Geographic differences in relationship between socioeconomic, clinical, urban-rural factors and stroke incidence in France

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Abstract

**Background:** Stroke remains a devastating disease in Europe and geographic disparities persist. Mapping spatial distributions of disease occurrence can serve as a useful tool for identifying exposures of public health concern. The purpose of this study was to investigate geographic differences in relationship between socioeconomic, clinical, urban-rural factors and stroke incidence in Pays de Brest (Western France) between 2008 and 2013.

**Methods:** We used cases and patient’s characteristics from the Brest stroke registry, and sociodemographic, urban -rural indicators constructed at the census blocks level. We generated maps using Poisson geographic weighted regression models, smoothing on longitude and latitude while adjusting for covariates.

**Results:** Women living in more deprived census blocks evidenced a significantly higher age standardized stroke incidence risk 1.24, [95%CI 1.09-1.39] and 1.21, [95%CI 1.04-1.49], in rural and urban census blocks respectively. For men, three clusters of census blocks with high stroke incidence risk were detected, one in rural and deprived and two in urban and low deprived census blocks.

**Conclusions:** Understand whether and how neighborhood and patient’s characteristics influence stroke risk, may be useful for both epidemiological research and health services planning.

**Background**

Stroke remains a devastating disease in Europe despite major improvements in management over recent decades. At the beginning of the 21st century, the age standardized stroke incidence in Europe ranged from 95 to 290 per 100,000 inhabitants-year. Because of the ageing population, the expected number of patients who will suffer a stroke each year will inevitably continue to rise over the next decades (1). In France, stroke constitute the first cause of mortality among women, with 18,343 deaths in 2013, the third among men, with 13,003 deaths, and is a leading cause of serious disability. Analysis of the French national health insurance database suggests that in 2013 the cost of stroke care amounted to 3.5 billion € (2).

The burden of stroke varies according to demographic, socioeconomic status (SES), and geographic factors. Past efforts have investigated the association between contextual SES position alone or after
controlling for individual SES characteristics and stroke (3). Studies have reported an increasing risk of stroke associated with decreasing levels of income (4-6), education (7,8), or with an increasing level of deprivation (9-13).

In the French context, previous literature have suggested that, Brittany (western part of France) has the highest ischemic stroke incidence observed in 2014 (137.9 / 100,000) (14) and demonstrated geographic variations in France with one cluster located in Brittany (15). Easy access to primary care could determine these geographic variations of incidence. This pathway may be explained, in part, by the impact of material infrastructures and services, on health, behaviour and healthcare utilization, which are sensible to the location (16,17). Moreover, in 2016 a meta-analysis showed that poor social support were associated with a 32% increase in risk of stroke (18) and Otto et al suggested that this social support is related to the urbanization of the residential neighbourhood (11).

Most stroke registries are based in urban settings; Brest stroke registry provides a unique opportunity to identify variations of stroke incidence along the rural-urban spectrum. It is important to understand whether and how neighborhood characteristics influence stroke risks so as to devise appropriate policies for its prevention and management in urban and remote rural areas (8).

The objectives of this study were i) to detect areas where the risk of stroke is higher according to their socioeconomic level and urban-rural degree and, ii) to explore the patient’s characteristics in these clusters.

Methods
Study area

The study area conducted in the Pays de Brest region: an area located in western France, is subdivide into 79 municipalities and 174 census blocks. Census blocks are small, county statistical subdivisions that contain around 2000 inhabitants. They are designed to be relatively homogeneous with respect to population characteristics, socioeconomic status and living conditions (19).

Data sources

Brest stroke registry

Brest Stroke Registry is an ongoing prospective community-based stroke register covering a total
population of 366 000 inhabitants in western France. Since 2008, it operates using multiple information sources for case identification: from public and private hospitals, radiology clinics performing brain imaging, neurologists and general practitioners. A validation comity ascertain cases and the Brest Stroke Registry performance was evaluated based on capture recapture analysis suggested level of completeness in excess of 90% (20). The characteristics of the study population, investigations and methods of assessment have been described in detail elsewhere (20). It was approved by the local ethics committee. Patients or their legal representatives gave their written informed consent for participation. Specific authorizations were obtained from the national “Comité consultatif sur le traitement de l’information en matière de recherche” and from the “Commission nationale informatique et liberté” for this study.

Stroke cases
All incident ischemic and hemorrhagic stroke cases aged 60 years or more living in Pays de Brest between 1 January 2008 and 31 December 2013 were extracted from the Brest stroke registry. Relevant ICD codes used were I63-I64 for stroke: 1) new focal neurological deficit with symptoms and signs coherent according to the criteria of the World Health Organizations, lasting for more than 24 hours or who died in the first 24 hours; 2) all neurological focal deficits lasting at least 1 hour or resolving within 1 hour but with abnormal brain imaging associated with a clinically relevant picture. Cases were geocoded to their respective census block based on the residential street address of patients.

Patient-level data were extracted from the Brest Stroke registry: the sociodemographic data (age and sex); clinical data including stroke type (ischemic or hemorrhagic), stroke severity (National Institute of Health Stroke Score (NIHSS) <6, 6-13, >13); the presence of cardiovascular risk factors before stroke (the presence of high blood pressure, cardiac arrhythmia, diabetes and dyslipidemia).

Socioeconomic and Urban-rural contextual effects
Firstly, the level of deprivation for each census block was estimated using the FDep index (French deprivation index) (21). This index have been defined and analyzed in previous studies in order to analyze environmental and health inequalities (14). It was generated using Principal component
analysis (PCA); based on four variables from the national census of 2013 collected by INSEE (National Institute for Statistics and Economic Studies): average household income, percentage of high school graduates in the population aged ≤ 15 years, percentage of blue-collar workers in the active population, and unemployment rate.

Secondly, an index SES & urban-rural was generated. In fact, the study area consists in mostly rural areas and this index may not always give a comprehensive representation of the socioeconomic level according to the degree of rurality. The construction of the SES & urban-rural index was carried out using the same method: a Principal component analysis, including the same variables more a new variable urban-rural. This urban-rural variable is categorized as urban, suburban, isolated towns and rural depending on their number of towns and respective populations and come from INSEE. The SES & urban-rural index is composed of 4 categories presented in Figure1.

Statistical analysis

Incidence risk and standardization

To assess the frequency and the spatial distribution of this disease among census blocks, we computed age standardized stroke incidence risk with 95% confidence intervals using the indirect standardization. This procedure ensured that differences in the geographic distribution of stroke risk were not affected by geographic difference of the distribution of age in the population. The stroke incidence risk was computed as the observed number of stroke cases >60 years old during each age-period divided by the expected cases, reported per census blocks respectively. The population data by sex and age period come from INSEE. The age standardized stroke incidence risk were presented per 1 000 inhabitants-year.

Ordinary Poisson regression and Local Poisson geographically weighted regression

Firstly, we investigate potential associations between stroke incidence risk, and contextual socioeconomic deprivation and urban-rural level separately for men and women using Poisson regression models. Poisson regression is a suitable regression model fitted the data using the generalized linear model function, dealing with count data applied to a small area. Significance overdispersion was detected for women models making Poisson regression inappropriate, the analysis
beyond this point have preceded with negative binomial models. Secondly, the application of Koenker (BP) Statistic aims to determine whether the explanatory variable in the ordinary model have a stationary relationship with the dependent variable throughout the study area. When the p value was < 0.10, a local Geographic Weighted Regression (GWR) was carried out, meaning that clusters of census blocks with higher risk of stroke incidence or/and lower risk of stroke incidence exist. When the p value was high, ordinary Poisson or negative binomial model fits better the dataset.

GWR was used to identify interesting locations (areas of variation according to the level of socioeconomic deprivation) for reducing stroke incidence investigation. Local GWR model allow to estimate as many local regression coefficients as the number of locations in the study area. In case of local Poisson GWR, this model is parameterized as follows:

**See Formula 1 in supplementary information.**

Where $X(k,i)$ and $\beta_k$ are the kth explanatory variable and its local regression coefficient that is unique to location U. Thus, the regression coefficients vary based on the spatial location $U_i = (u_i, v_i)$. The expected value of response of the ith observation, $E[y_i]$, is related to the linear predictor via a Poisson link function.

To calibrate this formula, a bi-square adaptive weighting kernel function is used to account for spatial structure (density, shape and size of the census blocks) and the appropriate bandwidth was selected using the golden section method (22). The locations near to i have a stronger influence in the estimation of $\beta_j(u_i,v_i)$ than locations farther from i. In the GWR model localized parameter estimates can be obtained for any location i which in turn allows for the creation of a map showing a continuous surface of parameter values and an examination of the spatial variability (nonstationarity) of these parameters. Additionally, we used corrected Akaike Information Criterion (AICc) and pseudo adjusted coefficient of determination (Adjusted $R^2$) as goodness of fit for comparing models. GWR models have been estimated with R using GWmodel (R Development Core Team, 2011). All maps layouts were performed using ArcMap v. 10.5 from ESRI.

**Results**

**Spatial distribution of stroke risk**
Between 2008 and 2013, 3088 incident stroke cases aged 60 years and more were recorded in Pays de Brest, the incidence of stroke was 6.67 per 1 000 inhabitants-year. Whereas, the incidence of women was nearly the same than for men 6.26 ± 3.5 vs 6.91 ± 3.3 per 1000 inhabitants-year, the mean age of women cases, 76.5 years ± 12.3 was significantly higher than for men 69.1 years ± 13.2 (p < 0.001).

For men, census blocks with a higher stroke incidence are mostly located in lower deprived census blocks located in the urban city of Brest, Fig. 2 and Fig. 3. For women, census blocks with a higher stroke incidence were located in rural, suburban and some of them in urban census blocks. The index of Fdep presented a gradient of deprivation from south to north, those lower deprived census blocks close to the littoral and the city of Brest from those in the rural and isolated census blocks.

**Socioeconomic deprivation as a determinant of stroke incidence for women**

Firstly, Table 1 evidenced a higher significantly age standardized stroke incidence risk of 1.24, [95%CI 1.09–1.39] for women living in low SES and rural census blocks (Class 2) and of 1.21, [95%CI 1.04–1.49] for women living in low SES and urban census blocks (Class 4) than for those living in high SES census blocks (Class 3). Secondly, the BP statistics have indicated stationary relationship with the stroke incident and explanatory variables throughout the study area for women analysis. Negative binomial model for women with the SES & urban-rural index is the best model; showing the smallest AIC.
Table 1

| Women Negative Binomial models |  |
|-------------------------------|--|
| SES index                     |  |
| Intercept                     | 0.002 |
| Index of deprivation          | -0.025 | 0.11 |
| AICc *                        | 883.1 |
| Pseudo R-square value **      | 1.5%  |
| SES & Urban-rural index       |  |
| Intercept                     | -0.08 |
| Class 1: High SES in suburban, isolated towns | 0.016 | 0.82 |
| Class 2: Low SES in rural areas | 0.237 | < 0.001 |
| Class 3: High SES in urban areas | REF   |
| Class 4: Low SES in urban areas | 0.212 | 0.01 |
| AICc *                        | 872.3 |
| Pseudo R-square value **      | 7.9%  |

* Corrected Akaike’s InformationCriterion offer used when observational data is small in number

** R square value = percentage of deviance explained by the model

Clusters of high stroke incidence risk for men

In the reverse, for men, the association between stroke incidence risk and the level of deprivation of the census blocks changes depending on the spatial location (the BP statistics after Poisson model indicates statistically significant lack of stationarity) so Poisson model is not appropriate and GWR models were run. This is evidenced by the higher pseudo $R^2$ (Poisson model $R^2=0.5\%$, GWR model $R^2=12.6\%$) and the lower small sample AIC (Poisson model AICc = 808.7, GWR model AICc = 593.8).

Three clusters of census blocks with higher risk of stroke incidence compare to those census blocks outside clusters were detected (Fig. 4). Cluster 1 in the northern and rural part of Pays de Brest, is associated with between 9 and 14% increase in risk of stroke for an increase level of deprivation.

Cluster 2 is located in the southeastern part and composed by suburban, isolated and rural census blocks located. The results evidences a positive relationship meaning that for those census blocks with a high Fdep index (favored census blocks), higher the risk of stroke incidence is (between 8.5% and 19%). Cluster 3 located in the southwestern (Pays de Brest and pays d’Iroise) is composed by urban and suburban census blocks. The results evidences a positive relationship between the level of deprivation and the risk of stroke incidence (between 3% and 8%).
Comparison of men patient characteristics between clusters

The patients’ cardiovascular risk factors (the presence of hypertension, cardiac arrhythmia, diabetes and dyslipidemia) were comparable within clusters and the rest of the study area (Table 2). No difference was observed concerning the stroke type with more than 88% of ischemic stroke cases in the three areas and also the proportion of different level of stroke severity (29.9%, 22.6% and 23.5% of patients with middle or high stroke severity in the three higher risk clusters, 26.5% in the rest of the study area; p = 0.49).

Table 2
Men patient’s characteristics between clusters of stroke and the rest of the study area.

|                  | Cluster 1 | Cluster 2 | Cluster 3 | Rest of the study area |
|------------------|-----------|-----------|-----------|------------------------|
| Number of patients inside | N = 57    | N = 31    | N = 644   | N = 588                |
| Sociodemographic |           |           |           |                        |
| Age (mean ± SD)  | 77.5 ± 8.1| 74.4 ± 8.2| 76.3 ± 8.6| 76.3 ± 8.6             |
| Cardiovascular risk factors (%) |           |           |           |                        |
| Dyslipidemia     | 22.8      | 29.1      | 38.7      | 39.3                   |
| Diabetes         | 8.8       | 0         | 16.9      | 14.5                   |
| Cardiac arrhythmia| 28.1      | 12.9      | 23.5      | 25.9                   |
| High blood pressure | 63.2      | 58.1      | 58.9      | 60.2                   |
| Stroke type (%)  |           |           |           |                        |
| Ischemic         | 89.5      | 93.5      | 87.9      | 89.9                   |
| Hemorrhagic      | 10.5      | 6.5       | 11.7      | 10.1                   |
| Stroke severity NIHSS (%) |           |           |           |                        |
| Low (0 to 5)     | 70.2      | 77.4      | 76.6      | 73.5                   |
| Medium (6-13)    | 24.6      | 12.9      | 15.4      | 16.8                   |
| High (14 or more)| 5.3       | 9.7       | 8.1       | 9.7                    |

Discussion

The spatial study produced health indicator maps of stroke incidence risk in Pays de Brest (Western France). We identified three clusters of census blocks with higher risk of stroke incidence for men compare to the rest of the study area. The degree of urbanization and the level of deprivation where men lived influence the unequal distribution of stroke incidence. Nevertheless the results indicate that the sens of the relation differ according to the location of the cluster. The men patient’s characteristics does not explained the risk difference. For women, the risk of stroke incidence is homogeneous through the study area, whatever the degree of urbanization of their residential census block, they seem more sensible to the level of deprivation.

Our study confirmed that the socioeconomic level of the women residential census blocks explained a large portion of stroke incidence risk in women. In other hand, women located in rural areas have the
same stroke incidence risk than women located in urban areas. The environmental pattern of census blocks with unfavorable socioeconomic levels represents lower level of education, higher proportion of blue collar or farmers and higher proportion of unemployment. Previous Swedish studies have demonstrated the same findings with an increased risk of stroke occurred with a decrease in annual income in women but not in men for Li et al (23), and a strong gradient in risk of stroke by years of education for women for Kuper et al (24). We hypothesize that effect of contextual deprivation on stroke incidence for women, may be partly mediated by the higher prevalence of health-damaging behavior, particularly cigarette smoking, poor dietary habits, sedentarily lifestyles, obesity and alcohol (3), and reduced used of healthcare services in deprived neighborhoods (25). Although the importance of individual and medical preferences in diet, (26) and the consummation of healthy food is well known for having benefits regarding chronic disease; this aspect is less real in deprived neighborhoods.

Our study revealed no difference in terms of presence of comorbidities as cardiovascular disease between women patients who have declared stroke according to the level of deprivation of their census block (data not shown). No difference was observed concerning the stroke type (around 87% of ischemic women patients) and the proportion of high or medium stroke severity are comparable whatever the level of deprivation of their residential census blocks (around 17% of women patients with medium and 12% with high stroke severity).

In our study, where men lived is a strong determinant of stroke incidence risk and four clusters were detected. Firstly, men located in the rural cluster composed by mostly deprived census blocks, have higher risk of stroke incidence. Previous studies demonstrate that rural and lower socioeconomic populations face barriers such as shortages of health professionals, lack of health insurance, transportation difficulties, later presentation, poor uptake of preventive or screening procedure, disparities in knowledge of risk reduction practices and geographic distance (27). Dobson et al conclude that people in rural areas may expose to double disadvantage: poor health services and exposure to health hazards (27). These census blocks are characterized by higher proportion of farmers and we hypothesized that population may be exposed to occupational hazards as pesticide
for example.

Secondly, men located in mostly favored and urban census blocks in the southern part of Pays de Brest have higher risk of stroke incidence too. The environmental patterns of these census blocks are different in nature. Firstly, census blocks in the city of Brest are urban and mostly unfavorable with higher proportion of blue collar, higher level of unemployment and lower education. They are surrounded by favorable suburban and isolated census blocks in the littoral of Pays de Brest with higher level of education, higher proportion of white collar or retirees. Secondly another cluster is composed by mostly rural and unfavorable census blocks located in pays de Landerneau. These different environmental patterns have a common point; they are close to the Stroke Center of Brest, the Stroke unit of Landerneau and the Stroke unit of the Army hospital of Brest too. So we hypothesis that patients in those clusters were more likely to receive regular and easy access to primary and specific care, in addition to having lower distance admission travel and higher accessibility of stroke units, which could explained a higher first stroke incidence.

To complete, our study reveal no differences in the presence of cardiovascular disease, or in term of severity between men patients within the three clusters. Grimaud et al, a recent study in Pays de Brest have found same results; patterns of risk factors, stroke type and severity were comparable among urban categories in both sexes (28). In Japan, a large population based prospective study reported the impact of neighborhood deprivation level on stroke incidence even after adjustment for individual socioeconomic indicators (29).

Local Poisson GWR models can be a valuable tool to explore the complex relationships between stroke, or others chronic disease, and risk factors when previous studies demonstrated spatial variability of the outcome. Using ordinary model, we make the assumption that the stroke incidence is equally distributed in the study area, whatever the degree of urbanization or the level of deprivation of the census blocks of the study area. However, it is not the case. This suggests that ordinary Poisson models are less accurate and reliable and GWR models bring significant improvement compare to ordinary Poisson regression, when it is appropriate. The ordinary and local modelling should be used to complement each other.
The main strength of our study included the use of the Brest stroke registry of Pays de Brest. This registry was validated by analysis of sources and capture-recapture method. This registry is the most relevant tool to study the epidemiology of stroke on condition that it complies with well-defined quality criteria so as to ensure both the quality and exhaustiveness of case-ascertainment (20). Small area analysis allows a deeper understanding of the geographic patterns of health inequalities and is essential for revealing local-level inequalities that are often masked when health estimates are produced at large area scales (cities, countries, and states). The study was carried out at the census block level in order to allow better investigation of spatial patterns of stroke incidence distribution.

One other strength of our approach is that we could draw in the map’s areas of significantly elevated risk of stroke incidence as baseline for future interventions and continued surveillance.

The interpretation of our findings must also consider some weaknesses. The excess stroke risk has mostly been attributed to variations in the distribution of stroke and risk factors such as race, socioeconomic status, geography (urban and rural) and prevalence of other chronic diseases.

Unfortunately, this study has not adjusted for variations in other chronic diseases and race. Some literature proposes the role of nutraceuticals in cardiovascular risk protection, information on the diets habits of patients would have been interesting to confirm this relation. Moreover, lower socioeconomic status of rural populations may influence access to quality care, information that we don’t have. Finally, we had no individual data on traditional risk factors such as physical inactivity, cholesterol and pharmacological treatments or the influence of genetics on the risk of cardiovascular disease of patients. Unfortunately, when patients arrived to the hospital for their first stroke, their physical aptitudes were altered and do not allowed them to respond correctly to a questionnaire.

Future studies could be focused on all dimensions of access as distance admission travel, accessibility of stroke units, regular and easy access to primary and specific care. Knowing that lipid levels control reduces cardiovascular risk of dyslipidemia individuals (26), pharmacological treatments, nutraceuticals that patient could have received need to be evaluated and comparing between clusters and the rest of the study area. Moreover, general efforts should be put in place to explore and investigate modifiable factors related to beliefs, diets and habits according to stroke prevention for
women in Pays de Brest.

Conclusions
In conclusion, we found geographic variation in stroke incidence in Pays de Brest. Our study confirms that for women, the highest rates were in the most deprived census blocks whatever the degree of urbanization in which they live. For men, clusters of higher risk of stroke incidence were detected: one cluster in the north of census blocks that combine rurality and deprivation. For the two others, whereas there environmental patterns are different by nature (urbanization and socioeconomic), they have lower distance and higher accessibility to stroke units as common point. These geographic differences do not appear to be attributable to differences in patient’s characteristics. This finding suggests that other factors as access to primary or secondary care may be responsible for this observed pattern and should be evaluated.

Declarations
Ethics approval and consent to participate: Not applicable
Consent for publication: Not applicable

Availability of data and materials: The access to Brest stroke registry data is regulated by a scientific committee, which analyzes each request. In this context, data available upon request. If readers need information about the data, they can contact Pr. Serge Timsit (who coordinates the Stroke registry).

Competing Interests: The authors declare that they have no competing interests.

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Author Contributions: OG, conception and design, AF, CP, OG; data analysis and interpretation; ST, EN, Data curation, CP drafting the article and OG, ST, EN revising it critically for important intellectual content. All authors read and approved the final manuscript.

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Abbreviations
AIC: Akaike Information Criterion, GWR: geographic weighted regression, INSEE: National Institute of Statistics and Economic Studies, NIHSS: National Institute of Health Stroke Score, SES: Socioeconomic
status.

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Figures
| Characteristics                        | Description                                                                 |
|----------------------------------------|-----------------------------------------------------------------------------|
| **Class 1: High SES in suburban, isolated towns** | Census blocks with high median income, high white collar, high retirees and high level of diploma |
| **Class 2: Low SES in rural areas**     | Census blocks with high farmers, high blue collar, low level of diploma       |
| **Class 3: High SES in urban areas**    | Census blocks with high white collar, without a car, high proportion of non-owner primary residence, alone in the household and low unemployment |
| **Class 4: Low SES in urban areas**     | Census blocks with high blue collar, without a car, high proportion of non-owner primary residence, alone in the household and high unemployment |

**Figure 1**

Description and geographic distribution of the SES & Urban-rural index categories, Pays de Brest.
Figure 2

Men and women age standardized stroke incidence risk per 1000 inhabitants-year, Pays de Brest.
Figure 3

Spatial distribution of the level of deprivation according to the Fdep index, Pays de Brest.
Figure 4

Clusters of higher risk of stroke and deprivation local parameters coefficients map using GWR models.

Supplementary Files
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formula1.JPG