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Incidence of multiple sclerosis in the Republic of Ireland: A prospective population-based study

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ABSTRACT

Background: Multiple sclerosis (MS) incidence and prevalence is increasing worldwide, with a disproportionally higher rate in women. Recent studies have questioned the presence of a latitudinal gradient in Europe. Ireland is a high prevalence country for MS with a previously reported North-South gradient making it ideal to further explore this concept.

Objectives: In this study we prospectively determined the incidence rate of newly diagnosed MS in Ireland over a 12-month period and demonstrated the presence of a North-South gradient.

Methods: A national prospective population-based observational study was performed to ascertain all new cases of MS diagnosed from 1st March 2014 – 28th February 2015 in the Ireland. Within the main study there was a smaller nested cohort study to explore clinical outcomes with a view to future prospective follow-up of this cohort. Sources of case ascertainment included neurologists, MS nurse specialists and MS support services. The Irish census 2011 was used to obtain population statistics and the incidence rate was age-standardized to a European Standardised Population (ESP 2011). The North-South gradient was assessed, by comparing incidence rates between northern and southern counties.

Results: 292 patients fulfilled the inclusion criteria equating to an age-standardised incidence rate (A-SIR) of 6/100,000 (95% CI: 5.3–6.6); for women the rate was 8.7/100,000 (95% CI: 7.7–9.6) and for men 3.3/100,000 (95% CI: 3.0–3.7). The female to male sex ratio was 2.7:1. Mean age at diagnosis amongst the RRMS group was 37 years (SD: 9.6) and 55 years (SD: 7.7) in the PPMS group; there were no gender differences associated with age of diagnosis. Onset was progressive in 10% of cases. A significant difference was seen in incidence rates between the northern region (A-SIR: 9.6×10^{5}, CI: 6.9–12.3) and the southern region (A-SIR: 5.1×10^{5}, CI: 3.8–6.3) (Z-score =3.34, $p < 0.05$). Amongst the nested cohort (n=113) mean age at symptom onset in the RRMS group (n=106) was 34 years (SD: 8.7) and 50 years (SD: 11.8) in the PPMS group (n=7). The female to male sex ratio was 3.5:1. Eighty percent had started or were due to start disease modifying therapy at time of review and 77% were taking supplemental vitamin D. Using the hospital depression and anxiety scale (HADS) mild to severe depressive symptoms were reported in 34% with no prior history of depression. Seventy-five percent were in full or part-time employment with 8% not working due to disability arising from their MS.

Conclusions: This is the first study to prospectively assess the incidence rate of MS in Ireland and shows that Ireland has a high incidence rate, comparable with the rest of the British Isles, with a persistent North-South gradient. The age of onset of relapsing remitting multiple sclerosis appears to be increasing over the last 20 years. It will be of interest to re-assess this population over time to see if increasing incidence rates, as well as improved survival, are driving the reported increases in MS prevalence.

1. Introduction

Multiple sclerosis (MS) is the commonest cause of non-traumatic neurological disability in young adults (Compston and Coles, 2008). It significantly affects quality of life and imposes a financial burden on patients, family and society (Karampampa et al., 2012). Epidemiological studies have informed our understanding of the interplay between genetic and environmental factors in disease pathogenesis (Ramagopalan et al., 2010). Secular temporal trends show evidence of an increasing incidence and prevalence of MS with disproportionate increase in women (Koch-Henriksen and Sorensen, 2010). Understanding the temporal dynamics of the epidemiology of

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MS is important, both for the delineation of potential aetiological factors, and for the planning of future service provision.

Ireland is a northern European country with a genetically relatively homogenous population. Consecutive epidemiological studies in Ireland dating back to the 1950's (Allison and Millar, 1954; McDonnell and Hawkins, 1998; McGuigan et al., 2004; Gray et al., 2008; Lonergan et al., 2011) have shown increasing prevalence over time and a persistent North-South gradient. To date incidence rates have been based on retrospective estimates from these prevalence studies and, as such, are open to recall bias. Thus the aim of our study was to carry out a prospective observational study to establish the incidence rate of MS in the Republic of Ireland for the first time. We wished to establish if this rate was comparable to other recently published studies from the British Isles (Mackenzie et al., 2014; Balbuena et al., 2016; Simpson et al., 2015) and if there was a persistent North-South gradient.

2. Materials and methods

2.1. Study design

This was a prospective, population-based, observational study carried out in the Republic of Ireland over a 12-month period from the 1st March 2014 to 28th February 2015. Within this main study there was a smaller nested cohort study, in which participants provided more detailed clinical data with a view to a prospective follow-up of this cohort.

2.2. Study population

The Republic of Ireland, situated between latitude 51°5 and 55°5 north, covers an area of 70,283 km^2. In the 2011 census (http://www.cso.ie), Ireland's population was 4,581,269 (2,268,698 men and 2,312,571 women), a population increase of 1.6% since the prior census of 2006. There are a relatively few neurologists (1/140,000 population) in Ireland with a long record of collaborative research in the epidemiology of a number of neurological conditions.

2.3. Ascertainment & recruitment methods

Multiple data sources were used to ascertain cases including all consultant neurologists, MS clinical nurse specialists (CNS), MS Ireland (a patient support organisation), MS support nurses (pharmaceutical sponsored) and participant self-referral. Letters and e-mails were regularly sent to all consultant neurologists and MS CNS in both public and private hospitals throughout the country and presentations were given regularly at local meetings. The study was advertised on the MS Ireland webpage and written information was sent out to each local MS society branch. Full written informed consent was obtained from each participant prior to any study procedures.

2.4. Data collection

Data collected for each participant included a unique code composed of date of birth, sex, initials and county of residence (to avoid duplication of cases from multiple sources), diagnosis and preferred method of contact by the study team. If a patient wished to be included, but not contacted by the study team, the case had to be confirmed and referral completed by their treating consultant neurologist to ensure they met with the inclusion/exclusion criteria.

2.5. Inclusion Criteria

Participants were included in the study if they met with the 2010 McDonald (Polman et al., 2011) criteria for diagnosis of MS made between 1st March 2014 and 28th February 2015. Referrals were also accepted for patients diagnosed with clinically isolated syndrome (CIS) who agreed to be contacted at the end of the study period to assess if they had converted to MS by the 2010 McDonald criteria.

2.6. Exclusion criteria

Participants were excluded if they did not meet the McDonald 2010 criteria over the study period or if the diagnosis could not be confirmed by the study team or their treating neurologist. The clinical course of participants' MS was defined using the recently published clinical course guidelines (Lublin et al., 2014).

2.7. Nested cohort study

In a nested cohort study, all consenting participants had a more detailed clinical assessment including full medical history and examination. A questionnaire aimed to determine family history and potential environmental factors including smoking history, and preceding illnesses was completed. Neuropsychiatric assessment included the Hospital Anxiety and Depression Scale (HADS) (Snaith, 2003; Honarmand and Feinstein, 2009). Quality of life and disease impact was assessed by the Multiple Sclerosis Impact Scale (MSIS-29) (Hobart et al., 2001). If it was not possible to carry out an assessment in person, relevant questionnaires were posted out to the patient and detailed history was gathered over the phone after the patient had provided informed consent in writing. The telephone EDSS (Lechner-Scott et al., 2003) was used to assess level of disability.

2.8. Statistical methods

The most recent Irish census of 2011 was used to obtain population statistics (http://www.cso.ie). The incidence rate was age-standardized to a European Standardised Population (ESP 2011) with 95% confidence intervals. North-South differences in population were compared using a Z value, where Z is a standard normal deviate. Quantitative variables were described using mean ± standard deviation (SD) or median and range. All tests were carried using SPSS version 20.

2.9. Ethical approval

Full ethical approval was received from the St Vincent's University Hospital Ethics and Medical Research Committee.

3. Results

3.1. Study population

Of the 391 patients referred over the 12-month study period, 278 (71%) were from hospital sources, 27 (7%) from MS Ireland, 71 (18%) from pharmaceutical sponsored support nurses and 15 (4%) were self-referrals. Ninety-nine referrals were excluded (48 patients were referred by more than one source, 27 had clinically isolated syndrome, 8 had a diagnosis other than MS and 16 were outside the study time window). There remained 292 unique incident MS cases fulfilling all the inclusion & exclusion criteria. Of the whole cohort (n=292) onset was progressive in 29 (10%) cases. Mean age at diagnosis amongst the RRMS group was 37 years (SD: 9.6) and 55 years (SD: 7.7) in the PPMS group; there were no significant differences in age at diagnosis by sex.

3.1.1. Incidence rates

Age and sex-specific crude incidence rates are outlined in Table 1. The MS age-standardized incidence rate (A-SIR) was 6.0/100,000 (95% CI: 5.3–6.6); for women the rate was 8.7/100,000 (7.7–9.6) and for men 3.3/100,000 (3.0–3.7). The female: male incident case ratio was 2.7:1. The geographical regions within Ireland and incidence rates per region are outlined in Fig. 1 and Table 2. A significant

Table 1
Age-specific crude incidence rate per 100,000 by sex and total population.

Age range	Male		Female		Total population	
(years)	No.	Crude	No.	Crude	No.	Crude
0–9	0	0	0	0	0	0
10–19	0	0	3	1	3	0.5
20–29	16	5	45	13.3	66	10
30–39	25	6.6	81	21.2	109	14.4
40–49	21	6.6	44	13.8	59	9.3
50–59	9	3.5	30	11.5	39	7.5
60–69	6	3.1	10	5.1	14	3.6
70+	2	1.3	0	0	2	0.6
Total	79	3.5 (3.3)	213	9.2 (8.6)	292	6.3 (6.0)

Values in parentheses are age-adjusted to the European standard population (ESP).

Northern-Southern difference was seen in incidence rates between the northern region, mean latitude 54°32 (A-SIR: 9.6×10^{5}, CI: 6.9–12.3) and the southern region, mean latitude 52°16 (A-SIR: 5.1×10^{5}, CI: 3.8–6.3) (Z-score =3.34, $p < 0.05$).

3.2. Nested cohort

3.2.1. Clinical and diagnostic history

In the nested cohort study 113 patients were assessed; 106/113

Table 2
Number of cases, crude and age-standardised incidence rate per 100,000 population and geographical region as outlined in Fig. 1.

Geographical region	No.	Crude (95% CI)	A-SIR (95% CI)
Border	50	9.7 (7–12.4)	9.6 (6.9–12.3)
Midland	21	7.4 (4.2–10.6)	7.1 (4.1–10.2)
West	16	3.6 (1.8–5.4)	3.5 (1.9–5.2)
Dublin	91	7.1 (5.6–8.6)	6.7 (5.3–8)
Mid-East	41	7.7 (5.3–10.1)	7.1 (4.9–9.2)
Mid-West	13	4.2 (1.9–6.5)	4 (1.8–6.1)
South-East	28	5.6 (3.5–7.7)	5.6 (3.5–7.7)
South-West	32	4.8 (3.2–6.5)	4.7 (3.1–6.3)

CI = confidence interval; A-SIR = age-standardised incidence rate.

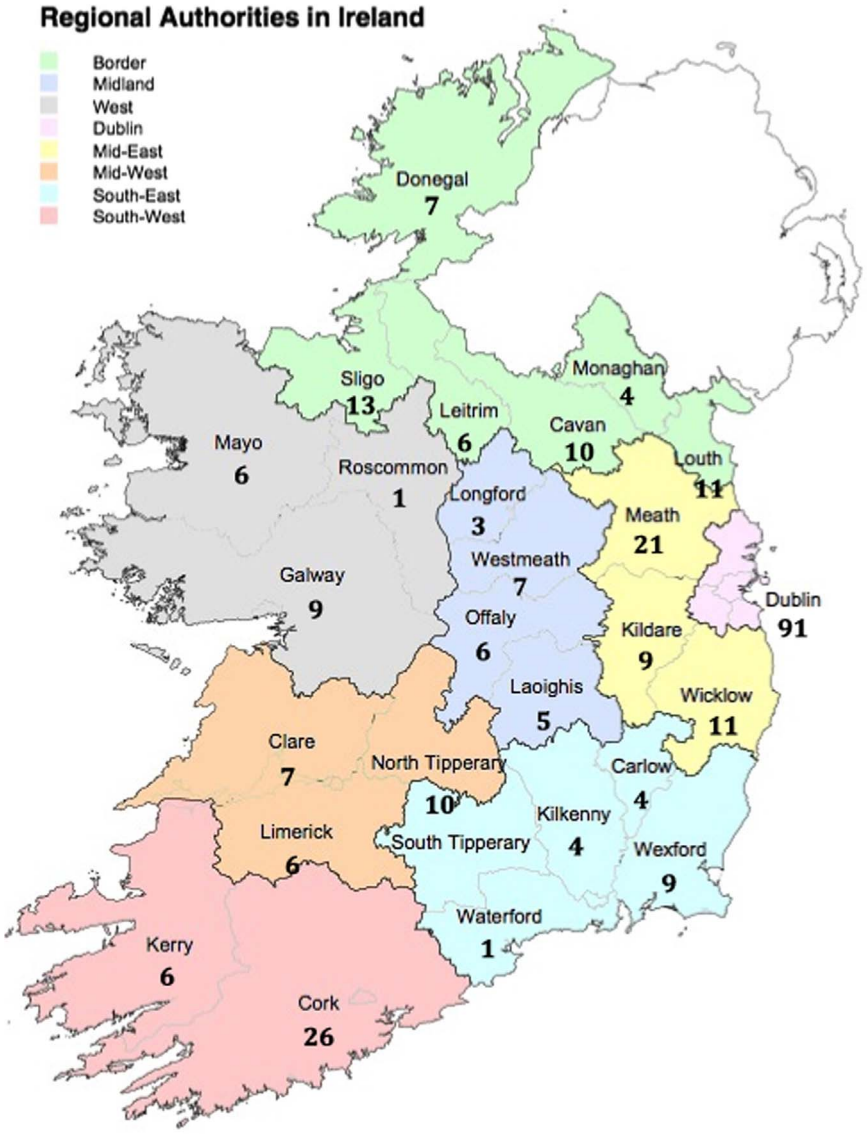

Fig. 1. Graphic showing number of cases per county with geographical region highlighted in colour (**Border:** Donegal, Sligo, Leitrim, Cavan, Monaghan and Louth; **Midland:** Longford, Westmeath, Offaly and Laoighis; **West:** Mayo, Roscommon and Galway; **Dublin**; **Mid-East:** Meath, Kildare and Wicklow; Mid-**West:** Clare, Limerick and N. Tipperary; **South-East:** S. Tipperary, Waterford, Kilkenny, Carlow and Wexford; **South-West:** Kerry and Cork). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Comparison between total cohort and nested cohort in terms of age, sex and subtype of MS.

	Total cohort (n=292)	Nested cohort (n=113)
Age at diagnosis Mean (SD)	37.9 (11.7)	38 (10.1)
Sex ratio Female: male	2.7:1	3.5:1
Subtype (%) Progressive/Relapsing	10/90	6/94

(94%) had RRMS, seven (6%) had PPMS. These 113 patients were considered to be representative of the total population with no significant differences seen in age, gender or MS course (Table 3). Baseline characteristics and disease history are outlined in Table 4. All patients had at least one MRI scan. Cerebrospinal fluid examination was done in 97/113 (86%) patients, 56/97 (80%) were oligoclonal band positive, 8/97 (8%) were negative and 13/97 (12%) unknown. Another autoimmune condition was reported in 23/113 (20%), with thyroid dysfunction accounting for 10/23 (43%). A family history of MS was reported by 29/113 (25%) patients; 15/29 having a first-degree, 8/29 (27%) a second-degree and 6/29 (23%) a third-degree relative affected.

3.2.2. Treatment history

Of the 113 cases, 75 (66%) patients had commenced disease modifying therapy (DMT): 62/75 (83%) on first-line DMT. Of the 38 not on treatment 15/38 (40%) were due to start, 7/38 (18%) were planning pregnancy, 7/38 (18%) were diagnosed with PPMS and 9/38 (24%) said they had been offered treatment but elected not to start.

Table 4
Showing baseline characteristics, diagnosis and disease history of the nested cohort study.

	RRMS (n=106)	PPMS (n=7)
Sex ratio (Female: male)	82:24 (3.4)	6:1
Age at symptom onset (years) Mean (SD)	34 (8.7)	49.9 (11.8)
Age at diagnosis (years) Mean (SD)	36.8 (9)	56.6 (6.6)
Time to diagnosis (years) Mean (SD)	2.5 (2.8)	4.2 (2.2)
Onset (%)	28	0
Optic neuritis		
Brainstem	19	0
Spinal cord	50	100
Other	3	0
Diagnosis confirmation[a] (%)	49	100
Clinical		
MRI	49	0
Biopsy	2	0
EDSS at diagnosis Mean (SD)	1.4 (1.5)	3.4 (1.4)
Number of relapses prior to diagnosis Mean (SD)	1.7 (0.6)	N/A

[a] Diagnosis confirmation refers to confirmation of dissemination in time by either new change on MRI or new clinical activity.

Supplemental vitamin D (median dose 2,000 IU, range: 400-5,000 IU) was being taken by 87/113 (77%) patients.

3.2.3. Psychosocial factors

Seventy-five percent were in full or part-time employment with 8% not working due to disability arising from their MS. Seventy percent were married or in a long-term relationship and 56% had children. Of those with children 10% felt their diagnosis would have affected their decision to have children compared with 23% of those who did not have children. A pre-existing diagnosis of depression was reported in 29%. Using the HADS as a screening tool, mild to severe depressive symptoms were identified in 34% of participants who had no history of depression. Mean MSIS-29 physical score was 33.8 (centile: 17) and MSIS-29 psychological score 18.8 (centile: 27).

4. Discussion

This first prospective Irish incidence study found a national incidence rate of newly diagnosed MS of 6/100,000 (almost 300 new cases per year). Direct comparison to previous calculated incidence rates is limited because these were regional estimates derived from prevalence studies with different study methodology. Incidence rates in Wexford in 2001 (McGuigan et al., 2004) were estimated at 4.47/100,000 (95% CI: 0.27–8.67) compared to 5.1/100,000 (95% CI: 3.8–6.3) in the current study. Rates in the northern counties of Donegal in 2001 (McGuigan et al., 2004) were reported as 5.12/100,000 (95% CI: 1.6–11.7) and Antrim/Derry in 1996 (Gray et al., 2008) as 9.3/100,000, compared with our finding of 9.6/100,000 (CI: 6.9–12.3). Thus the temporal trend, with increased MS incidence in Ireland varies from that in the United Kingdom (UK) where a decline in incidence has been seen since 1990 (Mackenzie et al., 2014).

Three recent publications from the UK have shown an incidence rate of 9.64/100,000 for the whole of the UK (Mackenzie et al., 2014), 9.1/100,000 for Wales (Balbuena et al., 2016) and 6.17/100,000 for the Isle of Man (Simpson et al., 2015). The UK study was generated from the General Practice Research Database (1990–2010) and used a screening period of two years prior to recording an incident case. Individual rates per country were not given but they did note a significant latitudinal gradient with Wales being a lower incidence country.

We found a significant North-South gradient in incidence rates in Ireland between the northern (mean latitude: 54°32N) and southern (mean latitude: 52°16N) counties (rates of 9.6/100,000 and 5.1/100,000 respectively). This is comparable to the gradient found in previous prevalence studies and considered to be due to ancestral genetic factors (Celtic in the Northwest and Anglo-Norman in the Southeast), supported by heterogeneity in distribution of HLA class II associations (specifically the HLA DRB1*1501eDQB1*0602 haplotype) amongst these areas (Lonergan et al., 2011; Dunne et al., 2006).

The average age at diagnosis was 40 years amongst the whole cohort (combined relapse onset MS/PPMS), comparable to that reported in the UK (Mackenzie et al., 2014), Australia (Ribbons et al., 2016) and Canada (Kingwell et al., 2015; Marrie et al., 2013). This is at the upper limit of the traditionally reported 20–40 year age range (Compston and Coles, 2008). There was no sex difference in age at diagnosis. There appears to be a temporal trend of increasing age at initial symptom onset as outlined in Fig. 2. Symptom onset of MS (combined relapse onset MS/PPMS) in previous Irish prevalence studies was: in 1996, 31.6 years (SD: 10.1) (McDonnell and Hawkins, 1998), in 2001, 33 years (range: 14–57) (McGuigan et al., 2004), in 2004, 32.6 years (SD: 10.5) (Gray et al., 2008) and in 2007, 32.3 years (range: 8–64) (Lonergan et al., 2011), compared with 35 (SD: 9.6) years in the current study. The rate of progressive onset MS in each of the studies has remained stable and would not account for this increase in age of onset.

Widespread geographical studies have shown an increasing inci-

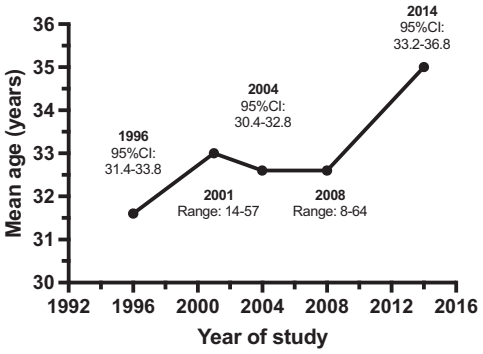

Fig. 2. Graph showing mean age at onset (combined relapse onset MS/PPMS) as documented in previous epidemiological studies from the island of Ireland (McDonnell and Hawkins, 1998; McGuigan et al., 2004; Gray et al., 2008; Lonergan et al., 2011) and current study. Results are shown for year of study and 95% confidence intervals reported where available.

dence amongst women (Koch-Henriksen and Sorensen, 2010; Alonso and Hernan, 2008) but there are exceptions and recent studies from Canada (Kingwell et al., 2015; Marrie et al., 2013) and the UK (Mackenzie et al., 2014) show a stable incidence ratio over the last 20 years and attribute increased survival amongst women as the main driver of increasing prevalence ratio. Our incidence ratio was 2.7:1, which seems comparable to the UK (2.4:1). More longitudinal studies are needed to assess the stability of our sex ratio over time.

Over two thirds of patients had commenced treatment at the time of their review with a further 15% due to start (total 80%). In a recent review from British Columbia (Kingwell et al., 2015) only 31–33% of all incident cases filled a prescription for DMT within three years of diagnosis although this was an older cohort (1991–2008). Studies examining the treatment burden in MS from the UK, Spain, France, Germany and Italy showed 75–94% had been treated with DMT (Karampampa et al., 2012) which would be more in keeping with our cohort. Patterns in vitamin D supplementation in the current study compared to the 2008 study (Lonergan et al., 2011) indicate an increase in both the proportion (from 62% to 77%) and the dose (from 400 to 1,500IU to 400-5,000IU (median: 2,000IU)) of supplemental vitamin D being taken. These doses are not routinely prescribed in Ireland and reflect the active role patients play in their care and also potential limitations to future trials to establish the effects of vitamin D on MS.

Employment rates in MS are lower than the general population and are influenced by MS subtype, disability, cognitive impairment and disease duration (Boe Lunde et al., 2014; Moore et al., 2013). This is highlighted in a recent population-based study from Norway (Boe Lunde et al., 2014) in which only 45% of all MS patients at a mean of 19 years follow-up were still employed with only 14% of PPMS still working. In a Welsh study (Moore et al., 2013) 43% of those working at diagnosis had left the workforce at a mean of 12 years follow-up with 55% of those in employment having changed their role or reduced their working hours. In our study a quarter were no longer working with 8% attributing it to their MS; since all patients were seen within 1 year of diagnosis this indicates a significant early socioeconomic impact of this condition.

Psychiatric co-morbidity is common in MS (Marrie et al., 2015) with a recent systematic review reporting a rate of 23% of co-existent depression. Thirty-one percent of our cohort reported co-existent diagnosis of depression with evidence of depressive symptoms on screening in 43%. Previous studies in recently diagnosed cohorts have shown this to range from 18% to 46%, (Simioni et al., 2007; Klevan et al., 2014) which, would be in keeping with our findings. Symptoms of depression are often unrecognised and therefore untreated, causing significant morbidity for the patient. Despite increased awareness of depression in MS among physicians, 34% of participants were considered symptomatic but undiagnosed. This is an increase of 9% compared to a prior study in 2001 (McGuigan and Hutchinson, 2006).

4.1. Strengths and weaknesses

The strengths of this study lie in the multiple sources of case referral used to identify cases. The prospective study design eliminated the criticism of potential recall bias from previous studies. Only cases with definite MS as per the McDonald 2010 criteria were included. Our findings are similar to studies carried out in the British Isles supporting the generalizability of these results within this geographical area.

A weakness of our study is the lack of previous prospective incidence data to examine temporal trends. A comparison of our data with incidence rates reported from previous prevalence studies has to be taken with caution given different study methodology.

5. Conclusions

In conclusion this is the first study to prospectively assess the incidence rate of MS in Ireland and shows that Ireland has a high incidence rate, comparable with the rest of the British Isles, with a persistent North-South gradient. The age of onset of relapsing remitting multiple sclerosis appears to be increasing over the last 20 years. It will be of interest to re-assess this population over time to see if increasing incidence rates, as well as improved survival, are driving the reported increases in MS prevalence. We also have a well-described modern cohort of MS patients to follow the natural history of in the era of advanced therapeutics in MS.

Conflict of interest statement

We would like to declare that no author has received any significant financial support for this work that could have influenced its outcome.

The conflict of interest statement of all contributing authors is outlined below:

1. Dr Karen O'Connell has received travel and educational grants from Biogen, Novartis, Abvie, Teva and Merck Serono.
2. Professor Michael Hutchinson has received speaker's honoraria from Biogen, Bayer –Schering, Merck Serono and Novartis and receives research grants from Dystonia Ireland, the Health Research Board of Ireland (CSA-2012/5) and the Irish Institute of Clinical Neuroscience.
3. Dr Christopher McGuigan has received honoraria, participated in advisory boards and/or received research funding from Biogen, Merck Serono, Novartis, Roche, Genzyme and Bayer.
4. Professor Niall Tubridy has received, on behalf of the Department of Neurology, St Vincent's University Hospital, educational and research grants from Novartis, Biogen, Teva and Bayer.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current,

correct email address which is accessible by the Corresponding Author and which has been configured to accept email from kazzoc@hotmail.-com.

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