Original Contribution

Exploring the Implications of Small-Area Variation in the Incidence of Multiple Sclerosis

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In this study, we describe the geospatial variation in the incidence of multiple sclerosis (MS) in Manitoba, Canada, and the sociodemographic characteristics associated with MS incidence. By using administrative health data, we identified all incident cases of MS in Manitoba from 1990 to 2006 (n = 2,290) and geocoded them to 230 neighborhoods in the City of Winnipeg and 268 municipalities in rural Manitoba. Age-standardized incidence rates for 1990–2006 (combined) were calculated for each region. By using the spatial scan statistic, we identified high-rate clusters in southwestern (incidence rate ratio (IRR) = 1.48) and central Winnipeg (IRR = 1.54) and low-rate clusters in north-central Winnipeg (IRR = 0.52) and northern Manitoba (IRR = 0.48). Multivariable Poisson regression showed a positive association between MS incidence rates and socioeconomic status. Despite our finding that MS incidence varied geographically and by socioeconomic status, the low Gini coefficient of 0.152 for MS incidence identified in this study suggests that the causes of MS are pervasive across all population groups. Searching for local-level causes of the disease may therefore not be as productive as investigating etiological factors operating at the population level. This may require an examination of macro-level differences in environmental exposures between high- and low-incidence regions of the world.

ecological analysis; geographic information system; incidence; multiple sclerosis

Abbreviations: IRR, incident rate ratio; MS, multiple sclerosis.

Multiple sclerosis (MS) affects more than 70,000 Canadians (1) and more than 2.5 million persons worldwide (2). Despite numerous studies, the etiology of the disease remains unknown. However, it is believed that multiple environmental factors act together in a genetically susceptible individual to cause disease (3). Studies of twins, half-siblings, and adoptees support the role of genetic factors in MS (4). However, the concordance of 25%–30% in monozygotic twins also supports a role for environmental factors.

Temporal and geographical variation in the incidence and prevalence of the disease also support a role for environmental factors. The incidence of MS is rising in some regions with stable populations (5). Along with the variation in prevalence between large geographical regions, such as North America and Asia (6), variation is also apparent within small geographical regions (7, 8). This likely reflects microscopic variations in genetic and environmental risk factors for the disease (9).

Most prior studies of microscopic geographical variations in MS, including those that used geospatial mapping approaches, have focused on measurements of prevalence rather than incidence (7, 10–12). However, prevalence is influenced by both the risk of the disease and survival; incidence is a more robust measurement of MS risk in a population. Further, few studies have used small-area spatial techniques to identify factors associated with increased MS incidence. Therefore, this study used various small-area visualization, exploration, and modeling techniques to describe the spatial variation in MS incidence in Manitoba and associated sociodemographic characteristics to gain insights into the etiology of MS.
MATERIALS AND METHODS

Setting and data sources

This study was conducted in the centrally located Canadian province of Manitoba. Manitoba has a population of 1.2 million people, more than 60% (660,000) of whom live within the provincial capital of Winnipeg (13). Manitoba has a universal health insurance plan; all residents of the province are eligible to receive health care services at no charge. All hospital, physician, and prescription claims are electronically captured at the time of service.

We identified all persons with MS in Manitoba by applying a validated case definition to physician, hospital, and prescription claims to identify persons with MS as previously described (14). Incident cases of MS for the years 1990–2006 were used in the analysis. Population denominator data for the years 1990–2006 were obtained from the provincial population registry, which captures nearly 100% of Manitoba residents. Ecological measures of socioeconomic status and ethnicity for the approximate study midpoint were obtained from the 2001 Canadian Census microdata files (15). Urban residence was assigned to persons living in the City of Winnipeg, which is the only urban center with a population greater than 50,000 in Manitoba.

Spatial methods

MS cases were geocoded to 230 neighborhoods in the City of Winnipeg by using 6-digit postal codes and to 268 health municipalities in rural Manitoba by using the municipal code recorded on the health record at the time of the first health claim for MS. Each of the resulting 498 geographical areas had an average population size of 2,300 persons. To visualize the spatial variation in MS rates across Manitoba, we calculated directly age-standardized incidence rates for the combined years 1990–2006 for each of the 498 geographical areas of interest. To control for unstable rate estimates resulting from small case counts, we generated stable rate estimates by using an adaptive mean nearest-neighbor smoothing algorithm (16–18) written in Epi Info, version 2003, software (Centers for Disease Control and Prevention, Atlanta, Georgia). This algorithm uses a spatial weights table calibrated to the case count of each geographical unit and identifies the spatial proximity of each geographical unit to all other geographical units in the study. Rates for geographical areas having fewer than 60 MS cases were stabilized by adaptively borrowing both numerator and denominator data from their closest geographical neighbors to the degree required to achieve a numerator of 60 or more cases. To facilitate comparison with previous studies, we calculated directly standardized rates by using the borrowed numerator and denominator data, with the 2001 general Canadian population as the standard population. The resulting small-area rate estimates are estimates of the incidence rates that would be expected to occur if there were sufficient time and population for the “true” underlying risk processes generating MS cases to manifest themselves in a stable manner. ArcGIS, version 10.0, software (Environmental Systems Research Institute, Inc., Redlands, California) was used to produce choropleth maps of rates, using the Jenks natural breaks algorithm to produce rate categories (19).

The spatial scan statistic was used to confirm that the patterns of spatial variation in the rates visualized above were not caused by random spatial variation. This statistic was calculated by using SaTScan, version 9.0, software (http://www.satscan.org), which identifies high- and low-rate cluster areas through the aggregation of contiguous geographical regions. The software was set to find age-adjusted clusters with a maximum size of 15% of the study population. Detected clusters were tested for significance by using 999 Monte Carlo random simulations, with only clusters significant at the P < 0.05 level retained for mapping. The SaTScan software assumes a Poisson distribution and calculates indirectly standardized rates for each identified geographical cluster. The specifics of the spatial scan statistic have been described elsewhere (20–23). Outputs from the SaTScan software were mapped by using ArcGIS, version 10.0, software (Environmental Systems Research Initiative) and were visually compared with the choropleth rate maps.

The Gini coefficient, which is a measure of the degree to which disease cases are distributed equally in relationship to the population risk across geographical areas (24, 25), was calculated by using the Epidat, version 3.1, software (Pan American Health Organization, Washington, DC). The Gini coefficient has been used previously to examine the geographical variability of infant mortality (26), obesity (27), and infection (28). It is calculated by ordering geographical areas from lowest to highest rank by case (incidence) rate, calculating a Lorenz curve, which is a plot of the cumulative proportion of the population (x-axis) against the cumulative proportion of cases in each risk category (y-axis), and then calculating the area between the axis of equality (Figure 1) and the Lorenz curve as a percentage of the total area below the axis of equality. The greater the degree to which cases are concentrated in a small number of high-risk geographies (i.e., distributed disproportionately in relationship to the population at risk), the greater the deflection of the Lorenz curve downward from the axis of equality and the higher the Gini coefficient. A high Gini coefficient (close to 1) indicates that most cases are located in a small proportion of the population, and a low Gini coefficient indicates that cases are distributed relatively evenly across geographical areas in proportion to the population at risk.

Figure 1. Gini coefficient analysis, province of Manitoba and the City of Winnipeg, Manitoba, Canada, 1990–2006. The Lorenz curve is a plot of the cumulative proportion of the population against the cumulative proportion of cases in each risk category.

We used Poisson regression analysis to model the relationship between MS incidence rates and ecological predictors including income, employment status, urban versus rural region of residence, and ethnicity (Table 1), all of which were entered as categorical variables. Overdispersion in the model was controlled by using the Φ overdispersion parameter in NCSS, 2007, software (NCSS, LLC, Kaysville, Utah). Regression modeling was undertaken at the individual level, and MS cases were attributed with ecological predictor characteristics of the geographical areas to which they were geocoded.

Because the primary objective of this step was to identify the broad population characteristics associated with variation in incidence, and not to develop a model with the best predictive power, a series of simple multivariable models was created, with each model containing the variable of interest at the ecological level and controlling for age at the individual level. A more complex multivariable model containing all predictor variables was created to identify the predictors having the greatest influence on MS risk. For each regression model, incidence rate ratios (IRRs), 95% confidence intervals, and the pseudo-$R^2$ were calculated.

The University of Manitoba’s Health Research Ethics Board approved the study, and the Manitoba Health Information Privacy Committee approved administrative data access.

**Table 1.** Incidence of Multiple Sclerosis, Determined by Poisson Regression Analysis, Province of Manitoba and the City of Winnipeg, Manitoba, Canada, 1990–2006

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Simple Model</th>
<th>Pseudo Model</th>
<th>Full Model</th>
<th>Full Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR 95% CI</td>
<td>Model $R^2$</td>
<td>IRR 95% CI</td>
<td>Model $R^2$</td>
</tr>
<tr>
<td>Region of residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1.00 Referent</td>
<td>0.27</td>
<td>1.00 Referent</td>
<td>0.33</td>
</tr>
<tr>
<td>Urban</td>
<td>1.25 1.15, 1.36</td>
<td>0.27</td>
<td>1.23 1.02, 1.47</td>
<td></td>
</tr>
<tr>
<td>Recent immigrant status, %f</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0–8.18</td>
<td>1.00 Referent</td>
<td>0.27</td>
<td>1.00 Referent</td>
<td></td>
</tr>
<tr>
<td>8.19–19.61</td>
<td>1.29 1.18, 1.42</td>
<td>0.96</td>
<td>0.81, 1.14</td>
<td></td>
</tr>
<tr>
<td>19.62–39.3</td>
<td>1.07 0.94, 1.22</td>
<td>0.76</td>
<td>0.57, 1.01</td>
<td></td>
</tr>
<tr>
<td>Self-reported Jewish ethnicity, %g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3.57</td>
<td>1.00 Referent</td>
<td>0.26</td>
<td>1.00 Referent</td>
<td></td>
</tr>
<tr>
<td>3.58–12.06</td>
<td>1.33 1.11, 1.59</td>
<td>1.22</td>
<td>1.01, 1.47</td>
<td></td>
</tr>
<tr>
<td>12.07–29.17</td>
<td>1.32 1.05, 1.66</td>
<td>1.19</td>
<td>0.92, 1.52</td>
<td></td>
</tr>
<tr>
<td>Visible minorities, %h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5.58</td>
<td>1.00 Referent</td>
<td>0.26</td>
<td>1.00 Referent</td>
<td></td>
</tr>
<tr>
<td>5.59–18.52</td>
<td>1.17 1.06, 1.29</td>
<td>1.0</td>
<td>0.87, 1.14</td>
<td></td>
</tr>
<tr>
<td>18.53–47.6</td>
<td>0.95 0.84, 1.09</td>
<td>1.08</td>
<td>0.82, 1.42</td>
<td></td>
</tr>
<tr>
<td>Unemployment, %i</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.61–8.59</td>
<td>5.52 3.42, 8.94</td>
<td>4.53</td>
<td>2.76, 7.42</td>
<td></td>
</tr>
<tr>
<td>8.60–18.80</td>
<td>3.82 2.32, 6.30</td>
<td>3.42</td>
<td>2.06, 5.66</td>
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<tr>
<td>18.81–34.92</td>
<td>1.00 Referent</td>
<td>0.32</td>
<td>1.00 Referent</td>
<td></td>
</tr>
<tr>
<td>Average family income j</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$14,866–$47,417</td>
<td>1.00 Referent</td>
<td>0.28</td>
<td>1.00 Referent</td>
<td></td>
</tr>
<tr>
<td>$47,418–$83,708</td>
<td>1.40 1.25, 1.57</td>
<td>1.14</td>
<td>1.01, 1.29</td>
<td></td>
</tr>
<tr>
<td>$84,709–$230,620</td>
<td>1.60 1.36, 1.89</td>
<td>1.25</td>
<td>0.93, 1.35</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incident rate ratio.

a Multivariable model containing only the single predictor variable of interest at the ecological level, controlling for age at the individual level.
b An estimate of the variation explained by the regression model.
c Multivariable model containing all predictor variables at the ecological level, controlling for age at the individual level.
d An estimate of the variation explained by the full regression model.
e Residents living within the City of Winnipeg.
g Percentage of the population in 2001 self-reporting Jewish ethnicity.
h Percentage of the population in 2001 who were not aboriginal, Caucasian, or white in skin color.
i Percentage of the population in the workforce in 2001 actively seeking employment.
j Average income (in Canadian dollars) of census families (married or common-law couples with or without children or lone parents of any marital status with at least 1 never married child living in the same dwelling) in 2001.
RESULTS

During the study period, we observed 2,290 incident cases of MS, with an average incidence of 12.1 cases per 100,000. Annual incidence rates per 100,000 population ranged from a low of 9.6 cases in 2006 to a high of 18.8 cases in 2000. The peak incidence occurred among those aged 35–44 years, with rates averaging 3 times higher in women than in men across all age groups.

Figure 2 shows a 4-fold variation in the rates of MS across Manitoba, ranging from 5.68 to 22 per 100,000 population. The highest rates occurred in the central and southwestern suburbs of Winnipeg and in a discrete rural area in western Manitoba, whereas the lowest rates were observed in northern Manitoba. Outputs from the spatial scan statistic (Figure 3) confirmed that these patterns were not caused by random spatial variation. As illustrated, the spatial scan statistic identified high-rate clusters of MS in southwestern (IRR = 1.48) and central suburbs (IRR = 1.54) of Winnipeg and low-rate clusters in northern Manitoba (IRR = 0.48) and in the north-central section of Winnipeg (IRR = 0.52). High-rate clusters contained 378 MS cases (16.5% of the total).

Although incidence rates of MS varied across Manitoba, the relatively low Gini coefficient of 0.152 (Figure 3) suggests that, for the population as a whole, the cumulative number of cases of MS is distributed relatively equally in relationship to the cumulative population at risk across geographical areas. As shown, only 15% of the MS cases are located in the 10% of the population residing in the highest-rate geographical areas for MS.

Simple multivariable regression modeling (Table 1) shows that rates of MS are tightly graded by measures of socioeconomic status and ethnicity, with the highest rates occurring in populations having the highest average family incomes (IRR = 1.60), the lowest levels of unemployment (IRR = 5.52), the highest levels of education (IRR = 1.56), and a high proportion of Jewish ethnicity (IRR = 1.32). Also, rates were elevated for populations containing a moderate proportion of recent immigrants (IRR = 1.29) and “visible minorities” (those who were not aboriginal, Caucasian, or white in skin color) (IRR = 1.17). Compared with rates in rural areas, MS rates were 25% higher in Winnipeg, the main urban center in Manitoba. All of these models had pseudo-$R^2$ values of greater than 0.26, demonstrating that they explained a moderate amount of the variation in the data set. In the full regression model, unemployment and urban residence retained statistical significance for all predictor categories, whereas recent immigrant status, Jewish ethnicity, and visible minority status lost significance for all predictor categories. Average family income retained statistical significance for the medium income category only. The full model had a pseudo-$R^2$ of 0.33.

DISCUSSION

In this study, we described the spatial variation in the incidence of MS in Manitoba, Canada. The incidence rates were
lowest in northern Manitoba and highest in 3 areas, 2 of which were in the City of Winnipeg and 1 of which was in rural western Manitoba. The spatial scan statistical analysis confirmed that these findings were not caused by random spatial variation, an observation further supported by the statistically significant association of MS incidence with sociodemographic factors.

Although studies of other regions have reported a latitude gradient, with increasing prevalence of MS on moving away from the equator (29), we did not observe such a gradient. A systematic review of the prevalence of MS noted that neither latitudinal nor longitudinal gradients were striking in Canada (30). A meta-analysis of incidence studies found that, after age standardization to a common population, the latitude gradient disappeared, although the studies included were largely limited to those conducted within 40–60 degrees of latitude. Investigators who have studied smaller regions in Italy have also argued that the latitude gradient for MS does not exist (11). The lack of a latitude gradient could also reflect a lack of variation in the underlying environmental risk factors.

We focused on mapping spatial variation of MS within 1 Canadian province (microvariation). Most prior studies that used spatial mapping techniques have used prevalence data, and those studies have also found variation in the prevalence of MS over small regions (10). One study that mapped incidence rates in France found that rates were higher in northeastern France and lower in southeastern France and along the Atlantic coast (7). In Sardinia, an unexpectedly high rate was identified in 1 village (8). We were unable to identify any such studies in North America.

These observed geospatial variations in incidence are likely to reflect variations in the underlying susceptibility of the population to disease and in exposure to environmental factors. Evidence supports an increased risk of MS in certain racial (Caucasian) and ethnic (Scandinavian and Scottish) groups and resistance among others including Maori, Samis, and First Nations Canadians (31), although they share similar environments. We were not able to explicitly evaluate the risk of MS among aboriginal populations, more of whom live in northern regions of the province. We found that incidence rates were 29% higher in populations with a moderate proportion of recent immigrants. In 2006, approximately 150,000 persons immigrated to Manitoba, of whom 41% were from Europe and 34% were from Asia (including 20% from southeast Asia) and the Middle East (15). Europe is recognized to be a high-prevalence region for MS (6). Although Asia and the Middle East have historically been considered to have low prevalence of MS, recent studies suggest this is changing (32). Further, studies of immigrants in Sweden (33), Norway (34), and British Columbia, Canada (35), suggest that some immigrants face an increased risk of MS after migration.

With respect to environmental factors, a positive dose-response relationship was noted between socioeconomic status
and the incidence of MS. This is consistent with observations made in the 1960s, in which ecological analyses suggested that MS was more common in regions with higher socioeconomic status and more urbanization (36), and that persons with MS were more likely to grow up under more sanitary conditions (37). The “hygiene hypothesis” suggests that immune regulation is impaired by lack of contact with infectious agents, including parasites, and by the loss of symbiotic microorganisms in the gut, thus enhancing susceptibility to allergic and autoimmune diseases (38). The observation of lower incidence rates in northern Manitoba is consistent with this hypothesis, because this region is home to many remote communities with substandard sanitation systems and crowded, poor-quality housing conditions. Impaired immune regulation as a causative factor in the development of MS is supported by a previously observed association between the incidence of MS and the incidence in Manitoba of inflammatory bowel disease, a disease for which impaired immune regulation related to early-life hygiene has also been proposed as a cause (39). An alternative explanation is that higher socioeconomic status is associated with better access to care and increased diagnosis of MS; however, health care in Canada is publicly funded, and thus this is unlikely to fully account for our findings.

We observed a very low Gini coefficient, indicating that, despite some spatial variability in incidence, MS cases are distributed relatively equally in relationship to the population at risk. Although the coexistence of significant spatial variability with a low Gini coefficient at first seems paradoxical, it occurred here because the populations experiencing a high incidence of MS are very small in size and therefore contribute little to overall variability. If all cases of MS could have been prevented in the 10% of the population living in the highest incidence areas of the province, 85% of the cases would remain (Figure 1). Similarly, the high-rate spatial clusters identified in the study by using the spatial scan statistic contained only 16.5% of the total MS cases. These observations suggest that the causes of MS are also pervasive and shared across population groups. The primary cause of a disease that is pervasive across all population groups may be difficult to detect and isolate in cross-sectional study designs because of a lack of variability in exposure. As illustrated by Rose (40), in a population where everyone smokes, it is difficult to establish an association between smoking and lung cancer; so other interindividual but less important causes, such as genetic susceptibility to disease, come to the explanatory forefront. Given the variation in MS incidence worldwide, it may be fruitful to consider the macro-level differences in environmental exposures between high- and low-incidence populations when searching for the etiology of MS.

This study has limitations. First, we used an ecological approach to model the relationships between sociodemographic characteristics and incidence. Such a design is often considered weak because it applies the ecological characteristics of geographical areas to individuals (41). However, ecological studies produce similar results to studies in which all predictors are measured at the individual level when geographical units have small, homogenous populations (42–44). We measured ecological predictors and applied them to individuals from a set of spatial units with an average population size of only 2,300 persons in 1998 (the study midpoint), minimizing the potential impact of population heterogeneity. Second, the reported pseudo-$R^2$ values only roughly estimate the amount of variance explained by the predictive models, because the $R^2$ statistic used in ordinary least squares regression does not extend to Poisson regression models, although it can be interpreted similarly (45), with 0 indicating no model fit and 1 indicating a perfect fit. Third, the study did not control for migration between the time of exposure and the development of MS. Despite this, we identified areas with a higher incidence of MS, findings that may have been more pronounced had migration been effectively controlled for. The low Gini coefficient observed in this study may partly be an artifact of uncontrolled migration. However, mobility rates are declining in North America, and the bulk of migration is now occurring over relatively short distances to adjacent neighborhoods with similar characteristics (46, 47), which suggests that migration may not be a large issue in ecological studies.

Fourth, the smoothing algorithm we used to stabilize risk estimates for geographical areas with small populations borrowed data from neighboring geographical areas to achieve a stable rate estimate. In some areas of the province, the smoother had to acquire data from neighboring geographies (north and south and rural) more aggressively than in others. However, the trade-off between the need to stabilize rates against the bias that arises from borrowing data from neighboring geographical areas was minimized by using an adaptive smoother that uses the minimum amount of extraneous data to achieve rate stability (16). Finally, we did not control for the effect of spatial autocorrelation on the standard errors of the predictive models because we modeled rates across individuals, not across geographical areas; the geographical location of individuals was used as a basis for attributing ecologically derived predictors of sociodemographic status. This differs from spatial regression analyses, which model outcomes against predictors at the aggregate geographical level and, therefore, must control for the effect of spatially correlated outcome values to generate a realistic inference from a sample to the population of interest (48). Because this study used the entire population of people with MS in Manitoba and not a sample, the precise calculation of the standard error was less critical (49).

This study also had several strengths. The study was population-based, and the incident cases of MS were identified on the basis of a previously validated administrative case definition for MS (14). We modeled MS incidence at the individual level by using categorical Poisson regression models, because they create rate stability for a relatively rare condition such as MS when rates are being calculated and compared across only 2 or 3 predictor categories instead of across all geographical areas. This avoids the need to build geographical models and load them with either unstable or smoothed rate estimates as would be the case when analyses are occurring at the geographical level instead of the individual level.

Although the diverse spatial techniques used in this study did not examine the impact of environmental factors directly, they provide insights into the etiology of MS that have implications for further research. The relatively even distribution of MS cases made explicit by the Gini coefficient analysis strongly suggests that there are population-level etiological factors for MS that need to be identified. Spatial modeling techniques such as geographically weighted regression (50),
which are more attuned to local heterogeneities in the relationships between variables, and demographic techniques that take into account migration and environmental exposures, may be helpful in revealing the population-level causes of MS in this context. Future investigative efforts might also productively focus on multiple immune-mediated diseases, including inflammatory bowel disease (39), that may share etiological factors.

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The results and conclusions presented are those of the authors. An official endorsement by Manitoba Health is not intended nor should it be inferred. Conflict of interest: none declared.

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