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Geographic variations of multiple sclerosis prevalence in France: The latitude gradient is not uniform depending on the socioeconomic status of the studied population

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Abstract

Background: In France, two studies analysed multiple sclerosis prevalence nationwide: one was carried out in farmers, and the other one in employees. A south-north gradient of prevalence was found solely in farmers.

Objective: In order to better describe the latitude gradient in France, which is not uniform depending on the studied population, we assessed whether a gradient exists in another population than farmers and employees: independent workers. The same methods of case ascertainment have been used.

Methods: Altogether 4,165,903 persons insured by the French health insurance scheme for independent workers were included. We searched the database for (a) long term disease status 'multiple sclerosis', (b) domicile, (c) gender and (d) age.

Results: A total of 4182 cases of multiple sclerosis were registered giving a prevalence of 100.39/100,000. Adjustment by age and sex and spatial smoothing with a Bayesian analysis showed a gradual increase of prevalence from the southwest to the northeast of France. Standardised morbidity ratio was correlated with latitude and longitude ($p<0.0001$; $p=0.0031$; adjusted $R^2=0.3038$).

Conclusion: A discrepancy of geographic distribution between farmers and independent workers on the one hand and employees on the other cannot be attributable to environment. Assuming that socioeconomic status by itself is not associated with multiple sclerosis risk, employees' geographic mobility at adulthood for professional reasons could have interfered with the gradient effect.

***Keywords*:** Multiple sclerosis, prevalence, Bayesian analysis, geographic distribution, epidemiology, socioeconomic status

Introduction

In Europe and North America the previously reported latitudinal gradient of incidence or prevalence for multiple sclerosis seems to have disappeared or decreased by comparison with prior published series of geographic data.[1–4] In France, a previous study found a southwest-northeast gradient of prevalence in farmers,[5] and a subsequent study did not find such a gradient in employees.[6] Change in such a short period of time cannot be attributable to improvement in diagnosis accuracy or case ascertainment, nor to a change in environmental factors. Labour mobility might be of relevance, economic migrations in employees diluting the spatial repartition of multiple sclerosis susceptibility genes.[4] Geographic mobility for job search could have interfered with the gradient effect as migration at adulthood (for instance for professional reasons) may contribute to modifying multiple sclerosis prevalence where migrants have moved; the migrants may bring (or not bring) the latent disease along with them when moving at adulthood, as the risk

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of developing (or not developing) multiple sclerosis has already been largely determined by the age of 15 years.[7,8]

In order to better describe the latitude gradient in France and to show that it is not uniform depending on the socioeconomic status of the studied population, we assessed whether the southwest-northeast gradient of multiple sclerosis that disappeared in employees, and that still exists in farmers, persists in another population which is also more sedentary than the employees: independent workers and their families.

Materials and methods

Setting and target population

The health insurance fund for independent workers or *Régime Social des Indépendants* (RSI) is the third main statutory health insurance scheme in France. It is dedicated only to independent workers and their families (i.e. independent workers from small businesses in the manufacturing industry, craft industry and commercial industry, as well as workers from learned professions). It covers 6% of the French population, spread all over the French territory. French territory is divided in 101 French administrative areas called *départements* (named 'departments' hereafter) including islands and overseas departments. Neighbouring departments are grouped into regions. The RSI covers all the departments and regions of the French territory. The target population was the population covered in the course of 2013.

Study type

Our study is a cross-sectional study carried out on two national databases based on the whole of France:

1. TITAM. The administrative database of benefits in kind and in cash provided by the health insurance (named 'benefit' hereafter).
2. ARCHIMED. The medico-administrative database of the insured who are entitled, through health insurance, to exemption from their side copayment due to a long-term disease status granted by the French National Health Insurance System.[a]

Statistical unit

The statistical unit is the person who received the benefit. It is identified in the database by the insured person's single social security number and the beneficiary's ranking, if the person who received the benefit is not the actual insured person but one of their beneficiaries.

Included population

All persons who received a benefit in 2013 are included in the study, i.e. 4,165,903 persons.

Outcome

The outcome was the number of included persons who had, or had had, a long-term disease status[a] of multiple sclerosis granted by the French National Health Insurance System. Those persons are identified in the medico-administrative database of long-term disease status as having, or having had, multiple sclerosis, whatever the date of recognition as a long-term disease before 31 December 2013, even if the long-term disease agreement has not been renewed till this date (expired long-term disease agreements which are not renewed are kept in the medico-administrative database as long as the person is affiliated to RSI, even if they do not receive any benefit at all for years or decades after disease onset). Crude prevalence rates were calculated as the number of persons who received a benefit of any kind in 2013 and had, or had had, a long-term disease status for multiple sclerosis granted by the French National Health Insurance System per 100,000 persons who received a benefit of any kind in 2013.

We calculated the crude prevalence rates in each modality of the independent variables.

Regional level (including islands and overseas departments). Pearson correlation was used to examine the relationship of crude prevalence rate and decimal degrees of north latitude (in absolute terms to take into account the southern hemisphere). Latitudes were those of capital cities of the 28 regions (*préfectures de region*).

[a]Decree n°2011–77 of January 19th 2011 updating the list and medical criteria used for the definition of diseases giving right to the exemption of copayment by the insured party (JORF n°0017 of January 21st 2011 page 1287 text n° 20) ; medical criteria used for the definition of the long term disease 'multiple sclerosis'. Multiple sclerosis is subject to the exemption of copayment by the insured party
— when a disease-modifying immunomodulatory drug is being prescribed as the outcome of the medical check-up, even in the absence of permanent disability;
— in case of a permanent disability (sometimes only consisting in asthenia or cognitive disturbances) requiring symptomatic treatment and justifying long term treatment)
Initial exemption of copayment is given for 5 years, extendable.

Departmental level (islands and overseas departments excluded). We applied the indirect method of standardisation: we calculated the expected number of cases in each department of France if they had the same age and sex-specific prevalence rates as the whole included population; then we divided the observed number of cases by the expected number of cases to provide the crude standardised morbidity ratio (SMR) in each department.

A spatial smoothing of the crude SMRs was performed accounting for differences in department size and their spatial correlation – adjacent departments may not be independent as their inhabitants probably share the same risk factors for multiple sclerosis. To that purpose, a Bayesian model was used.[9] This spatial smoothing reassessed the local values: the smaller the number of observed cases in a department, the more the smoothed value was influenced by the national reference value. It also took into consideration a spatial component by borrowing strength from neighbouring departments using a contiguity matrix. The extent of smoothing was determined by the size of the crude SMR, its precision and the underlying relative risk distribution. Thus the extent of smoothing was totally determined by the data.[10]

However this mapping method is most useful for capturing gradual regional changes in disease rates and is less useful in detecting abrupt localised changes indicative of clustering.[11] So, a SMR spatial association measurement was also implemented using the G statistic.[12] The G statistic (Getis-Ord Gi) identifies statistically significant spatial clusters of high values (hot spots) and low values (cold spots), highlighting the existence of spatial structures. To create a hot spot, the territory concerned with respectively high or low value of the SMR must be surrounded by other entities also associated with high or low values.

In addition, a multiple linear regression model (ordinary least squares (OLS)) was used to examine the relationship of crude SMR with latitude and longitude. Latitudes and longitudes were those of capital cities of the departments (*préfectures de département*). As an outlier the department of Lozère was excluded.

Independent variable (varying factors)

1. Insured party's age in 2013 broken down by age groups.
2. Insured party's gender: men, women.
3. Insured party's domicile in 2013 broken down by department and region of France, with the decimal degrees of latitude and longitude of the capital cities of each department and region.

Statistical analysis tools

1. ArcGIS 10.1 (which includes a graphical user interface application called ArcMap) for estimate of spatial structures and cartographic representations.[9–12]
2. SAS 9.3 for data processing: calculation of standardised morbidity ratio, non-spatial and spatial smoothing (GLIMMIX procedure performs estimation and statistical inference for generalized linear mixed models or GLMMs).

Ethics

The data were entirely anonymised before being sent for analysis to the research group.

For ethics purposes, the database study was approved by the Commission nationale de l'informatique et des libertés (CNIL) (French Data Protection Authority) (dossier no. 342521, amendment 2) and the study protocol was approved by the in-house RSI committee responsible for the research.

Results

Description of the included population

Demographic characteristics are shown in Tables 1 and 2.

The included population was made up of 4,165,903 persons of which 4182 had or had had a long term disease status for multiple sclerosis granted by the French National Health Insurance System. Their mean age was 42.69 years (standard deviation (SD) 23.02) and 52.44 years (SD 14.25) with 43.01% and 60.19% of women respectively. They were living in 28 regions and 101 departments. The smallest region (which is also a department) was Saint Pierre And Miquelon (one person; 0.00%) and the largest region was Ile-De-France (625,725 persons; 15.02%); the largest department was Paris (180,436 persons; 4.33%) (Tables 1 and 2).

Multiple sclerosis prevalence in the included population

Crude prevalence rates. Among RSI beneficiaries, multiple sclerosis national prevalence in France in 2013 was 4182 cases for 4,165,903 beneficiaries regardless of age, i.e. 100.39/100,000 beneficiaries (95% confidence interval (CI): 97.39–103.47), 140.48/100,000 beneficiaries in women (95% CI:

Table 1. Multiple sclerosis prevalence in France; 4,165,903 beneficiaries in 2013 including 4182 prevalent cases; crude prevalence rates by domicile region, age, and gender.

Domicile regions sorted by increasing multiple sclerosis crude prevalence rates	Capital city of the region	Decimal degrees of north latitude of the capital city of the region in absolute terms	Included population ($n = 4{,}165{,}903$)	Included population with the long term disease status 'multiple sclerosis' ($n = 4182$)	Crude prevalence rates per 100,000 persons
Guyane	Cayenne	4.9224	8568	0	0
Not filled			5625	0	0
Mayotte	Mamoudzou	12.7809	7	0	0
Saint Pierre et Miquelon	Saint Pierre	46.7786	1	0	0
Reunion	Saint-Denis	20.9203	47,197	9	19
Martinique	Fort-de-France	14.6161	19,446	7	36
Guadeloupe	Basse-Terre	17.3026	28,582	11	38
Corse	Ajaccio	41.9192	25,231	21	1st quartile 83
Languedoc-Roussillon	Montpellier	43.6108	232,144	201	87
Provence-Alpes-Cote d'Azur	Marseille	43.2965	427,068	379	89
Aquitaine	Bordeaux	44.8378	267,659	242	90
Pays-de-Loire	Nantes	47.2184	229,910	212	92
Rhone-Alpes	Lyon	45.7640	455,672	421	92
Midi-Pyrenees	Toulouse	43.6047	226,029	213	94
Ile-de-France	Paris	48.8566	625,725	626	100
Auvergne	Clermont-Ferrand	45.7772	97,337	100	103
Limousin	Limoges	45.8336	50,735	53	104
Poitou-Charentes	Poitiers	46.5802	133,370	140	105
Centre	Orléans	47.9030	150,436	162	108
Picardie	Amiens	49.8941	95,044	105	110
Bretagne	Rennes	48.1173	226,053	252	111
Haute-Normandie	Rouen	49.4432	98,206	113	115
Bourgogne	Dijon	47.3220	105,501	128	3rd quartile 121
Basse-Normandie	Caen	49.1829	97,892	119	122
Alsace	Strasbourg	48.5734	83,052	102	123
Nord-pas-de-Calais	Lille	50.6293	185,288	236	127
Lorraine	Metz	49.1193	107,337	139	129
Franche-Comte	Besançon	47.2378	66,724	91	136
Champagne-ardenne	Châlons-en-Champagne	48.9567	70,064	100	143
Age, years					
Mean			42.69	52.44	
Standard deviation			23.02	14.25	
Median			44.00	52.00	
Minimum			0	0	

(continued)

Table 1. Continued

Domicile regions sorted by increasing multiple sclerosis crude prevalence rates	Capital city of the region	Decimal degrees of north latitude of the capital city of the region in absolute terms	Included population ($n = 4{,}165{,}903$)	Included population with the long term disease status 'multiple sclerosis' ($n = 4182$)	Crude prevalence rates per 100,000 persons
Maximum			113	101	
0–13			637738	4	1
14–29			544871	181	33
30–39			540281	611	113
40–49			753382	1010	134
50–59			671542	1037	154
60–69			510889	845	165
70–79			265782	359	135
80 and above			241418	135	56
Gender					
Women			1791771	2517	140
Men			2374132	1665	70

Source: Health insurance fund for independent workers – whole of France.

Table 2. Multiple sclerosis prevalence in France; 4,165,903 beneficiaries in 2013 including 4182 prevalent cases; crude prevalence rates by domicile department.

			Included population ($n = 4{,}165{,}903$)	Included population with the long term disease status 'multiple sclerosis' ($n = 4182$)	Crude prevalence rates per 100,000 persons
Domicile department sorted by increasing multiple sclerosis crude prevalence rates (zip-code and name)					
	973	Guyane	8568	0	0
	975	Saint Pierre et Miquelon	1	0	0
	976	Mayotte	7	0	0
	Not filled	Not filled	5625	0	0
	974	Reunion	47,197	9	19
	972	Martinique	19,446	7	36
	971	Guadeloupe	28,582	11	38
	11	Aude	30,735	13	42
	53	Mayenne	18,037	12	67
	13	Bouches du Rhone	135,382	93	69
	82	Tarn et Garonne	20,239	14	69
	32	Gers	15,649	11	10th percentile 70
	73	Savoie	39,580	28	71
	40	Landes	31,520	23	73
	65	Hautes Pyrenees	18,844	15	80
	7	Ardeche	24,784	20	81
	79	Deux Sevres	23,470	19	81
	63	Puy de Dome	43,224	35	81
	26	Drome	37,721	31	82
	34	Herault	95,182	79	83
	20	Corse	25,231	21	83
	64	Pyrenees Atlantiques	53,471	45	84
	24	Dordogne	37,866	32	85
	49	Maine et Loire	47,228	40	85
	38	Isere	81,585	70	86
	92	Hauts de Seine	85,618	74	86
	12	Aveyron	24,035	21	87
	93	Seine Saint Denis	60,083	53	88
	19	Correze	18,049	16	89
	1	Ain	37,962	34	90
	72	Sarthe	30,096	27	90
	30	Gard	60,747	55	91
	31	Haute Garonne	89,346	82	92
	80	Somme	28,124	26	92
	9	Ariege	12,772	12	94
	95	Val d'Oise	49,529	47	95
	54	Meurthe et Moselle	35,504	34	96
	74	Haute Savoie	64,592	62	96
	84	Vaucluse	47,917	46	96

(continued)

Table 2. Continued

		Included population ($n = 4{,}165{,}903$)	Included population with the long term disease status 'multiple sclerosis' ($n = 4182$)	Crude prevalence rates per 100,000 persons
33	Gironde	118,296	114	96
83	Var	101,538	98	97
66	Pyrenees Orientales	39,325	38	97
56	Morbihan	57,544	56	97
44	Loire Atlantique	86,840	85	98
6	Alpes Maritimes	113,197	111	98
78	Yvelines	66,721	66	99
94	Val de Marne	66,071	66	100
71	Saone et Loire	37,028	37	100
85	Vendee	47,709	48	101
28	Eure et Loir	22,734	23	101
4	Alpes de Haute Provence	14,795	15	101
45	Loiret	36,257	37	102
55	Meuse	9765	10	102
69	Rhone	117,866	122	104
37	Indre et Loire	36,652	38	104
10	Aube	16,308	17	104
42	Loire	51,582	54	105
16	Charente	26,745	28	105
77	Seine et Marne	64,656	68	105
47	Lot et Garonne	26,506	28	106
87	Haute Vienne	23,638	25	106
60	Oise	40,453	43	106
75	Paris	180,436	192	106
50	Manche	32,740	35	107
58	Nievre	13,760	15	109
35	Ille et Vilaine	65,363	72	110
17	Charente Maritime	56,642	63	111
15	Cantal	12,528	14	112
5	Hautes Alpes	14,239	16	112
76	Seine Maritime	63,944	72	113
86	Vienne	26,513	30	113
18	Cher	19,401	22	113
91	Essonne	52,611	60	114
81	Tarn	29,768	34	114
36	Indre	13,975	16	114
68	Haut Rhin	32,083	37	115
8	Ardennes	15,597	18	115
59	Nord	116,070	134	115
29	Finistere	58,681	68	116
70	Haute Saone	14,497	17	117
3	Allier	24,249	29	120
27	Eure	34,262	41	120
41	Loir et Cher	21,417	26	121
61	Orne	19,090	24	126
22	Cotes d'Armor	44,465	56	126

(continued)

Table 2. Continued

		Included population ($n = 4{,}165{,}903$)	Included population with the long term disease status 'multiple sclerosis' ($n = 4182$)	Crude prevalence rates per 100,000 persons
43	Haute Loire	17,336	22	127
67	Bas Rhin	50,969	65	128
14	Calvados	46,062	60	130
23	Creuse	9048	12	133
21	Cote d'Or	32,704	44	135
2	Aisne	26,467	36	136
39	Jura	16,817	23	90th percentile 137
90	Territoire de Belfort	6356	9	142
25	Doubs	29,054	42	145
89	Yonne	22,009	32	145
62	Pas de Calais	69,218	102	147
52	Haute Marne	9457	14	148
57	Moselle	38,629	58	150
46	Lot	15,376	24	156
88	Vosges	23,439	37	158
51	Marne	28,702	51	178
48	Lozere	6155	16	260

Source: Health insurance fund for independent workers – whole of France.

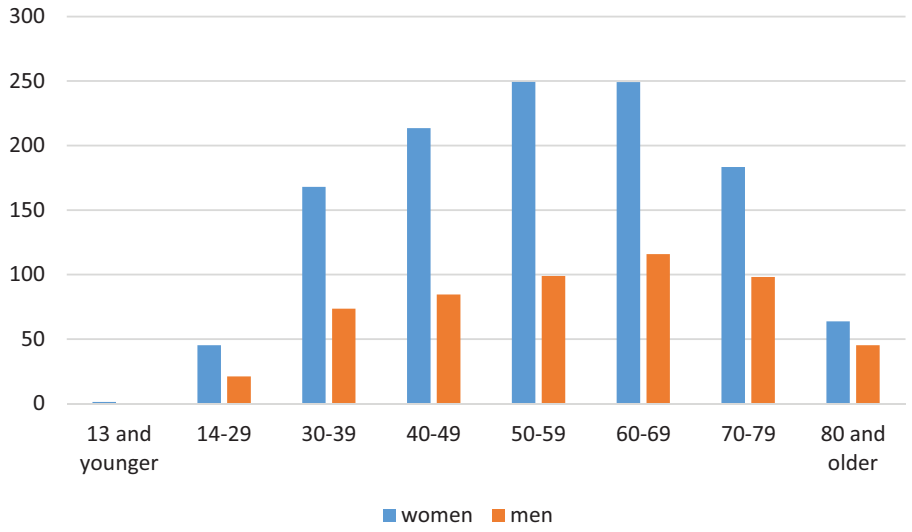

Figure 1. Multiple sclerosis prevalence in France; 4,165,903 beneficiaries in 2013 including 4182 prevalent cases; crude prevalence rates per 100,000 persons by age and gender.
Source: Health insurance fund for independent workers – whole of France.

135.10–146.07) and 70.13/100,000 beneficiaries in men (95% CI: 66.84–73.58).

The prevalence rates according to age and sex are shown in Figure 1.

RSI population size, crude prevalence rate, and decimal degrees of latitude in absolute terms for each of the 28 regions of the French territory are given in Table 1. Latitude (in absolute terms to take into account the southern hemisphere) was strongly

correlated with crude prevalence rate ($r = 0.68$, $p < 0.0001$) in the 28 regions.

Regions where multiple sclerosis prevalence was below the 1st quartile (84.91/100,000) and regions where multiple sclerosis prevalence was above the 3rd quartile (118.20/100,000) are shown in Table 1.

Departments where multiple sclerosis prevalence was equal or below the 10th percentile (70.29/100,000) and departments where multiple sclerosis prevalence was equal or above the 90th percentile (136.77/100,000) are shown in Table 2.

SMR. The following analyses were performed excluding islands and overseas departments.

We mapped the crude SMRs at the French department level (Figure 2(a)).

The Bayesian spatial smoothing of the crude SMRs captured the gradual regional changes in disease rates, revealing an obvious southwest/northeast gradient that visually clearly appeared when the smoothed SMRs were mapped (Figure 2(b)).

Two spatial structures with similar levels of SMR, were highlighted in Figure 3: a spatial cluster of low values (cold spots with a GiZScore below −2.58 SD) in the southwest for Haute Garonne and Gers and a spatial cluster of high values (hot spots with a GiZScore above + 2.58 SD) in the northeast for Territoire de Belfort, Haute Saone, Haute Marne and Aube.

Confirming the visual approach, the OLS multiple linear regression model showed the existence of a south-north effect and a west-east side effect. Crude SMR was correlated with latitude ($p < 0.0001$) and with longitude ($p = 0.0031$) in the departments of France: adjusted $R^2 = 0.3038$; regression equation:

$$\text{SMR predicted} = -1.618 + 0.056 \times \text{latitude} + 0.023 \times \text{longitude}$$

The OLS simple linear regression model, assessing the association of crude SMR with latitude, highlights the south-north effect: $p < 0.0001$; adjusted $R^2 = 0.2408$; regression equation:

$$\text{SMR predicted} = -1.476 + 0.054 \times \text{latitude}$$

Figure 4 shows the model fit and summarises some of the statistics.

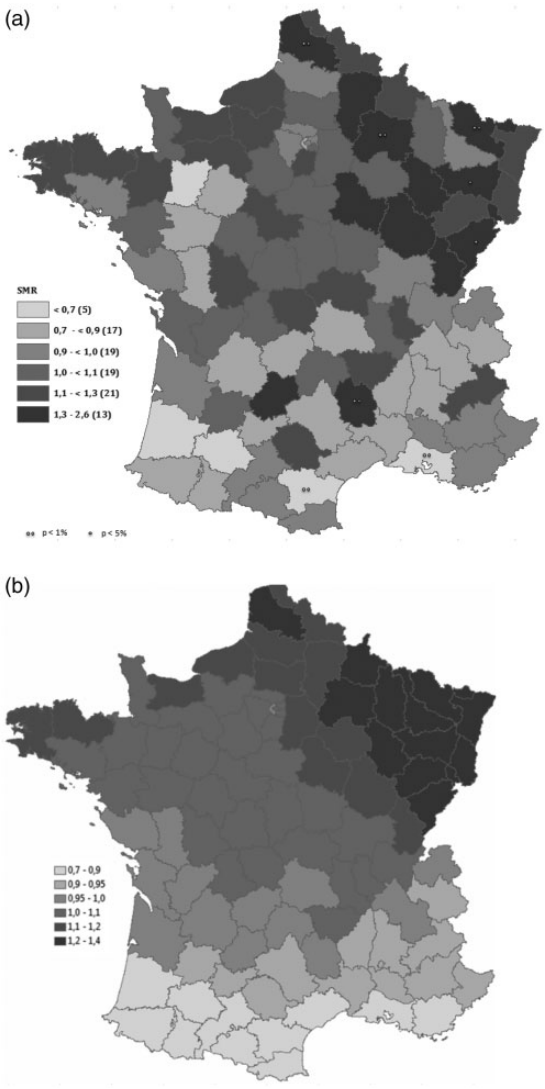

Figure 2. Multiple sclerosis standardised prevalence ratio for each department of France; 4,165,903 beneficiaries in 2013 including 4182 prevalent cases: (a) crude standardised morbidity ratios (SMRs); (b) smoothed SMRs. Islands and overseas departments are not shown.
Source: Health insurance fund for independent workers – whole of France.

Discussion

Analysing 4,165,903 independents workers and their families out of the 65,543,000 inhabitants of France (6%), our study completes the two previous French studies carried out in farmers and in employees (respectively 5% and 87% of the French population) and thus gives a complete overview of multiple sclerosis prevalence in France.[5,6]

Accounting for the age, sex, size difference and autocorrelation between geographic entities our study

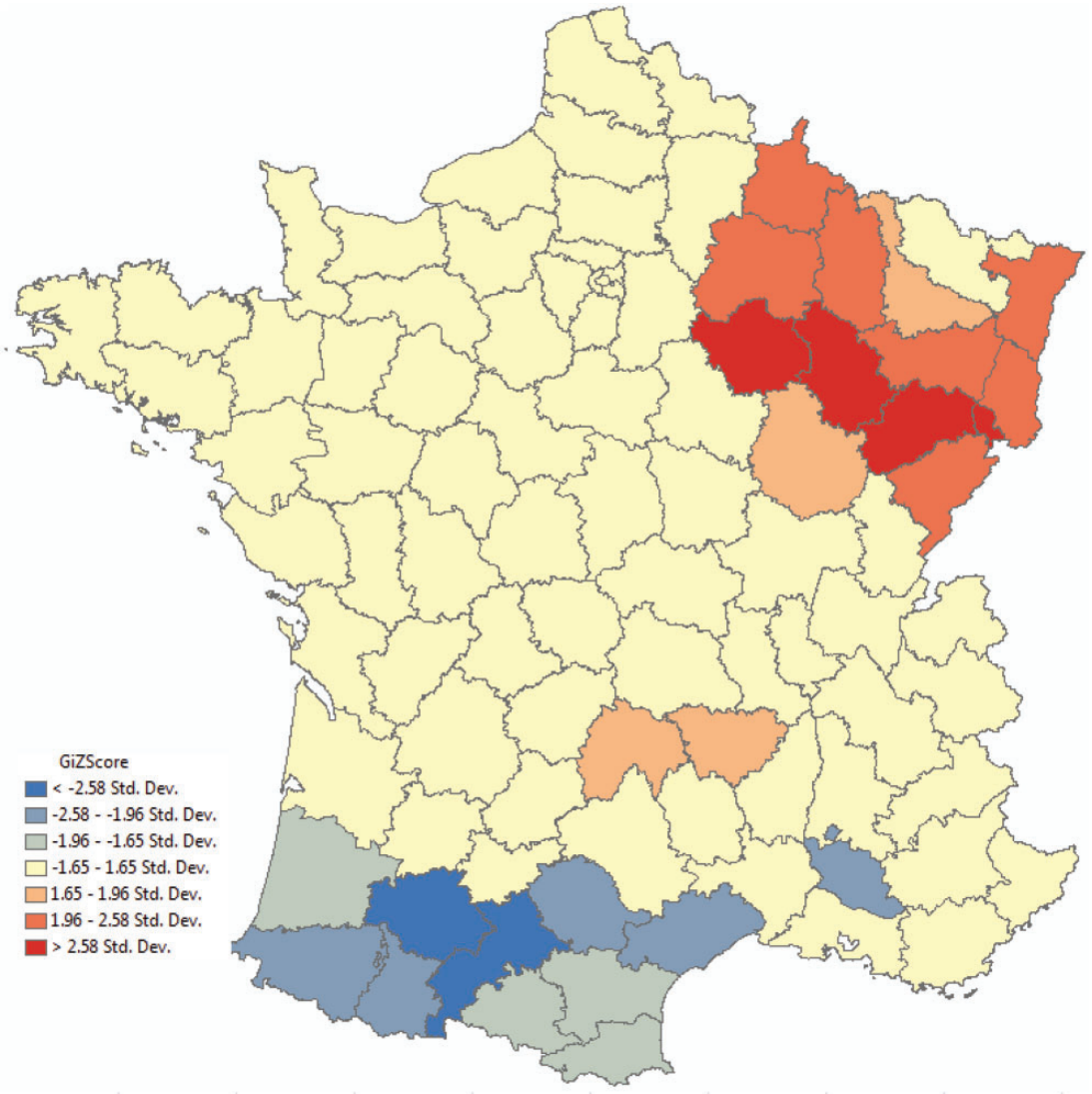

Figure 3. Multiple sclerosis standardised prevalence ratio for each department of France; 4,165,903 beneficiaries in 2013 including 4182 prevalent cases. Standardised morbidity ratio (SMR) spatial association measurement using the G statistic detecting spatial disease clustering (islands and overseas departments are not shown). Source: Health insurance fund for independent workers – whole of France.

found a latitudinal gradient of prevalence in the population of independents workers and their families, similarly to that which was found for farmers and their families,[5] but contrary to findings for employees and their families.[6] Three explanations can be proposed for the modification of the gradient effect in employees: compared to the other two populations, they are (a) younger, which implies that the onset of the disease is more recent; (b) more prone to move for professional reasons (Figure 5) as farmers are attached to their land and independents can create their own employment locally (geographic mobility in adulthood interferes with the gradient effect);[4] and (c) less exposed to outdoor work (ultraviolet (UV) radiation gradient over France also interferes).[13–17]

Moreover our study found a geographic clustering of the disease similar to that which was already found by Kurtzke and Delasnerie-Lauprêtre in 1986, indicating geographic stability of the clusters over time.[18] It is therefore unlikely that the observed change in geography of multiple sclerosis for the population of employees in France was due to a change in an environmental factor as it would have affected the independent and agricultural workers populations in the same way. Nor can it be due to a difference in the level of disease investigation or a better accuracy

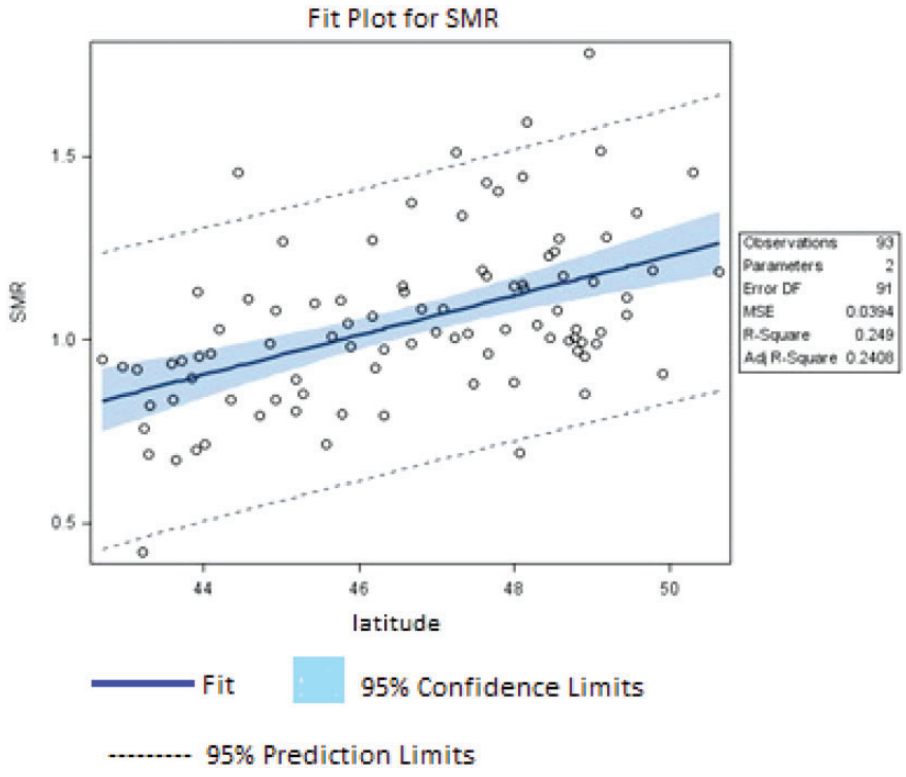

Figure 4. Fit plot showing the model fit and summarising some of the statistics, for the simple linear regression model assessing the association of multiple sclerosis standardised prevalence ratio (SMR) with latitude (degrees north, based on prefecture cities), for each department of France (islands and overseas departments excluded).
Source: Health insurance fund for independent workers – whole of France.

Figure 5. Departmental mobility of French populations according to their status (farmer, independent worker, employee).
Source: Institut national de la statistique et des études économiques (INSEE), 2008.

in the survey methodology, as the same methods of case ascertainment have been used. Geographic mobility for job search or other professional reasons could have diluted the geographical repartition of prevalent cases in the population of employees.

In our study, the six departments with the lowest multiple sclerosis crude prevalence rates are islands or overseas departments. They present a high rate of inhabitants born outside metropolitan France, a high amount of sunshine, and the smallest numeric values of degrees of latitude in absolute terms (excluding Saint Pierre and Miquelon) (Table 1). This was not unexpected, given the lower frequencies of high-risk alleles for multiple sclerosis (e.g. In the human leukocyte antigen (HLA) class II group of genes, statistically, an association of multiple sclerosis with the HLA-DRB1*15:01-HLA-DQB1 *06:02 haplotype has been demonstrated in northern European populations. Multiple sclerosis in African populations is characterized by greater haplotypic diversity and distinct patterns of linkage disequilibrium compared with northern Europeans.) in non-European-descent populations, the link between sun exposure and prevalence, and the significant positive correlation between latitude and prevalence worldwide.[13–17,19]

In the study on salaried workers, the two regions with the lowest smoothed relative risk of multiple sclerosis prevalence (i.e. Ile de France and Provence Alpes Côte d'Azur) present a high non-Caucasian population share.[4,6] A study conducted in the UK found the lowest multiple sclerosis prevalence rates in geographic areas where the non-UK born population share was the highest.[20]

A potential relationship between past exposure to sun and risk of multiple sclerosis has been observed by a number of authors.[13–17] So if multiple sclerosis was due to both genetics and environmental factors before adulthood,[7,21] it would be of interest to be aware of each patient's birth place, besides their residence, in order to diminish the impact of migration flows on the geographic gradient; this could be the subject of another study.

To compare our findings with other results in the literature, it is important to note that there are two different types of studies: those using primary data from medical records, and those, as in our study, using secondary administrative data.

The first type of studies estimated multiple sclerosis prevalence to be (a) between 128 and 171/100,000 in Brittany[22] (vs 132/100,000 in our study), (b) 188.2/100,000 in Lorraine[23] (vs 153/100,000 in our study), and (c) between 110 and 149/100,000 in Haute Garonne[24] (vs 109/100,000 in our study). The second type of study estimated multiple sclerosis prevalence to be (a) 65/100,000 in France in agricultural workers[5] (vs 100.39/100,000 in our study) and (b) 94/100,000 in France in employees[6] (vs 100.39/100,000 in our study). By comparing results from our study to these two previous studies using the same type of administrative data, there appears to be a temporal increase in multiple sclerosis prevalence although the increase observed could also be related to differences in the analysed populations.

Some authors reckon that at disease onset, during a period of a few months to several decades, disability results from focal inflammation (so that during this period of time immunomodulatory drugs are effective against disability). Thereafter, whatever the duration of this first phase, a diffuse degenerative process takes over for approximately seven years, with progression of irreversible disability (still with no therapeutic hope but for which treatments, to protect from neurodegeneration and enhance repair, are in phase III of clinical research).[25–29] Multiple sclerosis cases in our study are taken into account in the two phases of the disease, since recognition as a long-term disease status, with entitlement to exemption of copayment, requires either being treated with immunomodulatory drugs or permanent disability.[b] Although we could not determine individually to which phase of the disease our cases belonged, nevertheless we observed the highest relative frequency of prevalent cases, for women, in the 50–59 year-old age class and, for men, in the 60–69 year-old age class, which corresponds

[b]Decree n°2011-77 of January 19th 2011 updating the list and medical criteria used for the definition of diseases giving right to the exemption of copayment by the insured party (JORF n°0017 of January 21st 2011 page 1287 text n° 20); medical criteria used for the definition of the long term disease 'multiple sclerosis'. Multiple sclerosis is subject to the exemption of copayment by the insured party
— when a disease-modifying immunomodulatory drug is being prescribed as the outcome of the medical check-up, even in the absence of permanent disability;
— in case of a permanent disability (sometimes only consisting in asthenia or cognitive disturbances) requiring symptomatic treatment and justifying long term treatment)
Initial exemption of copayment is given for 5 years, extendable.

respectively to the median age to reach Kurtzke Disability Status Scale[c] (DSS) level of DSS 6 (women) and DSS 7 (men) according to the literature[30] (Figure 1), two scores corresponding to the second phase of the disease (diffuse neurodegenerative process).[25,26]

Limitations of the current approach

The current approach, using claims by the insured party for recognition of a long term disease status, may have ignored clinically isolated syndromes as long as they do not respond to the administrative definition of a long term disease entitling to exemption of co-payment by the insured party.[2] However, given that multiple sclerosis in itself, by its own natural history alone, entirely responds to the definition of a long term disease, as soon as a clinically definite multiple sclerosis has developed, the chances are high that the claim was made by the insured party; if so, whatever the clinical course of the disease at that time, this claim would have been immediately granted by RSI, even if it is a newly diagnosed case, since the disease is deemed to be a long-term disease and considered as such by the RSI.

Insured parties who did not perceive any benefit at all during the whole year 2013 were not included in our study (neither in the numerator nor in the denominator). It was assumed that they did not represent a significant part of the population affiliated to the health insurance system as benefits cover the entire spectrum of care, even for the most common diseases.

Given the risk of ecological fallacy, ecological data such as mobility, as a group, of farmers, employees, or independents, are limited in their ability to postulate conclusions at the individual level.

Conclusion

In France, in more sedentary and more exposed to outdoor work populations than employees, like farmers and independent workers, the north-south gradient of multiple sclerosis still exists while it has disappeared in employees. If we admit that the risk of developing multiple sclerosis is determined during childhood or adolescence and is not associated with socioeconomic status by itself,[31,32] our findings support the assumption that geographic mobility for job search or for professional reasons at adulthood could influence the latitudinal gradient of prevalence for multiple sclerosis. The findings suggest that labour mobility could play a role in altering the north-south gradient that exists in France and more broadly that migrations could explain the recent observations of disappearance or decrease of the north-south gradient of multiple sclerosis in Europe and North America.

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Conflicts of interest

None declared.

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[c]Kurtzke Disability Status Scale (DSS). Kurtzke scale is used to determine MS disability status. A score of 4 shows a limited walking ability but without aid or rest of more than 500m. A score of 6 shows the ability to walk with unilateral support no more than 100m without rest. A score of 7 shows the ability to walk no more than 10m without rest while leaning against a wall or holding onto furniture for support. Later on, an expanded disability status scale (EDSS) has been implemented (Kurtzke, 1983).

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