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...
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 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).

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*aDecree 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. 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.

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. So, a SMR spatial association measurement was also implemented using the G statistic. 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.
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** | | | | | |
| **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 | 226,035 | 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 | 1 |
| 0—13 | | | 637738 | 4 | 33 |
| 14—29 | | | 544871 | 181 | 113 |
| 30—39 | | | 540281 | 611 | 134 |
| 40—49 | | | 753382 | 1010 | 154 |
| 50—59 | | | 671542 | 1037 | 165 |
| 60—69 | | | 510889 | 845 | 135 |
| 70—79 | | | 265782 | 359 | 56 |
| 80 and above | | | 241418 | 135 | 56 |

Gender  
Women  
Men  

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.

| Domicile department sorted by increasing multiple sclerosis crude prevalence rates (zip-code and name) | 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 |
|---|---|---|---|
| 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)
The prevalence rates according to age and sex are shown in Figure 1.

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

Table 2. Continued

| Region          | 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 1\(^{st}\) quartile \((84.91/100,000)\) and regions where multiple sclerosis prevalence was above the 3\(^{rd}\) quartile \((118.20/100,000)\) are shown in Table 1.

Departments where multiple sclerosis prevalence was equal or below the 10\(^{th}\) percentile \((70.29/100,000)\) and departments where multiple sclerosis prevalence was equal or above the 90\(^{th}\) 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.

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**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 auto-correlation between geographic entities our study

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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, but contrary to findings for employees and their families. 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 \( (\text{Figure 5}) \) as farmers are attached to their land and independents can create their own employment locally (geographic mobility in adulthood interferes with the gradient effect); and (c) less exposed to outdoor work (ultraviolet (UV) radiation gradient over France also interferes). 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. 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) 65/100,000 in France in agricultural workers5 (vs 100.39/100,000 in our study) and (b) 94/100,000 in France in employees6 (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

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 (DSS) level of DSS 6 (women) and DSS 7 (men) according to the literature, two scores corresponding to the second phase of the disease (diffuse neurodegenerative process). 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. 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, 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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‘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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