS patients in the combined

study area using the Scottish population (June 2009).[21] This gave more than 80% power to detect a 25% increase or decrease in prevalence over time at the 5% significance level.

Statistical methods

Age–gender specific prevalence rates were calculated and standardised to the Scottish population (June 2009).[21] Capture–recapture methodology to adjust for incomplete ascertainment was not used because the search strategies were not independent. CIs were calculated assuming a Poisson distribution and, for the standardised rates, were calculated based on the original study area populations to avoid spurious narrowing of the interval. Differences in prevalence rates were analysed as differences in proportions. T tests were used to compare means. A χ^2 test was used to evaluate the socioeconomic status of patients in SIMD quintiles. The Wilcoxon signed rank test was used to compare medians for the EDSS. Calculations were done using SPSS, Excel, EpiInfo[22] and CI Analysis.[23]

RESULTS

Twenty-eight (87%) GPs in Aberdeen (population 205 446) agreed to participate in the survey, 13 in Orkney (93%, population 20 000) and 10 in Shetland (100%, population 22 656). The searches identified 2586 possible cases. This resulted in 782 possible MS patients, of whom 590 (420 women and 170 men) subsequently satisfied the diagnostic criteria (figure 2). Most (573, (97%)) were identified from the GP records or the MS specialist nurse databases (table S1; supplementary table S1 is available online only).

There was no significant difference in mean age (p=0.42), mean age at first symptom onset (p=0.94) or mean age at diagnosis (p=0.94) between men and women with MS (table 1). Mean disease duration from first symptom was 19.4 years. There was no evidence that the age of first symptom onset had changed significantly compared with previous studies from this area (table S2; supplementary table S2 is available online only), but unfortunately previous studies had not reported age at diagnosis. The most common subtype was relapse–remitting MS (50%) (table 1).
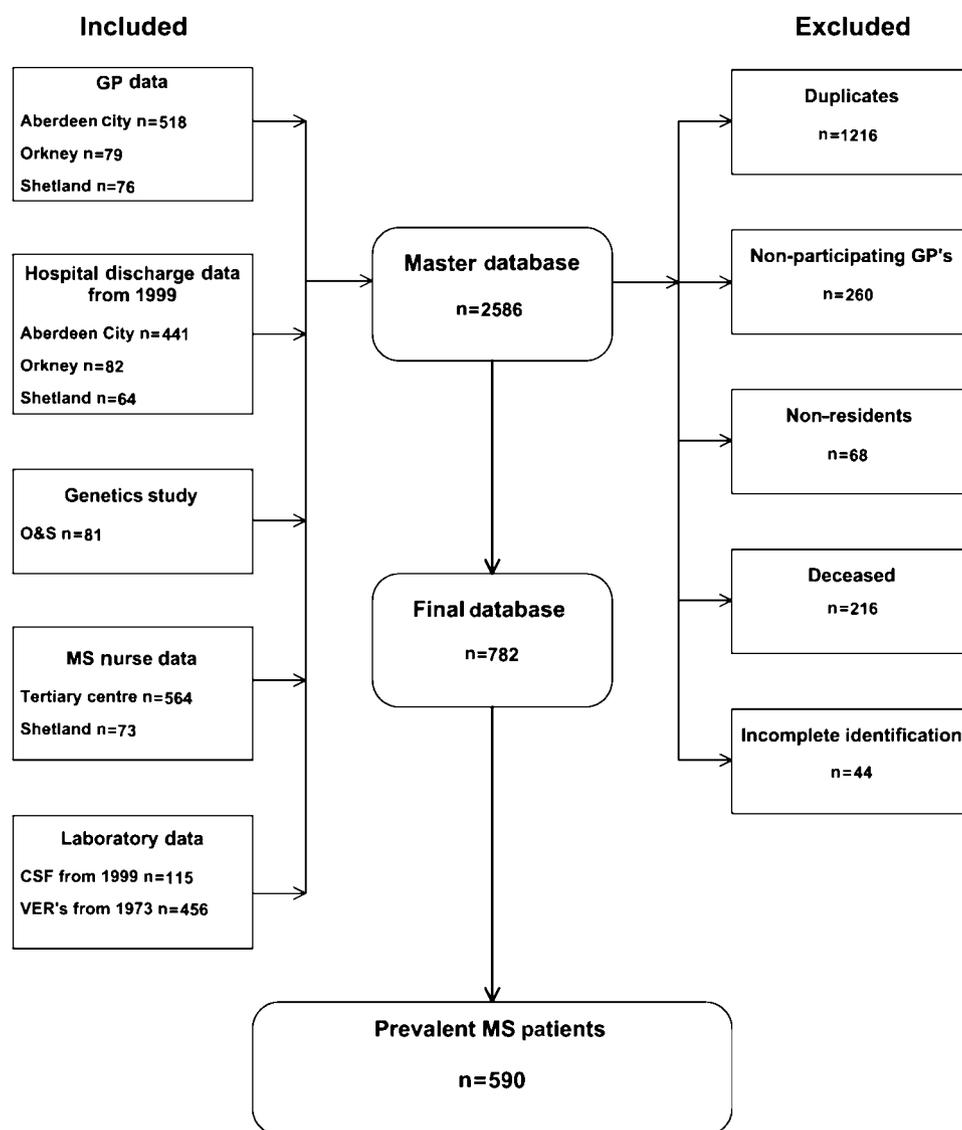
Prevalence rates

For the whole study area, the crude prevalence rate was 238/100 000 (95% CI 219 to 258) for all patients, 136/100 000 (CI 95% 117 to 158) for men (1 in 735) and 341/100 000 (95% CI 309 to 375) for women (1 in 293). After direct standardisation to the Scottish population, the overall rates increased slightly to 248/100 000 (95% CI 229 to 269) (table 2). The age standardised female to male ratio was 2.55:1 (95% CI 2.26 to 2.89), with evidence of an increasing sex ratio in younger prevalent patients when analysed by birth cohort (figure S2; supplementary figure S2 is available online only).

In the three different study areas, the overall standardised rates were 229/100 000 (95% CI 208 to 250) for Aberdeen, 402/100 000 (95% CI 319 to 500) for Orkney and 295/100 000 (95% CI 229 to 375) for Shetland (table 3). Orkney had a significantly higher prevalence rate than Aberdeen (p=0.0001), as high as 1 in 171 for women, and the difference between Orkney and Shetland (p=0.06) and between Shetland and Aberdeen (p=0.08) approached significance.

Previous prevalence studies in these areas did not publish the age–gender structure of patients needed for standardisation. However, Information Service Division data showed the age–gender population structures of the three study areas had not changed significantly from 1981 to 2009, allowing crude

Figure 2 Flowchart of case ascertainment and compilation of the database. CSF, cerebrospinal fluid; GP, general practice; MS, multiple sclerosis; O&S, Orkney & Shetland; VERs, visual evoked responses.

prevalence rates to be compared. There were significant increases in prevalence in the overall study area, in Orkney and Shetland but not in Aberdeen, compared with the previous prevalence studies from the 1980s (table 3).

Prevalence rates for the whole study area varied when applying different diagnostic criteria. Only 536 (91%) patients satisfied Poser's definite criteria, resulting in a crude prevalence of 219/100 000 (95% CI 215 to 224), while only 495 (84%)

Table 1 Demographic data of multiple sclerosis patients in the combined areas of Aberdeen city, Orkney and Shetland

Demographics	All patients	Men	Women
No of cases (n (%))	590	170 (29)	420 (71)
Age (years) (mean (SD))	52.5 (12.8)	53.8 (12.8)	51.9 (12.8)
Type of MS (n (%))			
Relapse—remitting	294 (50)	72 (42)	222 (53)
Secondary progressive	237 (40)	71 (42)	166 (40)
Primary progressive	59 (10)	27 (16)	32 (7)
Age at diagnosis (years) (mean (SD))	39.3 (11.0)	40.9 (10.9)	38.7 (11.1)
Age at onset (first symptoms) (years) (mean (SD))	33.2 (11.0)	34.7 (11.3)	32.6 (10.9)
Disease duration from first symptoms (years) (mean (SD))	19.4 (12.4)	19.1 (13.2)	19.3 (12.1)
Disease duration from diagnosis (years) (mean (SD))	13.2 (10.5)	12.9 (10.7)	13.3 (10.4)
EDSS from records (n=590)			
Score (median (IQR))	5.0 (0—7)	6.0 (2—6.5)	3.5 (1—6.5)
EDSS patient reported (n=327)			
Score (median (IQR))	5.5 (1—6.5)	5.75 (0—6.5)	5.5 (0—7)

See table S3 (available online only) for details on EDSS.
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Table 2 Crude and age—gender standardised prevalence rates of multiple sclerosis patients in the combined areas of Aberdeen city, Orkney and Shetland

Age (years)	Cases	Local population 2009	Scottish 2009 population	Crude prevalence per 100 000 (95% CI)	Standardised prevalence per 100 000 (95% CI)
All patients					
0—14	0	35 872	850 477	0 (-)	
15—24	4	35 645	684 947	11 (3 to 29)	
25—44	160	76 840	1 390 692	208 (177 to 234)	
45—64	323	64 011	1 399 372	505 (451 to 563)	
65—74	72	18 854	469 991	382 (299 to 481)	
75+	31	16 880	398 521	184 (125 to 261)	
Total	590	248 102	5 194 000	238 (219 to 258)	248 (229 to 269)
Men					
0—14	0	18 563	435 439	0 (-)	
15—24	2	17 254	349 684	12 (1 to 42)	
25—44	40	40 705	682 332	98 (70 to 134)	
45—64	92	32 997	679 452	279 (225 to 342)	
65—74	24	8855	217 419	271 (174 to 403)	
75+	12	6397	150 962	188 (97 to 328)	
Total	170	124 771	2 515 288	136 (117 to 158)	142 (127 to 158)
Women					
0—14	0	17 309	415 038	0 (-)	
15—24	2	18 391	335 263	11 (1 to 39)	
25—44	120	36 135	708 360	332 (275 to 397)	
45—64	231	31 014	719 920	745 (652 to 847)	
65—74	48	9999	252 572	480 (354 to 636)	
75+	19	10 483	247 559	181 (109 to 283)	
Total	420	123 331	267 8712	341 (309 to 375)	348 (338 to 386)

patients satisfied McDonald criteria, giving a prevalence of 202/100 000 (95% CI 198 to 206). The rates were identical for McDonald 2001 and 2005 criteria. The most common reason for failure to satisfy McDonald criteria was the absence of MRI (table S4; supplementary table S4 is available online only). No patients with clinically isolated syndromes satisfied McDonald 2005 criteria necessary for inclusion. A few patients (n=12, 11 in Aberdeen, one in Shetland) may have had MS clinically but did not satisfy any diagnostic criteria and were, therefore, excluded.

There was a statistically significant association between SIMD and prevalence rate (χ^2=25.36, 4 df, p=0.00004), with the lowest socioeconomic group having a prevalence about 2.5 times lower than the other groups, which were all similar (table 4). The same pattern was seen when the analysis was restricted to Aberdeen only. Orkney and Shetland had no areas in the lowest SIMD quintile but showed no difference in prevalence over the upper four quintiles.

Questionnaire results
Five hundred and five patients were sent questionnaires and 330 (66%) returned them. The median estimated EDSS from patient records (n=590) was 5 (IQR 1 to 6.5) compared with 5.5 (IQR

Table 3 Crude and age—gender standardised prevalence rates of multiple sclerosis in different areas for 2009 and 1980/84

Region	Sex	2009 Cases	2009 Local population	2009 Age—gender standardised prevalence per 100 000 (95% CI)	2009 Crude prevalence per 100 000 (95% CI)	1980s Cases	1980s Crude prevalence per 100 000 (95% CI)	Difference in prevalence from 1980s to 2009 per 100 000 (95% CI)	p Value difference
Overall	All	590	248 102	248 (229 to 269)	238 (219 to 258)	495	201 (184 to 219)[5 6 10]	37 (11 to 63)	0.0005
Aberdeen	All	442	205 446	229 (208 to 250)	215 (196 to 236)	407	200 (181 to 220)[10]	15 (−13 to 43)	0.28
	Men	130	103 350	134 (119 to 151)	126 (105 to 149)	N/A			
	Women	312	102 096	318 (306 to 356)	306 (273 to 341)	N/A			
Orkney	All	82	20 000	402 (319 to 500)	410 (326 to 509)	43	224 (162 to 302)[5]	186 (75 to 300)	0.003
	Men	23	9897	226 (165 to 302)	232 (147 to 349)	10			
	Women	59	10 103	569 (481 to 698)	584 (445 to 753)	33			
Shetland	All	66	22 656	295 (229 to 375)	291 (225 to 371)	45	192 (140 to 257)[6]	99 (10 to 192)	0.03
	Men	17	11 524	148 (102 to 207)	148 (86 to 236)	N/A			
	Women	49	11 132	429 (367 to 547)	440 (326 to 582)	N/A			

N/A, not available.

Table 4 Variation in prevalence of multiple sclerosis by socioeconomic status at postcode level

SIMD quintile	No of MS patients/ total population in each SIMD quintile*	Prevalence / 100 000 (95% CI)	OR (95% CI)
1 (Most deprived)	29/28 277	103 (65 to 140)	1
2	116/43 211	268 (220 to 317)	2.62 (2.07 to 3.99)
3	120/48 271	249 (204 to 293)	2.43 (1.95 to 3.72)
4	126/47 701	264 (218 to 310)	2.58 (2.04 to 3.93)
5 (Least deprived)	193/79 125	244 (210 to 278)	2.38 (1.90 to 3.64)

*No SIMD score was available for six patients in Orkney.
SIMD, Scottish Index of Multiple Deprivation.

0 to 7) from self-reported questionnaire data (n=327) (table S3; supplementary table S3 is available online only). There was no statistically significant difference between the median EDSS in men and women (p=0.23). Forty-six per cent (n=264) of patients were estimated from notes to be moderately to severely disabled (EDSS ≥6) compared with 50% from the self-reported questionnaire. In patients who had both notes based and self-reported EDSS, there was a significant correlation between the two (Spearman's ρ=0.774, p<0.0001), and the median difference between the two was 0 (IQR −1 to 1).

Thirty patients (5%) were residing in nursing, residential or care facilities on the prevalence day (mean age 62 years, SD 13). Of these, 25, four and one had secondary progressive, primary progressive and relapse—remitting MS, respectively. Fewer MS patients of working age were employed (n=129, (47%), 95 relapse—remitting, 26 secondary progressive, eight primary progressive) than the general population (85%).[24] Fifty-seven per cent of employed MS patients were working full time and 43% part time.

Sixty-two per cent (n=203) of the 330 questionnaire respondents were native to the study area. Of the 127 non-natives, only 5% (n=16, seven in Aberdeen, five in Orkney, four in Shetland) were diagnosed elsewhere before moving into the prevalence area. Twenty-seven patients moved into the area before the age of 15 years (16 from Scotland, seven from England, four from elsewhere), while 100 migrated into the area after age 15 years (59 from Scotland, 32 other parts of the UK, nine elsewhere).

DISCUSSION
We have shown that the prevalence of MS in northern Scotland has continued to increase since the early 1980s, particularly in Orkney where the rate remains the highest worldwide, as indicated in previous studies.

Several possible reasons for the increase in prevalence over time need consideration, including random variation, improved case ascertainment, altered diagnostic criteria, improved diagnosis, migration of high risk people into the area, longer survival and an increase in incidence. Given the small island populations, the islands' rates are more prone to chance fluctuations, which may partly explain why these showed the largest changes. However, random variation is less likely to explain the smaller but highly statistically significant increase over time in the total study area.

The increase in prevalence is unlikely to be due to improved case ascertainment (our search strategies were similar to previous studies) or changes in diagnostic criteria as previous studies used older, less specific, criteria,[25] which would artifi-

cially inflate the previous prevalence figures not reduce them, and included both possible and probable cases whereas we only included probable and definite cases. While there has been greater availability of specialist neurological services in the area over time, it is difficult to see how this could explain the large increase in prevalence, particularly on the islands.

Migration of pre-existing MS patients or those at high risk of developing MS into the study area is also unlikely to be an explanation of the rise in prevalence. Only 5% of prevalent patients moved into the area after diagnosis. Those who migrated into the area prior to diagnosis are unlikely to have brought with them a higher risk of MS. In this group, those who came at a young age would take on the risk of the study area,[26] while those who came later did not come from high risk areas.

Improved survival in people with MS over the past 30 years would increase prevalence and has been documented elsewhere.[27] However, again, this is unlikely to explain all of the increase. Others have shown that the increased survival in MS has been proportional to the increased survival in the general population.[28] Scotland's population survival has increased from 71 years in 1980 to 75 years in 2009,[29] implying that MS survival will have increased by about 1.5 years over the same time period given it was about 25 years in the 1980s.[30] This falls short of the 5 year increased survival needed to explain the total prevalence rise in the whole study area if the incidence of MS had remained unchanged (assuming prevalence=disease survival × incidence).

The final cause of an increased prevalence would be an increased incidence of MS in the area, as has been observed in other countries.[31 32] Although we did not perform an incidence study, it has been shown that an increasing female to male sex ratio is a good proxy for rising incidence[32 33] and our data did show such an effect both by 5 year birth cohort within our total study group (figure S2; supplementary figure S2 is available online only) and over time in prevalence studies from mainland northern Scotland where the sex ratio has increased from 1.3:1 in the 1950s to 2.4:1 in 2009 (table S5; supplementary table S5 is available online only). So, it is highly likely that there has been an increase in incidence in this study area. The cause of this increased incidence is unknown but purely genetic factors cannot account for the rising incidence over such a short period, which points towards an environmental factor. Recent evidence has suggested a significant role for vitamin D in the aetiology of MS and, therefore, changes in vitamin D levels may play a role in the rising incidence but we did not measure vitamin D levels in our cohort.

We found a socioeconomic effect, with a significantly lower rate of MS in the lowest socioeconomic category according to SIMD category, which has been seen in some but not all previous studies.[34 35] In the UK, where there is free access for all to a national health system, this is unlikely to be due to differential access to health services. The 'hygiene hypothesis' suggests that the difference may be due to people in higher socioeconomic groups having less immunity or later exposure to viruses than people in the lower socioeconomic groups, rendering them more vulnerable to infection with viruses (such as Epstein—Barr virus) which has been implicated in the aetiology of MS. Alternatively, other factors such as time spent outdoors or vitamin D may play a role but our study provided no direct data on these factors.

We demonstrated a significant impact of MS at the community level both in terms of disability and employment, particularly in the primary and secondary progressive patients, as expected. There was good agreement between the estimated and self-reported EDSS, the latter being slightly higher, probably because it was a more recent assessment. Although the EDSS is

widely used in MS research, it is largely focused on mobility and, therefore, we may have underestimated disability caused by other MS symptoms, such as cognitive impairment and pain.

The main strengths of this project were the multiple sources used for case ascertainment and the thorough review of primary and secondary healthcare records to verify each diagnosis. There were also some limitations. Some people with a false positive diagnosis of MS may have been included because most patients were not reviewed in person by the study team. In particular, there were a number of older patients diagnosed with MS before the widespread introduction of MRI who may have had other relapsing central nervous conditions that mimic MS. However, this limitation applies to previous prevalence studies as well and we excluded patients in whom there was diagnostic uncertainty after a thorough review of their medical records. In addition, some people with MS may have been wrongly excluded from our study (false negative diagnoses). For example, our searches may have missed some patients with longstanding benign MS if they were not coded on GP databases, had not been in contact with an MS specialist nurse and had not been admitted to hospital or had positive lumbar puncture after 1999. Brain MRI reports were not available for electronic searching and resources did not allow this project to do door to door case ascertainment. It is difficult to know whether the numbers of false positive and false negative diagnoses would balance out but we suspect our final prevalence rate may be an underestimate. Finally, despite using methods proven to increase response to postal questionnaires,[36] the questionnaire response rate was less than we hoped.

In conclusion, we found that the prevalence of MS in this part of Scotland is very high and has risen over the past 30 years, especially in the northern islands. We believe this rise is due to a combination of factors but is largely a result of a rise in incidence, while the disproportionate rise in the islands may relate to random fluctuation due to their small populations. The reasons for the very high prevalence in Orkney and Shetland remain unknown. The development of a high quality long term Scottish national register of incident patients will help determine the degree to which the incidence is rising in Scotland and whether the incidence in the islands is significantly higher than elsewhere.[37]

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