Short communication

Parkinson's disease prevalence and the association with rurality and agricultural determinants

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ABSTRACT

Introduction: Parkinson's disease prevalence has been associated with rurality and pesticide use in studies throughout the world. Here, Parkinson's disease (PD) medication usage was used to estimate prevalence in 79 urban and rural localities in Victoria, Australia (5.3 million people).

Methods: An ecological study design was used to determine whether PD medication usage, as a reporter of PD diagnosis, differed between 79 regions in Victoria, and whether variance in PD prevalence was associated with population demographics using multiple regression. Cluster formation probability was calculated using Monte Carlo modelling. The association between agricultural production and PD prevalence was conducted with Bonferroni-adjusted Mann-Whitney U tests.

Results: PD prevalence in Victoria was estimated to be 0.85%, which was greater in rural (1.02%) compared to urban (0.80%) locations; a difference that was abolished when corrected for demographic variables. Four of the highest prevalent regions (regardless of covariate adjustment) were clustered in northwest Victoria; a formation that was unlikely to be due to chance (P = 0.00095). These regions had increased production of pulse crops.

Conclusions: PD prevalence was not associated with rurality, but associated with areas of pulse production. Pulses are plants of the fabaceae family, where many of these species secrete the PD toxin, rotenone, as a natural pesticide, which may underlie increased risk. This study is limited by the data collection method, where people who do not take PD medication for their disease, or take PD-associated medication for other diseases, may impact the estimated prevalence.

1. Background

Parkinson's disease (PD) prevalence, estimated to range from 14 to 700 per 100,000 [1–11], has been associated with rurality and pesticide exposure in studies throughout the world [12,13]. We investigated the prevalence of PD in the state of Victoria, Australia. Victoria, approximately the size of the United Kingdom, has diverse land use and industry, which provides an opportunity to explore whether farming of different types of commodities is associated with increased PD prevalence. This study utilizes an ecological design to analyze the relationship between PD rates and farming intensity and rurality in Victoria, using multiple data sources and controlling for age, socioeconomic status, and gender.

2. Methods

2.1. Victorian local government areas

Victoria is divided into 79 local government areas (LGA). Population size, median age, socioeconomic status (determined by the Socio-Economic Index for Areas [SEIFA]), and gender proportion for each LGA was obtained through the Australian Bureau of Statistics (ABS) [14] census data. LGAs were classified as rural (n = 47) or urban (n = 32) according to the rural, remote and metropolitan area classifications (RRMA) developed by the Department of Primary Industries and Energy and the Australian Government Department of Health [15].
2.2. Estimation of Parkinson’s prevalence

Prescribing data for PD medication, as recorded by the Pharmaceutical Benefits Scheme, was accessed through the Australian Government Department of Health, and was used to estimate PD prevalence rates. The PD medications included were Benzhexol hydrochloride, Levodopa-carbidopa anhydrous, Rasagiline, Selegiline, Levodopa-benserazide, Benztrapine mesylate, Rotigotine, Biperiden hydrochloride, Pergoride, Amantadine hydrochloride, Pramipexole hydrochloride monohydrate, Apomorphine hydrochloride, Entacapone, Cabergoline, Levodopa-carbidopa anhydrous, entacapone and Pramipexole hydrochloride monohydrate. The number of individual patient prescriptions, by dispensing pharmacy, of all Parkinsonian drugs for the year 2011 was retrieved. The total number of individuals accessing prescriptions for PD medications in each LGA was expressed as a percentage of the LGA population. Multiple regression of PD prevalence rates in each region was performed, which included the demographic covariates for each region: median age, % male, socioeconomic status (SEIFA score), rurality (determined by RRMA criteria). PD prevalence rates were shown to be normally distributed using Shapiro-Wilk normality test (W = 0.988; P = 0.66).

The prevalence rates were adjusted for these covariates, and the adjusted prevalence rates for each LGA were then represented in a heat map of Victoria (Fig. 1).

2.3. Monte Carlo modelling

Monte Carlo modelling was used to determine the probability that the four highest prevalent regions form a cluster. The cluster was defined as each high prevalent LGA sharing at least one boundary with another high prevalent region and connected in a single land mass in any orientation. Using Excel, randomized prevalence rates for each of the 79 LGAs were allocated in 20,000 unique prevalence heat maps of Victoria. The probability of a cluster occurring was calculated by dividing the number of random clusters formed by the total number of maps generated.

2.4. Commodity production and farming intensity

Data on commodity production in 2011 and area used for commodity production according to each LGA was obtained from the ABS [16]. The area of production of each commodity was used as the estimate of commodity production, which was expressed as a proportion of the total area of that LGA.

Fig. 1. Parkinson’s disease prevalence and its association with agricultural determinants. (A–E) Covariate-adjusted (median age, sex proportion, socioeconomic status [SEIFA], rurality [RRMA]) prevalence rates for each LGA. (A–D): High prevalent region comprising the LGAs of (A) Yarriambiack (1.24%), (B) Buloke (1.73%), (C) Horsham (1.59%), and (D) Northern Grampians (1.43%). (E) Ballarat also had increased prevalence (1.35%), but is the only Victorian rural area with a movement disorders clinic. (F–J) Increased farming intensity of certain commodities in the high PD prevalent area of Victoria. Farming intensity of each commodity (n = 48) was calculated by dividing the total area dedicated to farming that commodity in each LGA by the total area of that LGA. The farming intensity of each commodity in the high prevalent LGAs were compared to that of the remaining LGAs by Mann-Whitney U test. The commodities in the high prevalent LGAs with significantly different farming intensities after correcting for multiple comparisons (Bonfornori correction) were (F) Barley, (G) Chickpeas, (H) Faba beans, (I) Lentils, and (J) Vetches.
Commodity production in Victoria is heterogeneous between regions; indeed most commodities are only produced in select regions—resulting in data structures that restrict the use of parametric statistical analysis. Therefore, the intensity of each commodity produced in the high prevalent region was compared with the rest of the rural LGAs in Victoria using Mann-Whitney U tests, corrected for multiple comparisons (Bonferroni, n = 48). Agricultural crops produced in Victoria are: Asparagus, Barley, Blueberries, Broccoli, Canola, Capsicums, Carrots, Cauliflowers, Chickpeas, Coriander, Faba beans, French Beans, Grapevines (drying grape), Grapevines (Table grape), Grapevines (Wine), Hay, Herbs, Hops, Kiwifruit, Lavender, Lentils, Lettuce, Lupins, Maize, Melons, Mang Beans, Mushrooms, Oats, Onions, Other Beans, Other Berries, Other fruit, Passionfruit, Peas, Peas, Potatoes, Pumpkins, Raspberries, Rice, Safflower, Sorghum, Soybeans, Sunflower, Sweet corn, Tomatoes, Triticale, Vetches, Wheat.

3. Results

We estimated that 45,375 individuals have PD in Victoria, which equaled 0.85% of the total population. The prevalence of PD was higher in rural (1.02%) compared to urban localities (0.80%; P = 0.001; Table 1). The average prevalence of each LGA (0.94%, SD: 0.32) was calculated to be higher than the prevalence calculated on a state-wide basis (0.85%; ie total number of PD subjects in the state divided by the total population of the state), because of a greater number of rural LGAs (47 vs 32), which have proportionally higher PD prevalence, influenced this mean analysis of each LGA. When PD prevalence was regressed by the demographic covariates: median age, proportion male, and the SEIFA socioeconomic indicator, rurality was no longer predictive of prevalence rates (β(S.E.) = -0.031[0.059]; P = 0.603). In this model, PD prevalence was positively associated with age (β(S.E.) = 0.017[0.0052]; P = 0.0016), and negatively associated with SEIFA score (β(S.E.) = -0.001[0.00050]; P = 0.019) and proportion of males in the population (β(S.E.) = -0.053[0.022]; P = 0.021).

A PD prevalence heat map of Victoria was constructed using adjusted prevalence data from the multiple regression model (Fig. 1). Four adjacent LGAs in northwest Victoria were identified with high prevalence, regardless of covariate adjustment: Yarriambiack (Fig. 1A; Adjusted: 1.24%; Raw: 1.48%), Buloke (Fig. 1B; Adjusted: 1.73%; Raw: 1.86%), Horsham (Fig. 1C; Adjusted: 1.59%; Raw: 1.61%) and Northern Grampians (Fig. 1D; Adjusted: 1.43%; Raw: 1.61%). The area of Ballarat also had a higher prevalence (Fig. 1E; Adjusted: 1.39%; Raw: 1.34%). Ballarat is the second most populous rural area in Victoria, however there was no association between area population of each LGA and PD prevalence (Pearson’s regression: r [2] = 0.0005, p = 0.841), so the increased prevalence in Ballarat could not be attributed merely to being a larger population center. The increased prevalence in Ballarat is likely attributed to the fact that it is the only rural area in Victoria with a specialized movement disorder clinic. The data collection method was based on the dispensing pharmacy, and it is likely that patients who travelled from other locations in Victoria to see a PD specialist would collect a new script of PD medication in Ballarat after the consultation. However, other underlying reasons for the increased prevalence in Ballarat cannot be excluded, nor can it be excluded that this higher rate occurred just by chance alone.

While we found that the adjustment for median age did not drive the increase in the high prevalent LGAs, we explored the age variable further to test whether the high prevalent LGAs had a disproportionate age demographic that could impact on our analysis. We found no difference in the median age in the 4 high prevalent LGAs (Mean = 45.0, SD = 4.2) compared to the other rural LGAs (Mean = 43.0, SD = 3.9; t-test: P = 0.34). We next looked at proportion of people aged over 65 (an age where PD risk increases). There was also no difference in the percentage of people over the age of 65 in the high prevalent region (mean in 22.2, SD = 4.9) compared to the other rural LGAs (Mean = 18.7, SD = 4.1; t-test: P = 0.12). So the proportion of people in the at-risk age demographic is not remarkable in the high prevalent region, and cannot explain our findings. To explore whether our analysis would differ if we corrected for a different age variable, such as proportion of people aged over 65, we performed a correlation analysis with this variable and the median age in each LGA. Supplementary Figure 1 demonstrates a very strong correlation between the proportion of people over the age of 65 and median age (r [2] = 0.67), and the high prevalent LGAs also map onto this relationship. We therefore can expect a very similar outcome if we adjusted for median age or proportion of people over the age of 65, especially since the adjustment for median age did not alter the sequence of high prevalent LGAs in the primary analysis.

Excluding Ballarat, the four highest areas for PD prevalence in rural Victoria were those identified above. Monte Carlo modelling was used to determine the probability of the four highest prevalent LGAs forming a cluster. In 20,000 reconstructions of the map of Victoria with randomized allocation of prevalence rates in each of the 79 LGAs, we identified 19 occasions where the four highest prevalent regions were all neighboring (each region connected to at least one other region, and all regions connected in a cluster). The probability that such a cluster occurred by chance was thus calculated to be P = 0.00095.

Given that the clustering of the four highest regions is unlikely due to chance, we next explored features of these four regions that might underlie the increased risk for PD. While the use of agricultural chemicals according to region was not possible to obtain, the ABS collects data for each agricultural commodity produced in each region of Victoria. In a survey of 48 commodities produced in Victoria, and after adjusting for multiple comparisons (Bonferroni correction), five commodities: barley, chickpeas, faba beans, lentils, and vetches (Fig. 1F–J), were identified with increased farming intensity in the high prevalent LGAs compared to the rest of the state. Except for barley, the commodities with increased farming intensity in the high prevalent LGAs were all from the pulse family of crops.

4. Discussion

To our knowledge, this is the first ecological study of regional PD prevalence in Australia and is the largest study exploring estimates for PD prevalence. We showed that rurality was not specifically associated with increased PD prevalence, but certain rural regions have increased prevalence. While high values, even outlier values, are normal features of any data set, and occur stochastically, our simulation modelling demonstrated that the clustering of four highly prevalent regions was unlikely to be due to chance. Epidemiological studies examining environmental exposures associated with PD have identified pesticide exposure as a possible risk factor for PD [12,13], including by comparing areas with high and low pesticide usage [17–19], and by investigating history of occupational exposure to pesticides in the agricultural industry [20]. Despite significant agricultural production and associated pesticide use throughout the state of Victoria, we found that

<table>
<thead>
<tr>
<th>Number of LGAs</th>
<th>Population</th>
<th>Median age (SD)</th>
<th>% Male (SD)</th>
<th>SEIFA score (SD)</th>
<th>Estimated individuals with PD</th>
<th>Ave crude prevalence % (SD)</th>
<th>Ave adjusted prevalence % (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>79</td>
<td>5,339,933</td>
<td>40.4 (4.9)</td>
<td>49.5 (0.89)</td>
<td>988 (50)</td>
<td>45,375</td>
<td>0.94 (0.32)</td>
</tr>
<tr>
<td>Urban</td>
<td>32</td>
<td>4,151,681</td>
<td>46.3 (3.3)</td>
<td>49.3 (0.84)</td>
<td>1024 (50)</td>
<td>33,231</td>
<td>0.80 (0.25)</td>
</tr>
<tr>
<td>Rural</td>
<td>47</td>
<td>1,188,252</td>
<td>42.0 (3.9)</td>
<td>49.7 (0.89)</td>
<td>962 (31)</td>
<td>12,144</td>
<td>1.03 (0.33)</td>
</tr>
<tr>
<td>Vic</td>
<td></td>
<td></td>
<td></td>
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</tbody>
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Table 1 Demographic comparisons between urban and rural LGAs.
in preference to that of the prescribing doctor, because it is more likely for a patient to travel to see their physician, rather than travel to a non-local pharmacy, however we cannot exclude the possibility that our analysis was impacted by the patient's choice of pharmacy. Finally, this was an ecological study; therefore postulates around causation associated with, for example, rurality or commodity production, cannot be made. This study does, however, provide a foundation for further investigation into the association between pulse production and PD risk.

**Authors roles**

1. Research Project:
   (A) Conception: DA, NW
   (B) Organisation: DA, NW
   (C) Execution: DA, NW, SA

2. Statistical Analysis:
   (A) Design: SA, ALB, AIB
   (B) Execution: SA, ALB, AIB

3. Manuscript Preparation:
   (A) Writing of the first draft: DA, SA, NW
   (B) Review and Critique: ALB, AIB

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.10.026.

**References**


