



ORIGINAL ARTICLE

Incidence and prevalence of multiple sclerosis in Spain: a systematic review

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KEYWORDS

Multiple sclerosis;
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Abstract

Introduction: Greater understanding of the prevalence and incidence of multiple sclerosis in Spain and their temporal trends is necessary to improve the allocation of healthcare resources and to study aetiological factors.**Methods:** We performed a systematic search of the MedLine database and reviewed the reference lists of the articles gathered. We collected studies reporting prevalence or incidence rates of multiple sclerosis in any geographical location in Spain, with no time limits. In 70% of cases, data were extracted by 2 researchers (FGL and EAC); any discrepancies were resolved by consensus.**Results:** We identified 51 prevalence and 33 incidence studies published between 1968 and 2018. In the adjusted analysis, the number of prevalent cases per 100 000 population increased by 26.6 (95% confidence interval [CI], 21.5–31.8) every 10 years. After adjusting for year and latitude, the number of incident cases per 100 000 population increased by 1.34 (95% CI, 0.98–1.69) every 10 years. We observed a trend toward higher prevalence and incidence rates at higher latitudes.**Conclusions:** The prevalence of multiple sclerosis in Spain has increased in recent decades, although case ascertainment appears to be incomplete in many studies. Incidence rates have also increased, but this may be due to recent improvements in the detection of new cases.© 2022 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).DOI of refers to article: <https://doi.org/10.1016/j.nrl.2022.02.006>.

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PALABRAS CLAVE

Esclerosis múltiple;
Incidencia;
Prevalencia;
Revisión sistemática

Incidencia y prevalencia de la esclerosis múltiple en España. Una revisión sistemática**Resumen**

Introducción: El conocimiento de la prevalencia y de la incidencia de la esclerosis múltiple en España y de sus tendencias temporales es necesario para planificar mejor los servicios clínicos y estudiar factores etiológicos.

Método: Se efectuó una revisión sistemática, mediante una búsqueda en Medline y en las referencias de cada artículo, de todos los estudios que describieran cifras de prevalencia o de incidencia de la esclerosis múltiple en algún lugar geográfico de España, sin límites temporales. En el 70% de los casos la extracción de datos la hicieron dos observadores (FGL y EAC), que resolvieron las discrepancias por consenso.

Resultados: Se identificaron 51 estudios de prevalencia y 33 de incidencia entre 1968 y 2018. En el análisis ajustado, por cada 10 años la prevalencia por 100 000 habitantes aumentó en 26,6 (intervalo de confianza —IC— del 95%, 21,5 a 31,8). Según los datos del análisis ajustado por el año y la latitud, por cada 10 años la incidencia por 100 000 habitantes aumentó en 1,34 (IC 95%, 0,98 a 1,69). Se observó una tendencia de mayores prevalencias e incidencias en latitudes más altas.

Conclusiones: La prevalencia de la esclerosis múltiple aumentó en las últimas décadas en España, aunque en muchos estudios la verificación de casos parece haber sido incompleta. La incidencia también aumentó, pero eso puede deberse a una detección de casos nuevos más exhaustiva en los últimos años.

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Introduction

Multiple sclerosis (MS) is a chronic neurological disease characterised by destruction of myelin in the central nervous system, leading to varying degrees of axonal and neuronal damage. It causes a wide range of symptoms, which frequently worsen over time, leading to disability. MS is the second leading cause of neurological disability in young adults, after trauma.^{1,2}

MS is an autoimmune disease with a progressive degenerative component. Although its aetiology is unknown, a combination of environmental factors and genetic predisposition are thought to play a role. Environmental factors include Epstein-Barr virus infection, low exposure to sunlight, and low vitamin D levels. At least 233 genetic loci associated with the disease have been identified, 32 of which are located in the major histocompatibility complex.^{3,4}

Temporal trends in the incidence of MS may help to improve our understanding of its aetiology. However, given the difficulty of studying the incidence of MS, many hypotheses are based on prevalence data. The most widely accepted hypothesis is that formulated by Kurtzke,⁵ who established 3 bands of high, medium, and low frequency according to geographical latitude, with prevalence being greater at higher latitudes. Spain is located in the medium-prevalence band.

Many prevalence studies have been conducted in Spain,^{6,7} revealing a steady increase in the crude prevalence of MS over time. Spain seems to have become a country with a high prevalence of MS. The incidence of MS in Spain has also been studied,^{6,7} though less extensively and with highly heterogeneous results.

The purpose of this study was to analyse and update the information on the incidence and prevalence of MS in Spain.

Methods**Design**

We performed a systematic review of the literature.

Data sources

We performed a literature search on MEDLINE, using the PubMed search engine. We also reviewed the works cited in the reference sections of the original articles and literature reviews gathered in the literature search.

The search strategy used was as follows: (('multiple sclerosis'[MeSH Terms] OR ('multiple'[All Fields] AND 'sclerosis'[All Fields]) OR 'multiple sclerosis'[All Fields]) AND ('epidemiology'[MeSH Subheading] OR 'epidemiology'[All Fields] OR 'prevalence'[All Fields] OR 'prevalence'[MeSH Terms] OR 'prevalence'[All Fields] OR 'prevalences'[All Fields] OR 'prevalences'[All Fields] OR 'prevalent'[All Fields] OR 'prevalently'[All Fields] OR 'prevalents'[All Fields] OR ('epidemiology'[MeSH Subheading] OR 'epidemiology'[All Fields] OR 'incidence'[All Fields] OR 'incidence'[MeSH Terms] OR 'incidences'[All Fields] OR 'incident'[All Fields] OR 'incidents'[All Fields])) AND ('Spain'[MeSH Terms] OR 'Spain'[All Fields] OR 'Spain s'[All Fields])).

Study selection

We selected all studies reporting prevalence or incidence rates for MS in any location in Spain, from 1966 to 29 March 2021.

Extraction of data

We gathered the following data from prevalence studies: location, date of estimation, diagnostic criteria used, sources for case collection, total number of prevalent cases and distribution by sex and age group, population of the geographical area under study and distribution by sex and age group, estimated prevalence, sex ratio, and mean age (standard deviation) at symptom onset.

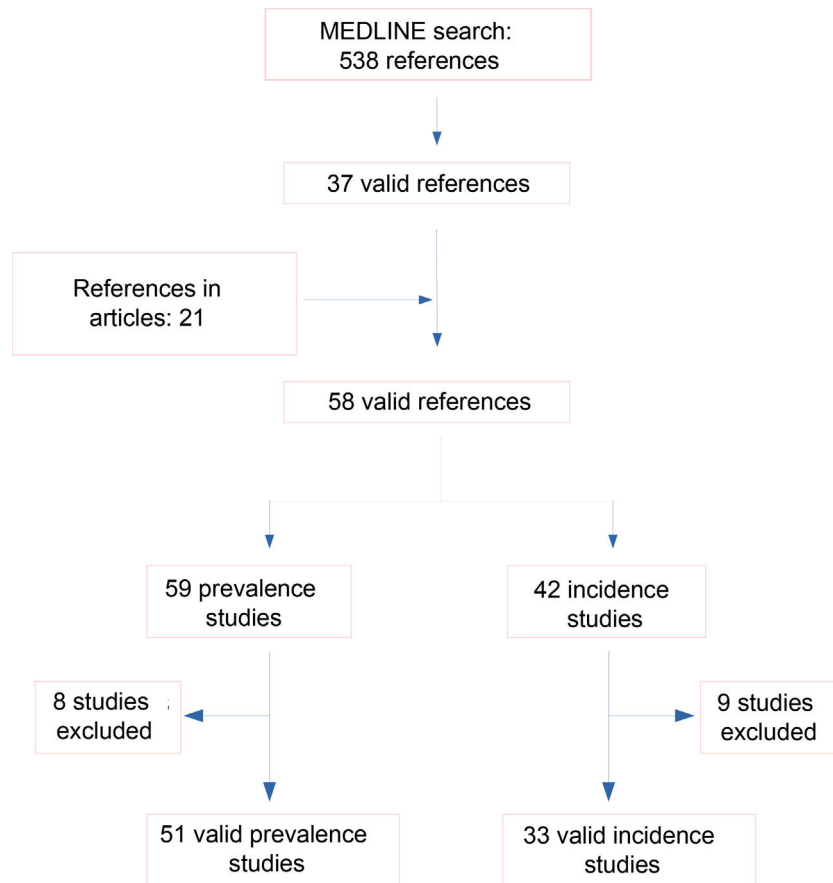


Figure 1 Flow chart of the study selection process.

From each incidence study, the following data were gathered: location, period of estimation, diagnostic criteria used, population of the geographical area under study, and estimated incidence.

For 70% of studies, data were collected by 2 researchers (FJGL and EAC); any discrepancies were solved by consensus.

Main outcome measures

Point prevalence and incidence are expressed as the number of cases per 100 000 population.

Data synthesis and analysis

We calculated 95% confidence intervals for prevalence and incidence rates using the Poisson distribution. For prevalence rates, we used the reported or calculated cases from each study and the population of the geographical area under study. For incidence rates, we used the population of the geographical area under study to calculate the population corresponding to the period of estimation (person-years) and the number of cases needed to reach the described incidence.

We built forest plots to analyse the results of the included prevalence and incidence studies.⁸ Given the expected heterogeneity of study results and methodological differences, we decided not to perform a meta-analysis of the data. However, we did assess study heterogeneity with random effects models.

We performed meta-regression analyses⁹ to analyse the impact of the calendar year and geographical latitude on the incidence and prevalence of MS. The meta-regression analysis of prevalence

also included the number of sources used to collect cases as an independent variable, whereas the meta-regression analysis of incidence included the length of the period of estimation, in years. In both cases, we conducted a sensitivity analysis exclusively including studies published in journals indexed in MEDLINE.

All statistical analyses were performed using Stata (version 15).¹⁰

Ethics approval

The study did not involve any patients, biological samples, or personal data; therefore, institutional ethics committee approval was not necessary.

Results

The results of our literature search are shown in Fig. 1. We finally selected 51 prevalence studies^{11–58} and 33 incidence studies,^{12,13,15,16,19,20,27,28,30–32,35–37,39–45,50,51,53–60} corresponding to a total of 50 bibliographic references (Table 1). We excluded 8 incidence and prevalence studies (conducted in Alcoy,^{61–63} Osona,⁶⁴ Ponent,^{65,66} La Coruña,⁶⁷ and Ourense⁶⁸) presenting very similar periods of estimation (less than 5 years apart) to those of other studies exploring the same geographical area. Furthermore, 2 incidence studies included the same period of estimation for overlapping geographical areas; therefore, we excluded the study with the shorter period of estimation.²³ Over the total period of over 50 years, studies have been conducted in all Spanish autonomous communities except Extremadura.

Table 1 Prevalence and incidence studies conducted in Spain included in our systematic review.

Authors	Reference	Location	Measure ^a	Year	Source type ^b
Oliveras de la Riva et al.	11	Barcelona	P	1968	Abs (no ML)
Miró et al.	12	Cantabria	I and P	1980 (P) and 1976-1980 (I)	A (ML)
Sosa Enríquez et al.	13	Las Palmas (province)	I and P	1981 (P) and 1971-1981? (I)	A (ML)
Fernández et al.	14	Malaga (province)	P	1984	A (ML)
Barduzal et al.	15	Aragon	I and P	1985 (P) and 1975-1985 (I)	A (ML)
Antón Aranda et al.	16	Navarre	I and P	1986 (P) and 1951-1986 (I)	A (ML)
Ruiz Ezquerro et al.	20	Salamanca and Zamora (provinces)	I	1980-1987	Abs, BC (no ML)
Barranquero et al.	17	Seville (1 healthcare centre)	P	1987	L (ML)
García et al.	18	Lanzarote	P	1987	A (ML)
Matías Guiu et al.	19	Hoya de Alcoy and Condado de Cocentaina	I and P	1988 (P) and 1986-1988 (I)	A (ML)
Mallada-Frechín et al.	59	Alcoy (healthcare district)	I	1986-1998	A (ML)
Ruiz Ezquerro et al.	20	Salamanca (province)	P	1988	Abs, BC (no ML)
Ruiz Ezquerro et al.	21	Zamora (province)	P	1988	BC (no ML)
López-Larrea et al.	22	Asturias	P	1989	A (ML)
Uría et al.	28	Gijón (healthcare district)	P	1989 (P) and 1987-1990 (I)	A (ML)
Buñill et al.	24	Osona	P	1991	A (ML)
Fernández et al.	25	Vélez-Málaga	P	1992	A (ML)
Navarro et al.	26	Catalonia	P	1993	A (no ML)
Sempere et al.	27	Segovia (healthcare district)	I and P	1994 (P) and 1980-1993 (I)	L (ML)
Uría et al.	28	Gijón (2 healthcare centres)	I and P	1994	A (ML)
Muñoz García et al.	29	Vigo	P	1994	BC (no ML)
Pina et al.	30	Calatayud	I and P	1995 (P) and 1990-1996 (I)	A (ML)
Casquero et al.	31	Menorca	I and P	1996 (P) and 1987-1996 (I)	A (ML)
Modrego Pardo et al.	32	Teruel (province)	I and P	1996 (P) and 1991-1996 (I)	A (ML)
Tola et al.	33	Valladolid (6 healthcare districts)	P	1997	A (ML)
Mallada-Frechín et al.	34	Alcoy (healthcare district)	P	1997	A (ML)
Benito-León et al.	35	Móstoles	I and P	1998 (P) and 1994-1998 (I)	A (ML)

Table 1 (Continued)

Authors	Reference	Location	Measure ^a	Year	Source type ^b
Hernández	36	La Palma	I and P	1998 (P) and 1995-1998 (I)	A (ML)
Antigüedad and Mendibe	37	Biscay	I and P	1999 (P) and 1988-1997 (I)	BC (no ML)
Ruiz Ezquerro	21	Salamanca and Zamora (provinces)	I	1990-1999	BC (no ML)
Ruiz Ezquerro	21	Zamora (province)	P	1999	BC (no ML)
García-Gallego and Morera-Guitart	38	Marina Alta	P	2001	A (ML)
Moral et al.	39	Ponent	I and P	2001 (P) and 1987-2001 (I)	Abs (no ML)
Modrego and Pina	40	Lower Aragon	I and P	1994 and 2002 (P) and 1994-2002 (I)	A (ML)
Aladro et al.	41	Las Palmas	I and P	2002 (P) and 1998-2002 (I)	A (ML)
Ares et al.	42	Santiago de Compostela	I and P	2003 (P) and 1998-2003 (I)	A (ML)
Hernández-Ramos	43	Lanzarote	I and P	2004 (P) and 2002-2004 (I)	T (no ML)
Carmona	44	Alt Empordà	I and P	2006 (P) and 2001-2006 (I)	Unpubl.
López-Real et al.	45	A Coruña	I and P	2006 (P) and 2004-2006 (I)	Abs (no ML)
Martín	44	Terres de l'Ebre	I and P	2007 (P) and 2002-2007 (I)	Unpubl.
Fernández et al.	46	Malaga (province)	P	2008	A (ML)
Otero-Romero et al.	47	Osona	P	2008	A (ML)
Fernández-Díaz et al.	48	Albacete (province)	P	2009	Abs (no ML)
Candeliere-Merlicco et al.	49	Murcia (healthcare district III)	P	2010	A (ML)
Bártulos Iglesias et al.	50	La Rioja	I and P	2011 (P) and 2001-2011 (I)	A (ML)
Izquierdo et al.	51	Seville (North district)	I and P	2011 (P) and 1991-2011 (I)	A (ML)
Otero-Romero et al.	60	Girona	I	2009–2013	A (ML)
Batlle Nadal et al.	52	Tarragona (province)	P	2014	Abs (no ML)
Pérez-Pérez et al.	53	Lanzarote	I and P	2015 (P) and 2008-2015 (I)	A (ML)
Costa-Arpín et al.	54	Santiago de Compostela	I and P	2015 (P) and 2000-2015 (I)	A (ML)
Llaneza González	55	Ferrol	I and P	2015 (P) and 2001-2015 (I)	T (no ML)
Carreón-Guarnizo et al.	56	Murcia (healthcare district I)	I and P	2016 (P) and 1999-2014 (I)	A (ML)
García-Estévez et al.	57	Ourense	I and P	2016 (P) and 2002-2016 (I)	A (ML)
Pérez-Carmona et al.	58	San Vicente del Raspeig	I and P	2018 (P) and 2006-2018 (I)	A (ML)

^a I: incidence; P: prevalence.^b A: article; Abs: abstract; BC: book chapter; L: letter to the editor; ML: indexed in MEDLINE; no ML: not indexed in MEDLINE; T: thesis; unpubl.: unpublished.

Table 2 Frequency of the sources used to identify cases of multiple sclerosis.

Source	No. (%)
Registry of neurology department at local hospital	37 (86)
Primary care physicians	23 (54)
Patients' associations	21 (49)
Private neurologists	15 (35)
Registry of neurology department at reference hospital	14 (33)
Minimum basic dataset and hospital clinical record databases	14 (33)
Media outlets	10 (23)
Registry of the Spanish Social Security System	9 (21)
Other specialists at hospital	8 (19)
Ophthalmologists	7 (16)
Rehabilitation physicians	7 (16)
Public lectures	6 (14)
Social workers	6 (14)
Other private physicians	6 (14)
Non-medical healthcare professionals	6 (14)
Local physicians	6 (14)
Registry of centres performing MRI studies	5 (12)
Registry of primary care diagnoses	4 (9)
Registry of hospital pharmacy department	4 (9)
Social organisations	3 (7)
Self-report by patients with multiple sclerosis	3 (7)
Registry of rehabilitation centre	3 (7)
Death registry	3 (7)
Registry of medical inspection services	3 (7)
Local offices of the Spanish National Statistics Institute	3 (7)
Lectures for medical professionals	2 (5)
Nursing homes	2 (5)
Registry of neurophysiology department	2 (5)
Registry of emergency department	2 (5)
Capture-recapture methods	1 (2)
Registry of home-based care unit	1 (2)
Non-hospital neurology outpatient clinics	1 (2)

Percentages were calculated with a denominator of 52 (total no. of studies indicating the sources for case collection).

Table 2 lists the sources used for collecting cases of MS in the studies included in our review. The main source was the registry of cases of MS of the neurology department at the local hospital. Other important sources were primary care physicians, patients' associations, neurologists working in private practice, the registry of cases of MS of the neurology department at the reference hospital, and the minimum basic dataset and hospital clinical record databases. The median number of sources reported in the studies was 4 (range, 0-16; Q_1 - Q_3 , 1-6) and the mean number was 4.65.

Regarding the relative importance of the sources used for case collection, most of the studies providing this information collected over 80%^{31-33,41} or 90%^{16,54,56} of the cases from neurology department registries, although in some studies this source provided only a small percentage of the cases (17%¹⁹ or 55%²⁴).

Of the 51 studies describing the diagnostic criteria used, 30 (59%) used the Poser criteria; 7 (14%) used the 2001 McDonald criteria; 5 (10%) used the Rose criteria; 4 (8%) used the Poser and the McDonald criteria; one (2%) used the Schumacher, the Poser, and the McDonald criteria; one (2%) used the Boston University Workshop criteria and the Poser criteria; one (2%) used the Poser criteria and the diagnostic criteria proposed by the Multiple Sclerosis International Federation (MSIF) International Medical and Scientific Board; and one (2%) used the McDonald and the Holliday criteria.

Prevalence

The prevalence of MS has increased over time (Fig. 2), with rates showing great heterogeneity (Cochran $Q = 113.28$, $df = 50$ [$P < .00001$]; $I^2 = 56\%$).

Table 3 shows the meta-regression coefficients for prevalence, considering the impact of year (mid-point of estimation period), latitude, and number of sources used. An association was observed between prevalence and the year of the study, with prevalence rates being higher in more recent years. This association was observed in analyses adjusted and unadjusted for latitude and number of sources. According to data from the adjusted analysis, the prevalence rate increased by 26.6 cases per 100 000 population every 10 years (95% CI: 21.5-31.8). This association was more marked after performing a sensitivity analysis exclusively including studies published in journals indexed in MEDLINE (increase of 29.4 cases per 100 000 population every 10 years; 95% CI, 22.5-36.4).

Fig. 3 shows the plot for the unadjusted meta-regression analysis of the point prevalence of MS over time. This association showed an I^2 of 97% and an adjusted R^2 of 72%.

Regarding latitude, the adjusted analysis showed an increase in point prevalence of 10.4 cases per 100 000 population with every 10° increment in latitude (95% CI, -2.5 to 23.4); in the adjusted

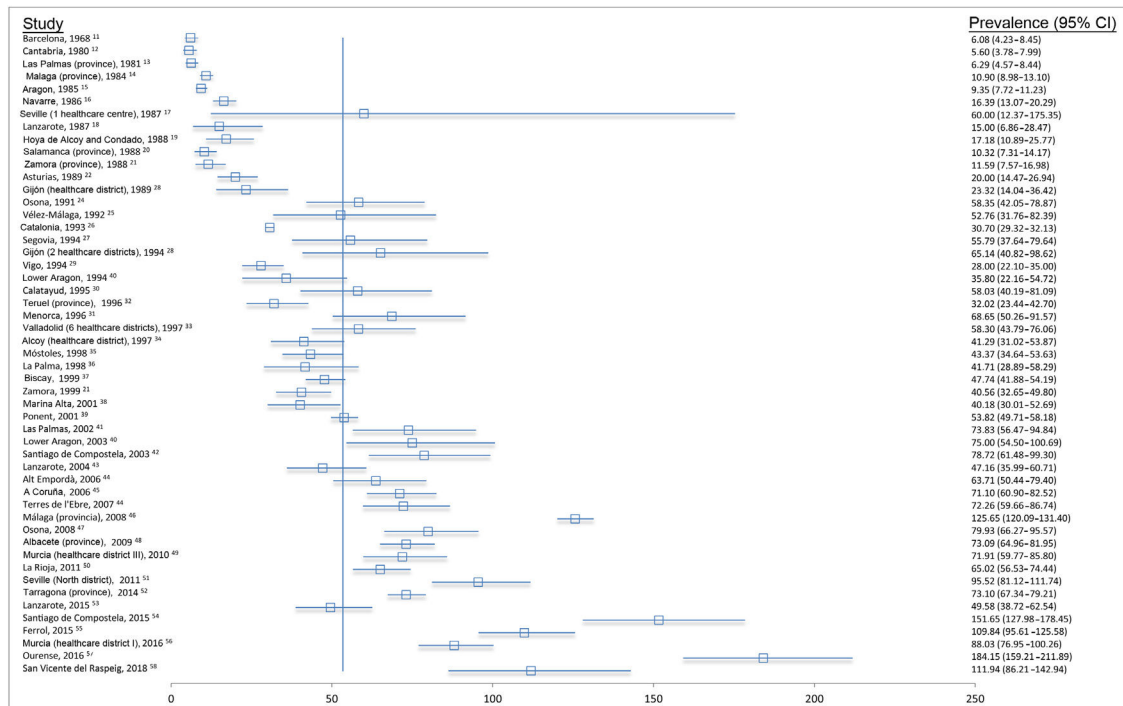


Figure 2 Forest plot of the point prevalence of multiple sclerosis in Spain. The figure shows all the studies, by year (mid-point of the estimation period), and their point prevalence estimates per 100 000 population along with 95% confidence intervals (Poisson distribution). The vertical line indicates the weighted average of the studies (53.41), although no meta-analysis was conducted.

Table 3 Meta-regression coefficients of the influence of several factors on the point prevalence of multiple sclerosis, in number of cases per 100 000 population. Adjusted and unadjusted analysis.

Variable	Unadjusted analysis		Adjusted analysis ^a	
	Coefficient	95% confidence interval	Coefficient	95% confidence interval
<i>All studies</i>				
Year (mid-point of estimation period)	2.65	2.12 to 3.18	2.66	2.15 to 3.18
Latitude	0.87	−1.49 to 3.22	1.04	−0.25 to 2.34
No. sources	0.84	−1.67 to 3.35	1.05	−0.36 to 2.47
<i>Studies published in journals indexed in MEDLINE</i>				
Year (mid-point of estimation period)	2.98	2.26 to 3.70	2.94	2.25 to 3.64
Latitude	1.23	−1.71 to 4.16	1.30	−0.29 to 2.90
No. sources	1.71	−1.38 to 4.80	1.26	−0.67 to 2.83

^a Adjusted models include all the variables indicated in the table.

analysis only including articles from journals indexed in MEDLINE, prevalence increased by 13.0 cases per 100 000 population (95% CI, −2.9 to 29.0).

Incidence

Fig. 4 presents a forest plot of incidence studies conducted in Spain, ordered by the mid-point of the estimation period. Our results show an increase in the incidence of MS over the years, with moderate heterogeneity of incidence rates (Cochran $Q = 51.40$, $df = 32$ [$P = .0163$]; $I^2 = 38\%$).

Table 4 shows the meta-regression coefficients for incidence, considering the year (mid-point of estimation period) and latitude. A correlation was observed between incidence and year, with more recent years presenting higher incidence rates. This association was

also observed in analyses adjusted and unadjusted for latitude and study duration (in number of years). According to the results of the analysis adjusted for year and latitude, incidence increased by 1.34 cases per 100 000 person-years every 10 years (95% CI, 0.98–1.69). According to the analysis of studies published in journals indexed in MEDLINE, incidence rates increased by 1.33 cases per 100 000 population every 10 years (95% CI, 0.87–1.80).

Fig. 5 shows the plot for the unadjusted meta-regression analysis of the incidence of MS over time. This association showed an I^2 of 90% and an adjusted R^2 of 69%.

Regarding latitude, the year-adjusted analysis showed an increase in the incidence rate of 0.87 cases per 100 000 person-years with every 10° increment in latitude (95% CI, −0.005 to 1.75); in the year-adjusted analysis of articles from journals indexed in MEDLINE, incidence increased by 1.08 cases per 100 000 with every 10° increment (95% CI, −0.12 to 2.28).

Table 4 Meta-regression coefficients of the influence of several factors on the incidence of multiple sclerosis, in number of cases per 100 000 population. Adjusted and unadjusted analysis.

Variable	Unadjusted analysis		Adjusted analysis ^a	
	Coefficient	95% confidence interval	Coefficient	95% confidence interval
<i>All studies</i>				
Year (mid-point of estimation period)	0.13	0.10 to 0.17	0.14	0.11 to 0.18
Latitude	0.08	−0.06 to 0.23	0.07	−0.02 to 0.16
Length of estimation period	0.02	−0.10 to 0.12	0.06	−0.002 to 0.12
<i>Studies published in journals indexed in MEDLINE</i>				
Year (mid-point of estimation period)	0.13	0.08 to 0.18	0.14	0.10 to 0.19
Latitude	0.09	−0.10 to 0.28	0.09	−0.03 to 0.21
Length of estimation period	0.02	−0.11 to 0.16	0.06	−0.02 to 0.14

^a Adjusted models include all the variables indicated in the table.

We were unable to conduct a meta-regression analysis of age at symptom onset as a function of the study year as few studies reported the standard deviation of mean age at symptom onset. The mean age at symptom onset was 31.14 years (range, 27.3–36.10), and the median age was 31.25 years (Q_1 – Q_3 , 29.37–32.37). We performed a simple linear regression analysis of the relationship between age at symptom onset and year, and found a slight increase in age in more recent years, although with a negative lower bound of the 95% CI (linear regression coefficient: 0.09; 95% CI, −0.02 to 0.16).

A simple linear regression analysis was also performed for sex ratio and year (median: 2.09; range, 1.1–3.29; Q_1 – Q_3 , 1.68–2.5). The female-to-male ratio barely increased over time (linear regression coefficient: 0.0043; 95% CI, −0.0123 to 0.0210).

Discussion

This systematic review of prevalence and incidence studies conducted in Spain revealed a clear increase in the prevalence and incidence of MS over the years, as well as a trend toward a positive correlation between latitude and prevalence/incidence.

This increase in prevalence rates may be due to multiple factors. Firstly, the number of detected cases has increased, which in turn results in fewer undiagnosed cases. The number of sources for case detection has also increased. However, it has been hypothesised that prevalence studies still fail to include all existing cases; this idea is further supported by the great number of records gathered from MS registries of neurology departments, while some studies have suggested the use of capture-recapture methods to achieve more complete estimates.^{46,69}

Secondly, improvements in diagnosis associated with the use of MRI and CSF analysis and updates in the diagnostic criteria for MS^{70–72} have increased the number of detected cases, including some patients who would not have been diagnosed with older criteria. Thirdly, the development of new pharmacological treatments has favoured the referral of suspected cases to neurology departments. Furthermore, the development and consolidation of the Spanish National Health System and the greater predisposition of the public to seek medical care may have also resulted in greater likelihood of patients with such neurological conditions as MS, which presents with relatively mild symptoms in early stages, consulting with their physician. These phenomena are reflected both in a marked decrease in diagnostic delay⁷³ and in a decrease in median Expanded Disability Status Scale score⁷⁴ in prevalent cases over time.⁴⁷

Lastly, the increased prevalence of MS is largely due to the fact that the mortality rate associated with the disease is lower than

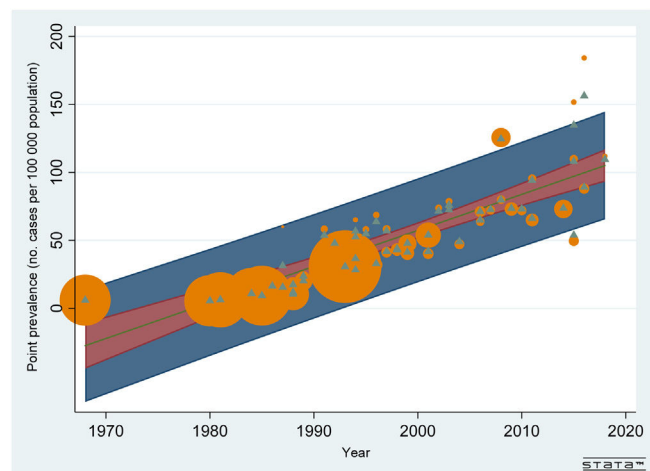


Figure 3 Meta-regression analysis of the impact of time on the point prevalence of multiple sclerosis. The straight line reflects the predicted prevalence by year (mid-point of the estimation period), the red area reflects the 95% confidence interval, and the dark blue area reflects the prediction interval. Orange circles indicate the observed prevalence rates (size is inversely proportional to total variance), while green triangles reflect empirical Bayes estimates (ie, the predicted prevalence rates of the random effects).

the incidence rate, despite the latter remaining stable. Prevalence comprises the set of all new and pre-existing cases of a condition (excluding cured or deceased patients). As MS is a chronic disease with a very low short-term mortality, its prevalence will necessarily increase over time as long as its incidence is higher than the associated mortality. In any case, survival may have increased with the introduction of disease-modifying treatments.⁷⁵

The extent to which a real increase in the incidence of MS in Spain has contributed to the increase in its prevalence is unclear. The heterogeneity of results, however, suggests that case detection may have been incomplete on many occasions.

The increase in incidence rates over time should be interpreted with caution, since the association does not necessarily imply causation. Improvements in the methodological quality of the studies, with greater diagnostic certainty of new cases (in line with the aforementioned changes in diagnostic and treatment criteria and greater patient awareness of the need to seek medical attention) may explain the greater numbers of cases detected in more recent

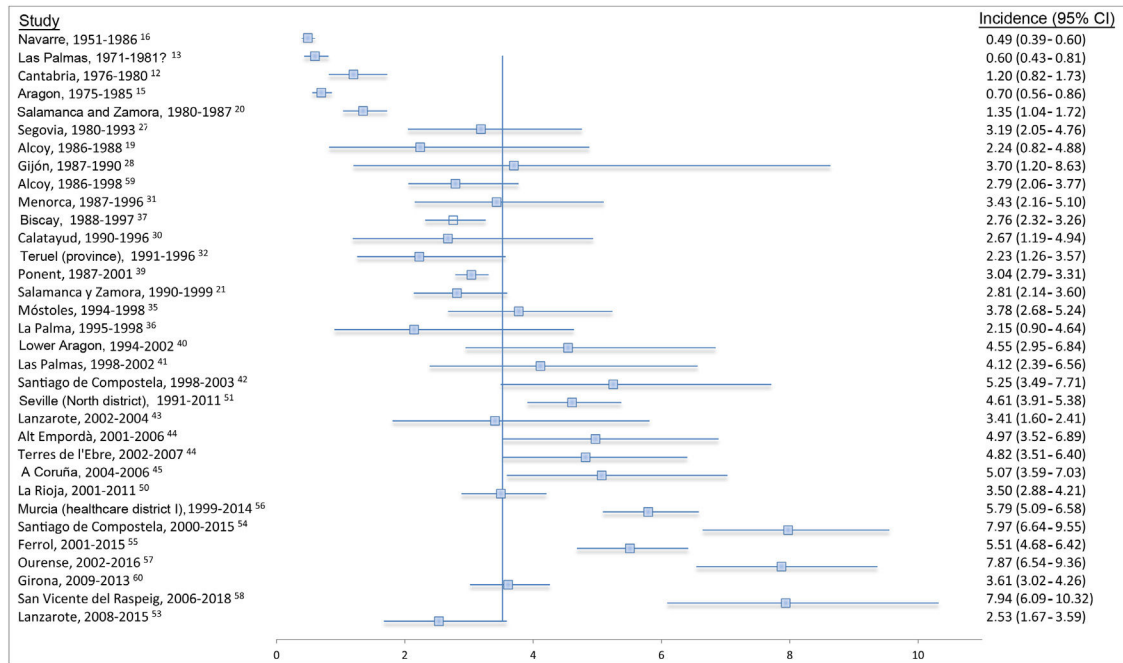


Figure 4 Forest plot of the incidence of multiple sclerosis in Spain. The figure shows all the studies, by mid-point of the estimation period, and their incidence estimates per 100 000 person-years along with 95% exact confidence intervals (Poisson distribution). The vertical line indicates the weighted average of the studies (3.52), although no meta-analysis was conducted.

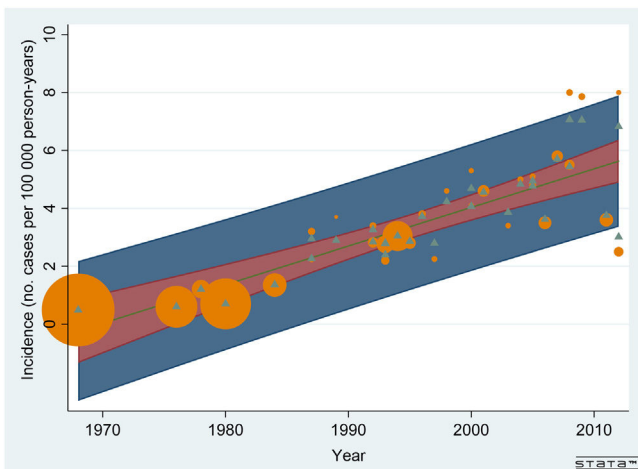


Figure 5 Meta-regression analysis of the impact of time on the incidence of multiple sclerosis. The straight line reflects the predicted incidence rate by year (mid-point of the estimation period), the red area reflects the 95% confidence interval, and the dark blue area reflects the prediction interval. Orange circles indicate the observed incidence rates (size is inversely proportional to total variance), while green triangles reflect empirical Bayes estimates (ie, the predicted incidence rates of the random effects).

studies, in the absence of a real increase in the incidence of MS. However, we cannot rule out the hypothesis that the observed increase in the incidence of MS is real.

Researchers from the Biomedical Research Networking Centre on Neurodegenerative Diseases and the applied epidemiology section of the Spanish National Centre for Epidemiology, in collaboration

with other authors, have recently published a systematic review of studies into the incidence of MS in the European Economic Area.⁷³ This review included 2 studies conducted in Spain (in lower Aragon and Alcoy), which provide serial determinations of the incidence of MS over time. These studies revealed a huge fluctuation in the number of cases per 100 000 person-years, rather than a homogeneous, increasing trend, probably due to the small number of new cases. In Spain, prevalence studies focusing on relatively small areas (30 000-100 000 inhabitants) have been extremely fruitful, as they were able to perform more exhaustive tracking of cases. However, the size of these populations is insufficient to obtain stable rates for incidence studies, a crucial tool for identifying environmental factors potentially linked to the aetiology of the disease. In the rest of Europe, 2 distinct patterns are observed: an increase in incidence in Northern European countries until the mid-1980s, with a subsequent decrease, and a sustained increase in Italy and Greece, with the latter starting at lower incidence rates.⁷³

Other European studies have reported diverging results. The results of the systematic review by Kingwell et al.⁶ are inconclusive, since the included studies were highly heterogeneous in terms of diagnostic criteria and definition of validated cases, and lacked standardised results. Our study also observed considerable methodological differences; data synthesis with such techniques as meta-analysis is therefore not recommended. A more recent study including data from a Danish registry did find a marked increase in the incidence of MS in women over the last 50 years (114%), especially at older ages, whereas incidence in men increased only slightly (30%).⁷⁶ This study benefits from the strengths of multiple sclerosis registries, which unify diagnostic criteria, standardise procedures, and provide extremely valuable information for evaluating temporal trends.

We found a trend toward an association between prevalence/incidence and latitude; however, after considering the year of the study (mid-point of the estimation period), we can neither confirm nor rule out Kurtzke's hypothesis,⁵ since the confidence intervals are very imprecise, though estimators are positive. Fur-

ther studies with greater statistical power should aim to clarify this issue, given the relatively small difference in prevalence and incidence rates between extreme latitudes in Spain.

Our study has a number of limitations. Firstly, we did not adjust rates using a standard population; this may have biased the comparison between regions with different age distributions (for instance, the Canary Islands and Andalusia have younger populations than those of Galicia and Castile-Leon). Some prevalence studies gave detailed data by sex and age group, but this was not the case for incidence studies. Secondly, we did not perform a formal assessment of study quality with a view to performing the corresponding sensitivity analyses. Although a number of validated instruments have been developed for quality assessment of randomised controlled trials and analytical observational studies, such as the Grading of Recommendations Assessment, Development and Evaluation tool,⁷⁷ no similar tools exist for incidence and prevalence studies due to the difficulty of evaluating them. The instrument used by Kingwell et al.⁶ was specifically designed for their study; therefore, it is not validated and its content is relatively inconsistent and of unclear applicability.

One of the strengths of our study is its comprehensiveness, as it includes nearly every study published on the topic, as well as evidence from some unpublished studies. Furthermore, it uses the methods of systematic reviews, although these are less developed for incidence and prevalence studies.

Despite the difficulty of drawing clear conclusions on the temporal trends of prevalence and, especially, incidence rates, our study reveals the existence of a vast network of research groups focusing on MS, which play an essential role in the organisation of healthcare, resource allocation, and the development of aetiological studies. This network may be integrated into a cooperative structure seeking to unify the criteria for case detection and perform a thorough search of all existing cases in the population of interest. This will surely shed light on the real prevalence and incidence of MS and its geographical and temporal variability.

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

- Rejdak K, Jackson S, Giovannoni G. Multiple sclerosis: a practical overview for clinicians. *Br Med Bull*. 2010;95:79–104, <http://dx.doi.org/10.1093/bmb/ldq017>.
- Renoux C. Natural history of multiple sclerosis: long-term prognostic factors. *Neurol Clin*. 2011;29:293–308, <http://dx.doi.org/10.1016/j.ncl.2011.01.006>.
- Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. *Handb Clin Neurol*. 2014;122:231–66, <http://dx.doi.org/10.1016/B978-0-444-52001-2.00010-8>.
- Goodin DS, Khankhanian P, Gourraud PA, Vince N. The nature of genetic and environmental susceptibility to multiple sclerosis. *PLoS One*. 2021;16:e0246157, <http://dx.doi.org/10.1371/journal.pone.0246157>.
- Kurtzke JF. Geographic distribution of multiple sclerosis: an update with special reference to Europe and the Mediterranean region. *Acta Neurol Scand*. 1980;62:65–80, <http://dx.doi.org/10.1111/j.1600-0404.1980.tb03006.x>.
- Kingwell E, Marriott JJ, Jette N, Pringsheim T, Makhani N, Morrow SA, et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *BMC Neurol*. 2013;13:128, <http://dx.doi.org/10.1186/1471-2377-13-128>.
- Pérez-Carmona N, Fernández-Jover E, Sempere AP. Epidemiología de la esclerosis múltiple en España. *Rev Neurol*. 2019;69:32–8.
- Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. *BMC Res Notes*. 2012;5:52, <http://dx.doi.org/10.1186/1756-0500-5-52>.
- Harbord RM, Higgins JP. Meta-regression in Stata. *Stata J*. 2008;8:493–519.
- StataCorp. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC; 2017.
- Oliveras de la Riva C, Aragonés Ollé JM, Mercadé Sobrequés T. Estudio de la incidencia relativa y absoluta de la esclerosis múltiple en nuestra región. *An Med Cir*. 1968;54:13.
- Miró J, Rebollo M, Combarros O, Polo JM, Leno C, Berciano J. Esclerosis múltiple en Cantabria. Estudio retrospectivo de 30 casos. *Rev Clin Esp*. 1984;175:153–6.
- Sosa Enriquez M, Betancor León P, Rosas C, Navarro MC. La esclerosis múltiple en la provincia de Las Palmas. *Arch Neurobiol Madr*. 1983;43:161–6.
- Fernández O, Izquierdo G, Campos VM, Pastor M. Epidemiología de la esclerosis múltiple en la provincia de Málaga (España). Un estudio de prevalencia. *Neurología*. 1986;1:3–5.
- Barduzal Angles S, Oliveros Juste A, Manubens Bertrán JM, Morales Asín F. Esclerosis múltiple: estudio epidemiológico retrospectivo en Aragón (1975–1985). *Neurología*. 1987;2:97–100.
- Antón Aranda E, Martínez-Lage JM, Maraví Petri E, Gállego Culleré J, de Castro P, Villanueva Eusa JA. Epidemiología y aspectos clinicoevolutivos de la esclerosis múltiple en Navarra. *Neurología*. 1991;6:160–9.
- Barranquero A, Martínez-Parra C, Bullón B, Izquierdo G. ¿La esclerosis múltiple es realmente una enfermedad infrecuente en España? *Neurología*. 1988;3:44.
- García JR, Rodríguez S, Sosa Henriquez HM, Batista E, Corujo E, Font de Mora Turon A, et al. Prevalence of multiple sclerosis in Lanzarote (Canary Islands). *Neurology*. 1989;39:265–7.
- Matias-Guiu J, Bolumar F, Martín R, Insa R, Casquero P, Moltó JM, et al. Multiple sclerosis in Spain: an epidemiological study of the Alcoy health region, Valencia. *Acta Neurol Scand*. 1990;81:479–83, <http://dx.doi.org/10.1111/j.1600-0404.1990.tb01003.x>.
- Ruiz Esquerro JJ, Ortín Castañó A, López Alburquerque JT, López García M, Cacho Gutiérrez J. Epidemiología de la esclerosis múltiple (Salamanca y Zamora). *Neurología*. 1988;3 Supl 1:S57.
- Ruiz Ezquerro JJ. Epidemiología de la esclerosis múltiple en Castilla y León. Los estudios de Zamora y Salamanca. In: Matías-Guiu J, Fernández O, editors. *Epidemiología de la esclerosis múltiple en España*. Barcelona: Prous Science; 2001. p. 113–9.
- López-Larrea C, Uría DF, Coto E. HLA antigens in multiple sclerosis of northern Spanish population. *J Neurol Neurosurg Psychiatry*. 1990;53:434–5, <http://dx.doi.org/10.1136/jnnp.53.5.434>.
- Uría DF, Virgala P, Alonso P, Crespo JR, Calatayud T, Arribas JM. Epidemiología de la esclerosis múltiple en Asturias. *Neurología*. 1991;6:41–5.
- Buñil E, Blesa R, Galán I, Dean G. Prevalence of multiple sclerosis in the region of Osona, Catalonia, northern Spain. *J Neurol Neurosurg Psychiatry*. 1995;58:577–81, <http://dx.doi.org/10.1136/jnnp.58.5.577>.
- Fernández O, Luque G, San Román C, Bravo M, Dean G. The prevalence of multiple sclerosis in the Sanitary District of Vélez-Málaga, southern Spain. *Neurology*. 1994;44:425–9, <http://dx.doi.org/10.1212/wnl.44.3.part.1.425>.

26. Navarro X, Bagunyà J, Galán I, Morales MA, Marquillas C, Martín M. Registro de esclerosis múltiple en Cataluña. Evolución 1988–1993. *Rev Neurol Barc.* 1994;22:391–6.
27. Sempere AP, Clavería LE, Duarte J, Coria F, Cabezas C. Multiple sclerosis in Spain. *Neurology.* 1995;45:202, <http://dx.doi.org/10.1212/wnl.45.1.202>.
28. Uriá DF, Abad P, Calatayud MT, Virgala P, Díaz A, Chamizo C, et al. Multiple sclerosis in Gijón health district, Asturias, northern Spain. *Acta Neurol Scand.* 1997;96:375–9, <http://dx.doi.org/10.1111/j.1600-0404.1997.tb00301.x>.
29. Muñoz García D, Lorenzo JR, Gómez-Alonso J. Epidemiología de la esclerosis múltiple en España. In: Matías-Guiu J, Fernández O, editors. *Epidemiología de la esclerosis múltiple en Vigo*. Barcelona: Prous Science; 2001. p. 127–8.
30. Pina MA, Ara JR, Modrego PJ, Morales F, Capablo JL. Prevalence of multiple sclerosis in the sanitary district of Calatayud, Northern Spain: is Spain a zone of high risk for this disease? *Neuroepidemiology.* 1998;17:258–64, <http://dx.doi.org/10.1159/000026178>.
31. Casquero P, Villoslada P, Montalbán X, Torrent M. Frequency of multiple sclerosis in Menorca, Balearic islands, Spain. *Neuroepidemiology.* 2001;20:129–33, <http://dx.doi.org/10.1159/000054772>.
32. Modrego Pardo PJ, Pina Latorre MA, López A, Errea JM. Prevalence of multiple sclerosis in the province of Teruel, Spain. *J Neurol.* 1997;244:182–5, <http://dx.doi.org/10.1007/s004150050070>.
33. Tola MA, Yugueros MI, Fernández-Buey N, Fernández-Herranz R. Prevalence of multiple sclerosis in Valladolid, northern Spain. *J Neurol.* 1999;246:170–7, <http://dx.doi.org/10.1007/s004150050329>.
34. Mallada-Frechín J, Matías-Guiu GJ, Martín R, López-Arlandis JM, Camacho-Cuartero JM, Beltrán I, et al. Prevalencia de la esclerosis múltiple en el área sanitaria de Alcoi. *Rev Neurol.* 2000;30:1131–4.
35. Benito-León J, Martín E, Vela L, Villar ME, Felgueroso B, Marrero C, et al. Multiple sclerosis in Móstoles, central Spain. *Acta Neurol Scand.* 1998;98:238–42, <http://dx.doi.org/10.1111/j.1600-0404.1998.tb07302.x>.
36. Hernández MA. Epidemiology of multiple sclerosis in the Canary Islands (Spain): a study on the island of La Palma. *J Neurol.* 2002;249:1378–81, <http://dx.doi.org/10.1007/s00415-002-0841-y>.
37. Antigüedad AR, Mendibe MM. Epidemiología de la esclerosis múltiple en Vizcaya. In: Matías-Guiu J, Fernández O, editors. *Epidemiología de la esclerosis múltiple en España*. Barcelona: Prous Science; 2001. p. 121–5.
38. García-Gallego A, Morera-Guitart J. Prevalencia y características de la esclerosis múltiple en el distrito sanitario de Marina Alta. *Rev Neurol.* 2002;34:732–7.
39. Moral E, Carmona O, Casado V, Callén A, Martín Ozaeta G, Yélamos AM, et al. Estudio de la incidencia de la esclerosis múltiple en la región sanitaria Costa de Ponent durante quince años consecutivos. *Neurología.* 2002;17:522.
40. Modrego PJ, Pina MA. Trends in prevalence and incidence of multiple sclerosis in Bajo Aragón, Spain. *J Neurol Sci.* 2003;216:89–93, <http://dx.doi.org/10.1016/j.jns.2003.07.007>.
41. Aladro Y, Alemany MJ, Pérez-Vieitez MC, Amela R, Conde M, Reyes MP, et al. Prevalence and incidence of multiple sclerosis in Las Palmas, Canary Islands, Spain. *Neuroepidemiology.* 2005;24:70–5, <http://dx.doi.org/10.1159/000081052>.
42. Ares B, Prieto JM, Lema M, Dapena D, Arias M, Noya M. Prevalence of multiple sclerosis in Santiago de Compostela (Galicia, Spain). *Mult Scler J.* 2007;13:262–4, <http://dx.doi.org/10.1177/1352458506069540>.
43. Hernández-Ramos F. Epidemiología de la esclerosis múltiple en la isla de Lanzarote y sus variaciones en los últimos años. Universidad de Sevilla; 2017.
44. Otero S, Batlle J, Bonaventura I, Brieua L, Buñell E, Cano A, et al. Situación epidemiológica actual de la esclerosis múltiple: pertinencia y puesta en marcha de un registro poblacional de nuevos casos en Cataluña. *Rev Neurol.* 2010;50:623–33.
45. López-Real AM, García-Estévez DA, Ursua-Díaz I, López-Díaz L, Marín-Sánchez M. Epidemiología de la esclerosis múltiple en la ciudad de La Coruña. *Rev Neurol.* 2007;44:628.
46. Fernández O, Fernández V, Guerrero M, León A, López-Madrona JC, Alonso A, et al. Multiple sclerosis prevalence in Malaga, Southern Spain estimated by the capture-recapture method. *Mult Scler J.* 2012;18:372–6, <http://dx.doi.org/10.1177/1352458511421917>.
47. Otero-Romero S, Roura P, Solà J, Altimiras J, Sastre-Garriga J, Nos C, et al. Increase in the prevalence of multiple sclerosis over a 17-year period in Osona, Catalonia, Spain. *Mult Scler J.* 2013;19:245–8, <http://dx.doi.org/10.1177/1352458512444751>.
48. Fernández-Díaz E, Palazón-García E, Gracia-Gil J, Hernández-Fernández F, Díaz-Maroto I, Rallo B, et al. Epidemiología de la esclerosis múltiple en Albacete. *Neurología.* 2010;25:169. *Espec Congr.*
49. Candelieri-Merlicco A, Valero-Delgado F, Martínez-Vidal S, Lastres-Arias MC, Aparicio-Castro E, Toledo-Romero F, et al. Prevalence of multiple sclerosis in Health District III, Murcia, Spain. *Mult Scler Relat Disord.* 2016;9:31–5, <http://dx.doi.org/10.1016/j.msard.2016.06.003>.
50. Bártulos Iglesias M, Marzo Sola ME, Estrella Ruiz LA, Bravo Anguiano Y. Estudio epidemiológico de la esclerosis múltiple en La Rioja. *Neurología.* 2015;30:552–60, <http://dx.doi.org/10.1016/j.nrl.2014.04.016>.
51. Izquierdo G, Venegas A, Sanabria C, Navarro G. Long-term epidemiology of multiple sclerosis in the North-western Seville District. *Acta Neurol Scand.* 2015;132:111–7, <http://dx.doi.org/10.1111/ane.12363>.
52. Batlle Nadal J, Martín Ozaeta G, Mañé Martínez MA, Ortiz Castellón N. Epidemiología de la esclerosis múltiple en la provincia de Tarragona. Registro de población a enero de 2014. *Neurología.* 2014;29:71. *Esp Congr.*
53. Pérez-Pérez S, Eguía Del RP, Domínguez-Mozo MI, García-Martínez MÁ, Zapata-Ramos MF, Torrejón MJ, et al. Epidemiology of multiple sclerosis and vitamin D levels in Lanzarote, Canary Islands, Spain. *PeerJ.* 2019;7:e8235, <http://dx.doi.org/10.7717/peerj.8235>.
54. Costa Arpín E, Naveiro Soneira J, Lema Bouzas M, González Quintela A, Prieto González JM. Epidemiology of multiple sclerosis in Santiago de Compostela (Spain). *Acta Neurol Scand.* 2020;142:267–74, <http://dx.doi.org/10.1111/ane.13265>.
55. Llana González MÁ. Epidemiología de la esclerosis múltiple en el área sanitaria de Ferrol. Universidade da Coruña; 2016.
56. Carreón-Guarnizo E, Andreu-Reinón E, Cerdán-Sánchez M, Carrasco-Torres R, Hernández-Clares R, Prieto-Valiente L, et al. Prevalencia de la esclerosis múltiple en la Región de Murcia. *Rev Neurol.* 2016;62:396–402.
57. García-Estévez DA, Fraga-González C, Ramos-Pacho ME, López-Díaz LM, Pardo-Parrado M, Prieto JM. Prevalencia de la esclerosis múltiple en la ciudad de Ourense, Galicia, noroeste de la Península Ibérica. *Rev Neurol.* 2020;71:19–25.
58. Perez-Carmona N, Gimenez-Martinez J, Borrego-Honrubia C, Sempere AP. Multiple sclerosis prevalence and incidence in San Vicente del Raspeig, Spain. *Mult Scler Relat Disord.* 2019;33:78–81, <http://dx.doi.org/10.1016/j.msard.2019.05.022>.
59. Mallada-Frechín J, Matias-Guiu Guia J, Martín R, López-Arlandis JM, Camacho-Cuartero JM, Beltrán I, et al. Incidencia de la

- esclerosis múltiple en el área sanitaria de Alcoi. Estudio de 12 años (1986–1997). *Rev Neurol*. 2000;30:1128–31.
60. Otero-Romero S, Ramio-Torrenta L, Pericot I, Carmona O, Perkal H, Saiz A, et al. Onset-adjusted incidence of multiple sclerosis in the Girona province (Spain): evidence of increasing risk in the south of Europe. *J Neurol Sci*. 2015;359:146–50, <http://dx.doi.org/10.1016/j.jns.2015.10.042>.
 61. Martín R, Matías-Guiu J, Calatayud E, Sola D, Aranaz J. Prevalencia de la esclerosis múltiple en España. *Neurología*. 1988;3:166–7.
 62. Rivera C. Epidemiología de la esclerosis múltiple en el área sanitaria de Alcoi. Estudio de prevalencia e incidencia desde 1986–1991. Universidad de Alicante; 1991.
 63. Martín R, Matías-Guiu J, Calatayud E, Molto JM, Insa R, Aranaz J. Epidemiología de la esclerosis múltiple en la comarca de Alcoi (Alicante). *Neurología*. 1998;3 Supl 1:56–7.
 64. Bufill E, Blesa R. High prevalence of multiple sclerosis in Catalanian area. In: International MS Conference. 1988.
 65. Callén A, Turbau J, Martínez Yélamos A, Martín Ozaeta G, Hernández Regadera, Arbizu T. Estudio de la incidencia de la esclerosis múltiple en la región sanitaria Costa de Ponent durante diez años consecutivos. *Neurología*. 1999;14:79.
 66. Callén A, Turbau J, Martín G, Martínez-Yélamos A, Hernández JJ, Casado V, et al. Incidencia de la esclerosis múltiple en la región sanitaria Costa de Ponent (Barcelona). In: Matías-Guiu J, Fernández O, editors. Epidemiología de la esclerosis múltiple en España. Barcelona: Prous Science; 2001. p. 93–9.
 67. García-Estévez DA, Marín-Sánchez M, López-Real A, Ursúa-Díaz I, Lema-Facal T. Descriptive epidemiology of multiple sclerosis in La Coruña (northwest Spain). *Mult Scler J*. 2006;12 Supl 1:S1–228. Abstract P477.
 68. Fraga González C. Epidemiología de la esclerosis múltiple en la ciudad de Ourense. Universidad de Vigo; 2018.
 69. de Sá J, Alcalde-Cabero E, Almazán-Isla J, Sempere A, de Pedro-Cuesta J. Capture-recapture as a potentially useful procedure for assessing prevalence of multiple sclerosis: methodologic exercise using Portuguese data. *Neuroepidemiology*. 2012;38:209–16, <http://dx.doi.org/10.1159/000337534>.
 70. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol*. 1983;13:227–31, <http://dx.doi.org/10.1002/ana.410130302>.
 71. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*. 2001;50:121–7, <http://dx.doi.org/10.1002/ana.1032>.
 72. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69:292–302, <http://dx.doi.org/10.1002/ana.22366>.
 73. Alcalde-Cabero E, Almazán-Isla J, García-Merino A, de Sá J, de Pedro-Cuesta J. Incidence of multiple sclerosis among European Economic Area populations, 1985–2009: the framework for monitoring. *BMC Neurol*. 2013;13:58, <http://dx.doi.org/10.1186/1471-2377-13-58>.
 74. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444–52, <http://dx.doi.org/10.1212/wnl.33.11.1444>.
 75. Kingwell E, Leray E, Zhu F, Petkau J, Edan G, Oger J, et al. Multiple sclerosis: effect of beta interferon treatment on survival. *Brain J Neurol*. 2019;142:1324–33, <http://dx.doi.org/10.1093/brain/awz055>.
 76. Koch-Henriksen N, Thygesen LC, Stenager E, Laursen B, Magyari M. Incidence of MS has increased markedly over six decades in Denmark particularly with late onset and in women. *Neurology*. 2018;90:e1954–63, <http://dx.doi.org/10.1212/WNL.0000000000005612>.
 77. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–6, <http://dx.doi.org/10.1136/bmj.39489.470347.AD>.