Geographic variations of multiple sclerosis in France

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France is located in an area with a medium to high prevalence of multiple sclerosis, where its epidemiology is not well known. We estimated the national and regional prevalence of multiple sclerosis in France on 31 October 2004 and the incidence between 31 October 2003 and 31 October 2004 based on data from the main French health insurance system: the Caisse Nationale d’Assurance Maladie des Travailleurs Salariés. The Caisse Nationale d’Assurance Maladie des Travailleurs Salariés insures 87% of the French population. We analysed geographic variations in the prevalence and incidence of multiple sclerosis in France using the Bayesian approach. On the 31 October 2004, 49 417 people were registered with multiple sclerosis out of the 52 359 912 insured with the Caisse Nationale d’Assurance Maladie des Travailleurs Salariés. Among these, 4497 were new multiple sclerosis cases declared between 31 October 2003 and 31 October 2004. After standardization for age, total multiple sclerosis prevalence in France was 94.7 per 100 000 (94.3–95.1); 130.5 (129.8–131.2) in females and 54.8 (54.4–55.3) in males. The national incidence of multiple sclerosis between 31 October 2003 and 31 October 2004 was 7.5 per 100 000 (7.3–7.6); 10.4 (10.2–10.6) in females and 4.2 (4.0–4.3) in males. The prevalence and incidence of multiple sclerosis were higher in North-Eastern France, but there was no obvious North–South gradient. This study is the first performed among a representative population of France (87%) using the same method throughout. The Bayesian approach, which takes into account spatial heterogeneity among geographical units and spatial autocorrelation, did not confirm the existence of a prevalence gradient but only a higher prevalence of multiple sclerosis in North-Eastern France and a lower prevalence of multiple sclerosis in the Paris area and on the Mediterranean coast.
North–South prevalence gradient has also been described within called ‘the latitudinal gradient’ (Kurtzke, 1975). In Europe, arities. This increase in prevalence with increasing latitude has been conditions, cultural and dietary habits as well as genetic particula-

These variations may reflect a combination of environmental factors and using adequate Bayesian approaches would improve the clarity of the geographical variations in multiple sclerosis prevalence (Besag et al., 1991; Banerjee et al., 2004; Lang and Brezger, 2004).

France is situated in the middle of Western Europe and is considered a country of medium to high multiple sclerosis prevalence (Debouverie et al., 2007b). At present, the prevalence of multiple sclerosis in France is estimated to be around 50 cases for 100 000 inhabitants (Debouverie et al., 2007b). However, this estimation relies on data collected at a regional level or on non-representative samples. The method for estimating the prevalence of multiple sclerosis needs to be more clearly defined. To our knowledge only one study has been performed at the national level (Vukusic et al., 2007). However, this study was based on a sample of 7% of the French population, insured by the Caisse Collective de la Mutualité Sociale Agricole, which insures mostly farmers, agricultural employees and their families. This study brought to light a North-East/South-West gradient. However, as the population in this study was not representative, the existence of this gradient in the population at large needs to be confirmed. Thus, in order to obtain a better estimate of multiple sclerosis prevalence in France as well as its geographic variations, we initiated a study at the national level based on data from the main French National Health Insurance system, which insures 87% of the French population. This is the first large-scale study using the same methodology at the national level.

Introduction

Multiple sclerosis prevalence is heterogeneous worldwide. Multiple sclerosis is known to be more prevalent in temperate than in tropical regions. In Europe, there are dramatic differences between its prevalence in Northern and Southern countries; prevalence varies from 224 per 100 000 inhabitants in Orkney and the Shetland Islands, to ∼40–90 per 100 000 in Italy (Rosati, 2001). These variations may reflect a combination of environmental conditions, cultural and dietary habits as well as genetic particularities. This increase in prevalence with increasing latitude has been called ‘the latitudinal gradient’ (Kurtzke, 1975). In Europe, a North–South prevalence gradient has also been described within a number of countries including Ireland (McGuigan et al., 2004), the UK (Williams and McKeran, 1986; Phadke and Downie, 1987; Roberts et al., 1991; Forbes and Swingler, 1999) and Germany (Lauer et al., 1984), with a higher prevalence in the Northern regions of these countries. However, these gradients are a subject of debate because they could be due to methodological artefacts. Indeed they are often highlighted by studies comparing some specific regions of a country that are not representative of the country as a whole (McGuigan et al., 2004), or even hospital cohorts, sometimes with data collected at different periods of the year. Moreover, most of these studies do not account for age and gender distribution in the areas compared. Adjusting for these factors and using adequate Bayesian approaches would improve the clarity of the geographical variations in multiple sclerosis prevalence.

Materials and methods

Setting

This cross-sectional study was conducted in the French metropolitan territory (including Corsica) located between latitudes 42° and 51° north. There were 60 028 292 inhabitants in France in 2004 (www.insee.fr). France covers 535 280 km² divided into 96 French administrative areas called ‘départements’ (Fig. 1). These départements are grouped into 22 regions (Fig. 1). The population density of these French administrative areas varies greatly (from 15 inhabitants/km² in Lozère to 20 569 inhabitants/km² in the Paris administrative area), as does age distribution.

Data sources

In France, multiple sclerosis is one of the 30 long-term illnesses (affections de longue durée; ALDs) for which patients are covered for 100% of their health care costs. Once the diagnosis of multiple sclerosis has been established by a neurologist, a detailed request is addressed to the health insurance system by the neurologist to obtain ALD status for the patient. This status is authorized if the patient needs disease-modifying treatment and/or if permanent disability exists and the patient needs symptomatic management. All the data corresponding to the ALD request and to the subsequent health care are systematically collected by the French National Health Insurance System covering 96% of the French population that includes three main independent subsystems: the Caisse Collective de la Mutualité Sociale Agricole (mentioned above), which covers farmers and their families (7% of the French population); the Régime Social des indépendants, which provides coverage to self-employed professionals and their families (2% of the French population); and the Caisse Nationale d’Assurance Maladie des Travailleurs Salariés (CNAMTS), which insures private salaried employees, civil and non-civil servants and their families. The CNAMTS covers 87% of the French population.

To reach our objectives, we used data collected by the CNAMTS from patients with multiple sclerosis, residing in metropolitan France (including Corsica) alive at 31 October 2004 and classified as having ALD status for multiple sclerosis.

Data obtained from the CNAMTS for patients with multiple sclerosis included in our study were: date of birth, gender, French administrative area of residence, date of request for ALD status related to multiple sclerosis, date of death and new ALD status for multiple sclerosis granted between 31 October 2004 and 31 October 2005, and between 31 October 2005 and 31 October 2006.

The number of insured people in 2004 stratified in 5-year age groups and according to gender for each French administrative area was obtained from the CNAMTS. In accordance with French law, this study was approved by the National Commission of Data Processing and Civil Liberties.

Statistical analysis

Prevalence

The overall prevalence of multiple sclerosis in France according to ALD status for the disease was defined as the number of patients with...
multiple sclerosis and ALD status identified in the CNAMTS database, divided by the number of subjects insured by the CNAMTS.

In order to study the geographical variations of multiple sclerosis prevalence, we calculated the standardized prevalence and the standardized prevalence ratio for each of the 96 départements individually and grouped in 22 regions, and their 95% confidence intervals (CI). The same calculation was made for the 22 regions of France. These standardized prevalence ratios were estimated using a similar approach to that used to estimate standardized incidence ratios (Breslow and Day, 1980). The standardized prevalence ratio was defined as the ratio between the observed number of multiple sclerosis subjects according to the CNAMTS database and the expected number. In each French administrative area, the expected number was estimated by multiplying the gender- and age-specific prevalence of the overall CNAMTS population by the number of people in each age and gender stratum of the area.

**Incidence**

The overall incidence of multiple sclerosis in France according to ALD status for the disease between 31 October 2003 and 31 October 2004 was defined as the number of new ALD status granted for multiple sclerosis during this period divided by the number of subjects insured by the CNAMTS. We calculated the standardized incidence and the standardized incidence ratio for each of the 96 French administrative areas and their 95% CI using the same strategy as that applied for the calculation of the standardized prevalence ratio. The same calculation was made for the 22 regions of France. We calculated the incidence of new ALD status for multiple sclerosis granted between 31 October 2004 and 31 October 2005, and between 31 October 2005 and 31 October 2006.

**Spatial model**

See Supplementary material for full details.
We tested for a North-East/South-West gradient in multiple sclerosis prevalence. We used the standardized prevalence ratio coefficient of variation, obtained by dividing the standard deviation by the mean of the 96 standardized prevalence ratios corresponding to each administrative area. However, the large differences in population size between areas may have induced variations in the accuracy of standardized prevalence ratio from one département to another making it difficult to distinguish random fluctuations from true variations in standardized prevalence ratio. Thus, we used the Poisson–Whittinghill test (Pothoff and Whittinghill, 1966) in order to determine the extent of these discrepancies. This test is used to check geographical heterogeneity among all the observed number of multiple sclerosis cases, while taking into account differences in population size. Moreover, we had to take into account the fact that contiguous areas may not be independent as they probably share more risk factors than more distant administrative areas. To detect the existence of this phenomenon, called spatial correlation, we applied the Moran test (Cliff and Ord, 1981; Upton and Fingleton, 1985).

Because results from the preceding tests were significant, we applied a hierarchical Bayesian Poisson model (Olsen et al., 1996; Maiti et al., 1998; Pascutto et al., 2000). This model allowed us to estimate the relative prevalence (or relative risks) in département ‘i’ compared with the mean value for the population as a whole, while accounting for spatial autocorrelation and adjusting for gender and age. Posterior distributions of relative risks were obtained by Monte Carlo Markov chain sampling techniques. More or less informative parameters for hyperpriors were compared and the model leading to the most conservative results was retained (Colonna, 2006). We tested the interaction between the geographical area and gender in order to highlight a potential difference in geographical distribution of cases according to gender. Models were compared using the deviance information criterion, a Bayesian version of the Akaike criterion (Spiegelhalter et al., 2002). The same methodology was applied to study geographical variations in multiple sclerosis incidence.

Disease mapping
Maps of standardized prevalence ratios, standardized incidence ratios and smoothed relative risks at the level of the French administrative area were established to visualize the geographical distribution of multiple sclerosis prevalence. Standardized prevalence ratios and standardized incidence ratios of the 96 French administrative areas were classified into three groups according to their value and significance: (i) French administrative areas with a prevalence or incidence significantly lower than the mean national level; (ii) areas with a prevalence or incidence no different from the mean national level; and (iii) areas with a prevalence or incidence significantly higher than the mean national level. Smoothed relative risk estimates were also classified into three groups according to their posterior distribution with respect to the number 1: (i) 95% of the posterior distribution below 1 indicating a lower prevalence or incidence than the mean national level; (ii) 95% of the posterior distribution above one corresponding to a higher prevalence or incidence than the mean national level; and (iii) the other cases.

We used R 9.2.1 (http://cran.univ-lyon1.fr/) for calculating Moran and Poisson–Whittinghill tests, Philcarto V5.05 (http://philcarto.free.fr) for mapping, SAS for preparing the data for Bayesian analyses and finally BayesX (http://www.stat.uni-muenchen.de/bayesX) for fitting Bayesian models.

Results

Description of the population
On the 31 October 2004, the CNAMTS insured 52,359,912 out of the 60,028,292 inhabitants of France (87%). Among inhabitants insured by the CNAMTS, 49,417 patients with multiple sclerosis were registered as having ALD status for their disease. The sex ratio (female to male) was 2.6. The distribution of ages at which ALD status for multiple sclerosis was granted is shown in Table 1. The mean age at the time of request for ALD status for multiple sclerosis was 40.1 ± 11.7 years. The years when ALD status was first granted for multiple sclerosis are shown in Table 1. The first ALD status allocated to a patient still alive in 2004 was requested in 1987.

Prevalence
The national prevalence of multiple sclerosis in France was 94.7 per 100,000 patients covered by the CNAMTS (95% CI: 94.3–95.1), 130.5 per 100,000 in females (95% CI: 129.8–131.2) and 54.8 per 100,000 in males (95% CI: 54.4–55.3). Standardized multiple sclerosis prevalence by region is shown in Table 2.

When considering départements, the standardized prevalence ratio of ALD multiple sclerosis among people covered by the CNAMTS in France varied from a minimum of 0.73 (95% CI: 0.58–0.92) in Corse du Sud (a département in the Southern area of France) to a maximum of 1.75 (95% CI: 1.51–2.01) in Territoire de Belfort (in the Eastern area). The same trends were found for both genders with a standardized prevalence ratio varying from 0.73 (95% CI: 0.55–0.95) in Corse du Sud to 1.90 (95% CI: 1.61–2.22) in Territoire de Belfort among females; and from 0.56 (95% CI: 0.39–0.77) in Ardèche to 1.53 (95% CI: 1.25–1.87) in Ardennes among males. The map of standardized prevalence ratios showed a higher prevalence of ALD multiple sclerosis in North-Eastern France for the overall population and a lower one in the South-West (Fig. 2). The same trends were observed when the data were stratified according to gender (data not shown).

In our study, the P-value of Poisson–Whittinghill test was equal to 0.01, showing a statistically significant spatial heterogeneity. The Moran test was of 0.3698 (P < 10⁻⁴) leading us to use a model taking into account spatial autocorrelation. The results of these two tests led us to use a Bayesian model. This model fitted the data rather well as the relative difference between the standardized prevalence and its Bayesian estimation was below 20% for almost 85% of départements. When using the Bayesian approach, the North-Eastern part of France also seemed to have a higher prevalence than the rest of France. The smoothed relative risks varied from 1.22 (95% Bayesian credible interval: 1.02–1.49) in Meurthe et Moselle, to 1.45 (95% Bayesian credible interval: 1.15–1.86) in Haute Marne. Two main regions seemed to have a lower risk for the overall population: Ile de France [e.g. 0.84 (95% Bayesian credible interval: 0.70–0.99) in Essonne] and a part of the Mediterranean coast.
When considering females alone, an additional département in the south of France (Hérault) seemed to have a lower prevalence (data not shown). For females, the North-Eastern and central parts of France had the highest prevalence of multiple sclerosis. For males, fewer départements in the North-East of France (Haute-Marne and Haute-Saône) had a higher prevalence, and a lower prevalence was also observed in the south, such as in Bouches-du-Rhône—Fig. 3.

### Table 1 Characteristics of patients with multiple sclerosis with chronic disease status (ALD) granted by the French National Health Insurance System

<table>
<thead>
<tr>
<th>Administrative region of France</th>
<th>Affiliation to the CNAMTS N (%)a</th>
<th>Number of ALD for multiple sclerosis</th>
<th>Overall Multiple sclerosis standardized prevalence</th>
<th>Male Multiple sclerosis standardized prevalence</th>
<th>Female Multiple sclerosis standardized prevalence</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorraine</td>
<td>2 008 606 (86.3)</td>
<td>2507</td>
<td>123.7</td>
<td>121.2–126.2</td>
<td>70.8</td>
<td>68.1–73.5</td>
<td>171.5</td>
<td>167.5–175.5</td>
</tr>
<tr>
<td>Champagne Ardenne</td>
<td>1 107 627 (83.2)</td>
<td>1348</td>
<td>122.9</td>
<td>119.5–126.2</td>
<td>73.4</td>
<td>69.6–77.1</td>
<td>166.5</td>
<td>161.1–171.8</td>
</tr>
<tr>
<td>Picardie</td>
<td>1 614 238 (86.1)</td>
<td>1853</td>
<td>116.8</td>
<td>114.1–119.5</td>
<td>65.4</td>
<td>62.4–68.3</td>
<td>163.5</td>
<td>159.0–167.9</td>
</tr>
<tr>
<td>Bourgogne</td>
<td>1 330 427 (82.4)</td>
<td>1568</td>
<td>116.2</td>
<td>113.3–119.1</td>
<td>62.9</td>
<td>59.8–66.1</td>
<td>162.6</td>
<td>157.8–167.4</td>
</tr>
<tr>
<td>Franche-Comte</td>
<td>973 046 (86.1)</td>
<td>1115</td>
<td>115.3</td>
<td>111.8–118.7</td>
<td>63.2</td>
<td>59.5–66.9</td>
<td>162.2</td>
<td>156.5–167.8</td>
</tr>
<tr>
<td>Nord-pas-de-Calais</td>
<td>3 627 506 (90.2)</td>
<td>3949</td>
<td>113.3</td>
<td>111.5–115.1</td>
<td>71.7</td>
<td>69.6–73.7</td>
<td>151.3</td>
<td>148.4–154.2</td>
</tr>
<tr>
<td>Alsace</td>
<td>1 597 543 (89.3)</td>
<td>1799</td>
<td>112.0</td>
<td>109.4–114.7</td>
<td>65.8</td>
<td>62.8–68.7</td>
<td>154.6</td>
<td>150.3–159.0</td>
</tr>
<tr>
<td>Centre</td>
<td>2 077 615 (83.9)</td>
<td>2158</td>
<td>103.1</td>
<td>100.8–105.3</td>
<td>57.4</td>
<td>54.9–59.7</td>
<td>143.9</td>
<td>140.3–147.5</td>
</tr>
<tr>
<td>Auvergne</td>
<td>1 065 898 (80.5)</td>
<td>1118</td>
<td>101.5</td>
<td>98.4–104.5</td>
<td>47.1</td>
<td>44.1–50.1</td>
<td>149.7</td>
<td>144.7–154.8</td>
</tr>
<tr>
<td>Basse-Normandie</td>
<td>1 179 272 (81.8)</td>
<td>1140</td>
<td>94.0</td>
<td>91.5–100.9</td>
<td>54.7</td>
<td>51.5–57.8</td>
<td>136.2</td>
<td>131.4–140.8</td>
</tr>
<tr>
<td>Haute-Normandie</td>
<td>1 619 807 (89.9)</td>
<td>1510</td>
<td>94.7</td>
<td>92.3–97.1</td>
<td>57.2</td>
<td>54.4–60.0</td>
<td>128.7</td>
<td>124.8–132.7</td>
</tr>
<tr>
<td>Bretagne</td>
<td>2 381 321 (79.4)</td>
<td>2333</td>
<td>94.7</td>
<td>92.7–96.7</td>
<td>52.3</td>
<td>50.1–54.5</td>
<td>131.4</td>
<td>128.2–134.6</td>
</tr>
<tr>
<td>Limousin</td>
<td>556 268 (78.1)</td>
<td>542</td>
<td>93.2</td>
<td>89.2–97.2</td>
<td>43.1</td>
<td>39.1–47.2</td>
<td>136.2</td>
<td>129.6–142.8</td>
</tr>
<tr>
<td>Aquitaine</td>
<td>2 416 622 (79.6)</td>
<td>2165</td>
<td>87.9</td>
<td>86.0–89.8</td>
<td>50.6</td>
<td>48.5–52.7</td>
<td>120.1</td>
<td>117.1–123.1</td>
</tr>
<tr>
<td>Midi-Pyrénées</td>
<td>2 158 845 (80.8)</td>
<td>1900</td>
<td>87.4</td>
<td>85.3–89.4</td>
<td>47.8</td>
<td>45.6–50.0</td>
<td>122.2</td>
<td>119.0–125.4</td>
</tr>
<tr>
<td>Rhône-Alpes</td>
<td>5 184 135 (88.4)</td>
<td>4450</td>
<td>87.3</td>
<td>86.0–88.6</td>
<td>53.5</td>
<td>52.0–55.0</td>
<td>118.2</td>
<td>116.0–120.2</td>
</tr>
<tr>
<td>Pays-de-Loire</td>
<td>2 837 379 (85.1)</td>
<td>2374</td>
<td>86.7</td>
<td>84.9–88.5</td>
<td>45.2</td>
<td>43.3–47.0</td>
<td>123.9</td>
<td>121.0–126.8</td>
</tr>
<tr>
<td>Poitou-Charente</td>
<td>1 319 698 (78.5)</td>
<td>1151</td>
<td>85.5</td>
<td>83.0–88.1</td>
<td>46.8</td>
<td>44.1–49.5</td>
<td>118.9</td>
<td>114.9–123.0</td>
</tr>
<tr>
<td>Ile-de-France</td>
<td>10 935 798 (97.3)</td>
<td>9139</td>
<td>84.3</td>
<td>83.4–85.2</td>
<td>50.4</td>
<td>49.4–51.4</td>
<td>115.7</td>
<td>114.2–117.2</td>
</tr>
<tr>
<td>PACA</td>
<td>4 176 207 (89.8)</td>
<td>3561</td>
<td>84.1</td>
<td>82.7–85.5</td>
<td>49.5</td>
<td>47.9–51.8</td>
<td>114.6</td>
<td>113.2–116.8</td>
</tr>
<tr>
<td>Languedoc-Roussillon</td>
<td>1 981 166 (81.1)</td>
<td>1655</td>
<td>83.1</td>
<td>81.1–85.2</td>
<td>49.5</td>
<td>47.2–51.8</td>
<td>112.0</td>
<td>108.8–115.3</td>
</tr>
<tr>
<td>Corse</td>
<td>210 886 (77.9)</td>
<td>183</td>
<td>81.1</td>
<td>75.1–87.1</td>
<td>50.6</td>
<td>43.8–57.5</td>
<td>108.5</td>
<td>98.9–118.1</td>
</tr>
<tr>
<td>Total France</td>
<td>52 359 912 (87.2)</td>
<td>49 418</td>
<td>94.7</td>
<td>94.3–95.1</td>
<td>54.8</td>
<td>54.4–55.3</td>
<td>130.5</td>
<td>129.8–131.2</td>
</tr>
</tbody>
</table>

a Percentage of people affiliated to the CNAMTS in the general population.

[0.73 (95% Bayesian credible interval: 0.57–0.92) in Bouches-du-Rhône—Fig. 3]. When considering females alone, an additional département in the south of France (Hérault) seemed to have a lower prevalence (data not shown). For females, the North-Eastern and central parts of France had the highest prevalence of multiple sclerosis. For males, fewer départements in the North-East of France (Haute-Marne and Haute-Saône) had a higher prevalence, and a lower prevalence was also observed.
in the Western départements of Loire Atlantique and Vendée (data not shown). Interactions between gender and French administrative area did not improve the model. The deviance information criterion of the model including the interaction with gender was 31 791.5, and without interaction with gender was 31 739.7, indicating that geographic variations could not be considered as different according to gender: the lower deviance information criterion being considered the most valid. We tested the North-East to South-West gradient of multiple sclerosis hypothesized from the results of Vukusic et al. (2007) by including trend for latitude ($X$) and longitude ($Y$), either linearly (terms in $X$ and $Y$) or quadratically (terms in $X$, $Y$, $X^2$, $Y^2$ and $XY$). Neither improved the fit to the data (deviance information criterion were 31 740 and 31 741, respectively).

### Incidence

The incidence of ALD multiple sclerosis in France between 31 October 2003 and 31 October 2004 calculated among French inhabitants covered by the CNAMTS was 7.5 per 100 000 (95% CI: 7.3–7.6); 10.4 (95% CI: 10.2–10.6) in females and 4.2 (95% CI: 4.0–4.3) in males. The standardized incidence of ALD multiple sclerosis in each region is shown in Table 3. The map of standardized incidence ratios revealed a higher incidence of multiple sclerosis in North-Eastern France, in two départements in the north of France (Somme and Oise) and in two départements in central France (Eure et Loire and Loire et Cher) (Fig. 4). In these high incidence areas, standardized incidence ratios varied from a minimum of 1.26 (95% CI: 1.02–1.53) in Bas-Rhin to a

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**Figure 2** Multiple sclerosis standardized prevalence ratio for each département according to their significance (France, 2004). Départements in red correspond to areas with a higher prevalence than the mean French level. Départements in green correspond to areas with a lower prevalence than the overall French mean level.
maximum of 2.37 (95% CI: 1.48–3.58) in Territoire de Belfort (two départements in the North-Eastern area of France). Some départements appeared to have a lower incidence of multiple sclerosis. Among them, we found two départements on the Atlantic coast: one in Western France (Loire Atlantique) and the other in the South-West (Gironde); and three départements in central eastern France (Ain, Rhone and Saône et Loire). In these low incidence areas, standardized incidence ratios varied from a minimum of 0.48 (95% CI: 0.27–0.78) in Ain to a maximum of 0.80 (95% CI: 0.69–0.93) in Paris. As the number of new ALD for multiple sclerosis was rather low in 2004, we choose to not present the results of the smoothed relative risk estimation for incidence. We only used the Bayesian approach to test the interaction between gender and French administrative area. The deviance information criterion of the model including the interaction with gender was 1624.4, compared to 1616.8 without interaction with gender; the lower deviance information criterion being considered the most valid. The incidence of ALD multiple sclerosis in France between 31 October 2004 and 31 October 2005, and between 31 October 2005 and 31 October 2006 was the same as during the previous 12-month period between 31 October 2003 and 31 October 2004 (data not shown).

**Discussion**

Only one reliable study has estimated the national prevalence of multiple sclerosis in France (Vukusic et al., 2007). In 2003, multiple sclerosis prevalence was estimated to be 65.5 per 100 000 (95% CI: 62.5–67.5). However, this study was performed among the population covered by the Caisse Collective de la Mutualité Sociale Agricole, which insures only 7% of the French population,
soon as secondary progressive multiple sclerosis with superim-

prescribed as soon as definite relapsing multiple sclerosis, or as 
multiple sclerosis. Since 1995, disease modifying treatment can be 
from the health authorities for their patients in order to provide 
disease-modifying treatment, neurologists require ALD status 
before prescribing several disease modifying treatments obtained authorization 
and a disability were registered as ALD. Between 1995 and 2000, 
mated because before 1995, only patients with multiple sclerosis 
sclerosis was around 13 years. This value is certainly underesti-
mance suggested that the duration of ALD status for multiple 
incidence remained stable in 2005 and 2006. Multiple sclerosis incidence among this population 
be 94.7 per 100 000 among subjects covered by the CNAMTS. 
Vukusic et al. (2007) study in order to estimate multiple sclerosis preva-
et al. (2007) in order to estimate multiple sclerosis preva-
the CNAMTS, which covers 87% 
of the French population, we decided to replicate the Vukusic 
the main 
Percentage of people affiliated to the CNAMTS in the general population.

<table>
<thead>
<tr>
<th>Administrative region of France</th>
<th>Affiliation to the CNAMTS n (%a)</th>
<th>Number of ALD for multiple sclerosis</th>
<th>Overall Multiple sclerosis standardized incidence</th>
<th>Male Multiple sclerosis standardized incidence</th>
<th>Female Multiple sclerosis standardized incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picardie</td>
<td>1 614 238 (86.1)</td>
<td>181</td>
<td>11.0</td>
<td>6.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Lorraine</td>
<td>2 008 606 (86.3)</td>
<td>227</td>
<td>10.8</td>
<td>6.2</td>
<td>15.0</td>
</tr>
<tr>
<td>Alsace</td>
<td>1 597 543 (89.3)</td>
<td>161</td>
<td>9.7</td>
<td>5.9</td>
<td>13.2</td>
</tr>
<tr>
<td>Centre</td>
<td>2 077 615 (83.9)</td>
<td>188</td>
<td>9.0</td>
<td>5.2</td>
<td>12.4</td>
</tr>
<tr>
<td>Champagne Ardenne</td>
<td>1 107 627 (83.2)</td>
<td>100</td>
<td>8.9</td>
<td>4.8</td>
<td>12.6</td>
</tr>
<tr>
<td>Franche Comte</td>
<td>9 73 046 (86.1)</td>
<td>85</td>
<td>8.6</td>
<td>3.7</td>
<td>13.2</td>
</tr>
<tr>
<td>Auvergne</td>
<td>1 065 898 (80.5)</td>
<td>89</td>
<td>8.1</td>
<td>4.1</td>
<td>11.7</td>
</tr>
<tr>
<td>Bretagne</td>
<td>2 381 323 (79.4)</td>
<td>196</td>
<td>8.1</td>
<td>4.3</td>
<td>11.4</td>
</tr>
<tr>
<td>Haute Normandie</td>
<td>1 619 807 (89.9)</td>
<td>132</td>
<td>8.0</td>
<td>4.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Nord pas de Calais</td>
<td>3 627 506 (90.2)</td>
<td>289</td>
<td>7.7</td>
<td>4.7</td>
<td>10.5</td>
</tr>
<tr>
<td>PACA</td>
<td>4 176 207 (89.8)</td>
<td>308</td>
<td>7.3</td>
<td>4.2</td>
<td>10.1</td>
</tr>
<tr>
<td>Basse Normandie</td>
<td>1 179 272 (81.8)</td>
<td>83</td>
<td>7.0</td>
<td>3.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Midi Pyrenees</td>
<td>2 158 845 (80.8)</td>
<td>158</td>
<td>7.0</td>
<td>4.5</td>
<td>9.2</td>
</tr>
<tr>
<td>Ile de France</td>
<td>10 935 798 (97.3)</td>
<td>816</td>
<td>7.0</td>
<td>4.0</td>
<td>9.7</td>
</tr>
<tr>
<td>Limousin</td>
<td>556 268 (78.1)</td>
<td>39</td>
<td>6.9</td>
<td>2.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Poitou Charente</td>
<td>1 319 698 (78.5)</td>
<td>91</td>
<td>6.8</td>
<td>2.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Bourgogne</td>
<td>1 330 427 (82.4)</td>
<td>90</td>
<td>6.8</td>
<td>2.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Corse</td>
<td>210 886 (77.9)</td>
<td>15</td>
<td>6.8</td>
<td>2.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Languedoc Roussillon</td>
<td>1 981 166 (81.1)</td>
<td>134</td>
<td>6.6</td>
<td>2.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Aquitaine</td>
<td>2 416 622 (79.6)</td>
<td>153</td>
<td>6.2</td>
<td>2.0</td>
<td>8.9</td>
</tr>
<tr>
<td>Pays de Loire</td>
<td>2 837 379 (85.1)</td>
<td>174</td>
<td>6.1</td>
<td>2.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Rhone Alpes</td>
<td>5 184 135 (88.4)</td>
<td>323</td>
<td>6.1</td>
<td>3.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Total France</td>
<td>52 359 912 (87.2)</td>
<td>4032</td>
<td>7.5</td>
<td>4.2</td>
<td>10.4</td>
</tr>
</tbody>
</table>

a Percentage of people affiliated to the CNAMTS in the general population.
which includes all the private and hospital neurologists of the Lorraine Region, using capture recapture methodology, in a population-based cohort in an area of high prevalence. In 2004, the prevalence estimated by the Lorraine Network was 120 per 100 000 (95% CI: 119–121) (Debouverie et al., 2007a). This result was very close to that calculated from the CNAMTS data (124 per 100 000; 95% CI: 121–126). Similar values were also obtained for females and males using both data sources. The comparison between these values allowed us to validate our data.

Thus, it seems reasonable to conclude that the number of new multiple sclerosis-related ALD, after an increase between the mid-1990s and the early 2000s, was relatively stable thereafter. Our incidence, which was stable during 2004–06, confirms this stability.

Vukusic et al. (2007) have shown differences in multiple sclerosis distribution in France. They observed a higher prevalence in North-Eastern France in a particular population comprising essentially farmers and their families. In our study, we also confirmed this higher prevalence in North-Eastern France in a large population representative of the French population. Despite the differences between the populations studied (older age and lower proportion of females in the population described by Vukusic et al. in 2007) the same tendency of geographical distribution was found.

One could argue that this higher prevalence could be related to differences in gender and age distribution according to area. However, this result was observed after adjusting for these two variables. Another explanation could be that there were considerable differences in population sizes among the compared areas.
which might have made it difficult to distinguish between random and true variations in standardized prevalence ratios. Moreover, neighbouring areas may not be independent as they probably share more risk factors than more distant administrative areas do. In order to account for this spatial autocorrelation as well as population size heterogeneity, we used the Bayesian approach. This type of model can provide smoothed relative risks that are more accurate than standardized prevalence ratios. An alternative method to account for spatial autocorrelation would have been to use a generalized additive model, including a multidimensional smoothing surface (Wood, 2006) with a structured variance–covariance matrix to account for heterogeneity. However, such model is not applied routinely and requires specific methodological development and validation without a clear benefit in terms of results. Thus we preferred to use Bayesian validated approach. With this latter approach, we showed that the higher prevalence of multiple sclerosis was observed in North-Eastern France, confirming that this could not be considered as a mere artefact.

Vukusic et al. (2007) pointed out that prevalence diminished from the North-East to the South-West of France suggesting the existence of a geographical gradient. We were not able to show such a gradient for France formally, but rather areas of high and lower prevalence. However, many other authors in non-European countries have highlighted gradients of gradually decreasing prevalence from North to South. For example, this tendency was observed in the US (Kurtzke, 2008) as well as in the former Soviet Union (Boiko et al., 1995). However, a higher prevalence was observed in the South of Norway compared to the North of the country (Rosati, 2001). These trends have not yet been explained. These geographical variations may be related to genetic, environmental or socioeconomic factors such as cultural, dietary, income and interacting with each other. Several hypotheses may be evoked to explain the higher multiple sclerosis prevalence in the North-Eastern France. Indeed, it could be related to environmental factors, for example amount of sunshine. In a review, Ebers et al. (2008) showed that ultraviolet radiation measured by satellite was inversely proportional to multiple sclerosis prevalence. Sunshine is the main determinant of vitamin D concentration (Holick et al., 1987). In France, Chapuy et al. (1996) showed a significant relationship between latitude and vitamin D concentration (r = −0.79) as well as between vitamin D concentration and sunshine (r = 0.72). In Tasmania, multiple sclerosis risk was lower for patients who had spent a lot of time in the sun during childhood (Van der Mei et al., 2003). This low risk of multiple sclerosis correlated with actinic damage measured on the dorsal side of the hand, which reflects past exposure to sunshine. Moreover vitamin D seems to interact with genetic material through a vitamin D response element located on the promoter region of HLA-DRB1 gene (Ramagopalan et al., 2009). This vitamin D response element can influence gene expression and imparts vitamin D sensibility to HLA-DRB1*15. In patients bearing HLA-DRB1*15, a lack of vitamin D during childhood could allow auto reactive T cells to escape thymic deletion and thus increase immune disease risk. Other factors like racial mixing may also be implicated in geographical variations of multiple sclerosis. Low multiple sclerosis prevalences were observed in areas with a high immigrant rate like in Paris (17%) and on the Mediterranean coast (10%) (the national level of immigrant’s rate being 8%) (www.insee.fr). Conversely, in North Eastern regions like Burgundy and Champagne Ardennes where multiple sclerosis prevalence is high, the immigration rate is low (6%). However this hypothesis is probably not sufficient for explaining the geographical distribution of multiple sclerosis. Other factors should be also considered like living in a rural or urban area. While an excess of multiple sclerosis in rural populations has been shown in studies from Sweden (Sallstrom, 1942), Norway (Swank et al., 1952), Denmark (Hyllested, 1960) and Lower Franconia (Bammer, 1960), other studies have suggested an excess in urban areas (Bebee et al., 1967; Leibowitz and Alter, 1973). The availability of care facilities or socioeconomic factors could also be involved, as there are also considerable socioeconomic disparities between areas of high and low multiple sclerosis prevalence.

In our study using Bayesian methodology, which takes into account differences in population sizes in geographical units as well as spatial autocorrelation, we found no gradient. Only a higher prevalence in North-Eastern France and a lower prevalence in Paris and its suburbs and on the Mediterranean coast were observed. This distribution is not yet explained. Further studies that explore environmental and socioeconomic factors are needed to understand better the reasons for such geographical variations. Among variables that could influence this distribution, population movement, percentages of non-Caucasian subjects, degree of urbanization and socioeconomic peculiarities seem important.

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Supplementary material

Supplementary material is available at Brain online.

References

Epidemiology of multiple sclerosis in France

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