



## 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. LGA's 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].

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### 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, Bzotropine mesylate, Rotigotine, Biperiden hydrochloride, Pergolide, 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

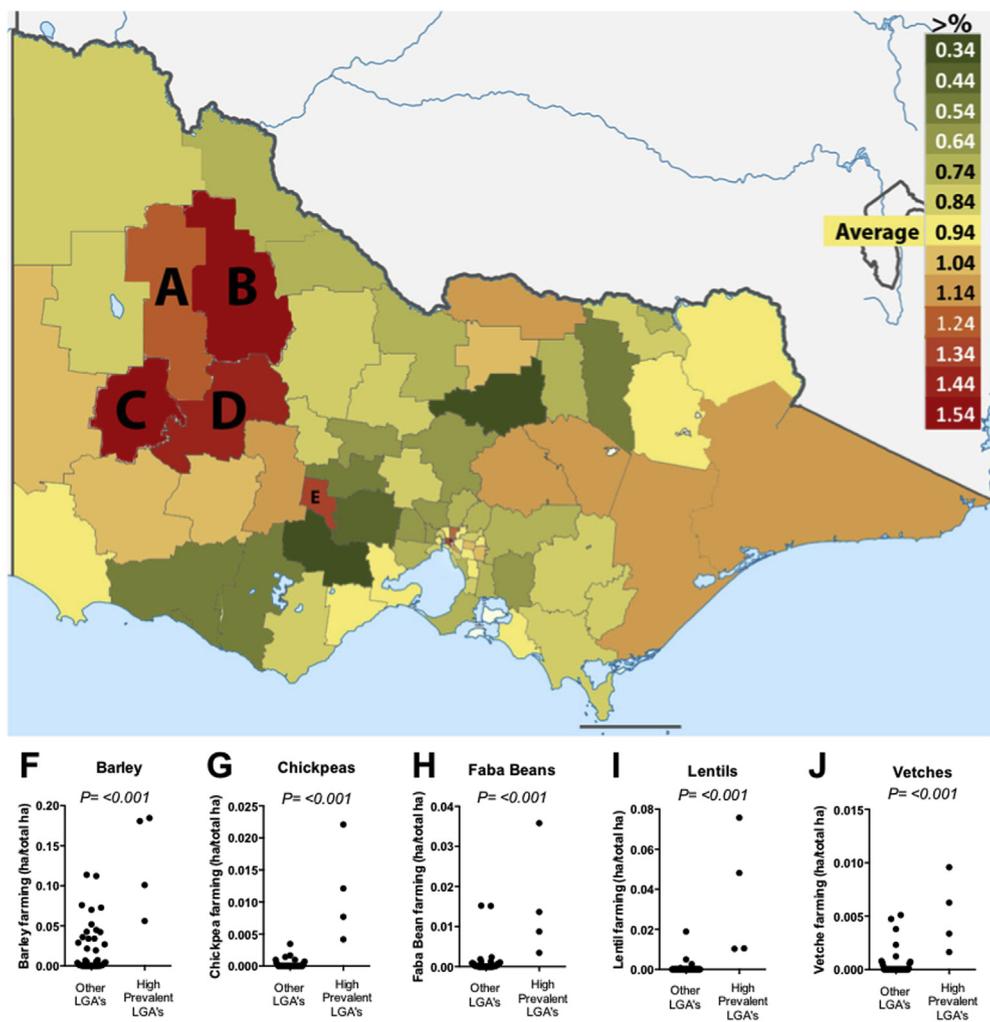
Monte Carlo modelling was used to determine the probability that

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.

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-Whiney 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, Mung Beans, Mushrooms, Oats, Onions, Other Beans,



**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 (Bonforoni correction) were (F) Barley, (G) Chickpeas, (H) Faba beans, (I) Lentils, and (J) Vetches.

**Table 1**  
Demographic variables comparison between urban and rural LGAs.

	Number of LGAs	Population	Median age (SD)	% Male (SD)	SEIFA score (SD)	Estimated individuals with PD	Ave crude prevalence % (SD)	Ave adjusted prevalence % (SD)
Total	79	5,339,933	40.4 (4.9)	49.5 (0.89)	988 (50)	45,375	0.94 (0.32)	0.94 (0.27)
Urban	32	4,151,681	36.43 (3.3)	49.3 (0.84)	1024 (50)	33,231	0.80 (0.25)	0.94 (25)
Rural	47	1,188,252	42.20 (3.9)	49.7 (0.89)	962 (31)	12,144	1.03 (0.33)	0.94 (0.28)
P Value	NA	NA	< 0.001	0.0499	< 0.001	NA	0.001	0.603

Other Berries, Other fruit, Passionfruit, 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 ( $\beta$ [S.E.] = -0.031[0.059];  $P = 0.603$ ). In this model, PD prevalence was positively associated with age ( $\beta$ [S.E.] = 0.017[0.0052];  $P = 0.0016$ ), and negatively associated with SEIFA score ( $\beta$ [S.E.] = -0.0011[0.00050];  $P = 0.019$ ) and proportion of males in the population ( $\beta$ [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 (Pearsons 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 PD prevalence was not generally increased in rural areas. However, we show that areas of pulse production were associated with increased risk for PD, which, to our knowledge, has not previously been observed. Increased prevalence in the identified region may be due to other factors, but the association with pulse production warrants further examination.

Pulses come from the fabaceae family, a family containing many species that produce the insecticide, rotenone, as an endogenous chemical defense mechanism. Rotenone, most commonly produced from *Derris elliptica*, *Derris mallaccensis*, *Lonchocarpus utilis* and *Lonchocarpus urucu*, has been used as an organic pesticide for more than 100 years, although its use in recent times has declined [21]. The concentration of rotenone in fabaceae plant material is biologically significant - there are several examples of the use of crushed root from fabaceae plants as fish poisons by tribal people around the world [22], and it was reported that consuming rotenone-containing plant material was a common means of suicide in New Ireland and Papua New Guinea [23]. While the toxicity of rotenone in humans is not well defined, a case study reported that deliberate ingestion of 200 ml of 0.8% commercial solution of rotenone was lethal, despite medical intervention [24].

Rotenone has been extensively linked to PD. Rotenone intoxication is used as a rodent model of PD [25], and historical exposure to rotenone is associated with 2.5 fold increase risk of developing PD [26]. *Cicer arietinum* (chickpea) produces rotenone in roots (0.105%), callus tissue (0.078%) and seeds (0.036%) [27,28]. We were unable to confirm the concentration of rotenone in the other fabaceae crops that we identified with increased production in this region (vetches, lentils and faba beans). It is therefore possible that the increased risk of PD - observed in those areas of pulse production - is contributed by exposure to the endogenous pesticide, rotenone, in plant material of pulses (potentially as aerosols during harvesting), and not exogenous application of pesticides. However, given the extensive literature linking pesticide usage and PD prevalence, we do not exclude the possibility that agricultural chemicals in this farming area might contribute to increased PD prevalence.

This study design is limited by failure to identify individuals who do not take PD medication for their disease, and imprecise exclusion of non-PD patients who take parkinsonian drugs for other conditions. A prior industry study into Parkinsonian drug use in Australia identified that 40% of patients received PD-related drugs for other conditions (e.g. Restless Legs Syndrome, Schizophrenia) [29]. Therefore, it is likely that we overestimated the PD prevalence in Victoria. However, we have no reason to assume that the dispensing of these medications for diseases other than PD would be disproportionate across different regions. Since the purpose of this study was to compare relative rates between different localities, we do not anticipate that this over-estimation would impact on our primary analysis. However, we cannot exclude the possibility that dispensing of PD-related medications for conditions other than PD was sufficiently disproportionate to impact on our estimate of PD prevalence according to location.

An usual finding from our study was that proportion of males in each location was inversely associated with PD prevalence. While this result was only modestly significant, this trend is unexpected, because it is often reported that PD incidence is higher in males than females [30]. This finding may point to another limitation of our study, that males are less compliant than females for PD medication usage [31], which may have impacted on the analysis.

This study also could not determine the age of each person receiving PD medication, so we therefore adjusted for this variable at the level of each LGA. This is a limitation of our analysis, but we found that median age or proportion of people aged over 65 did not differ between the high prevalent LGAs and the other rural LGAs, and therefore age could not be driving our results. We chose to use the median age as the adjustment variable in preference to other variables such as proportion over the age of 65 because PD also occurs in people below this age, and we also found that these two variables were highly related.

In addition, this study is limited by the fact that the data was collected at the level of the dispensing pharmacy. We chose to use data from pharmacies 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>.

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