

## ORIGINAL ARTICLE

# Parkinson's disease hospitalization rates and pesticide use in urban and non-urban regions of Brazil

## Hospitalizações por doença de Parkinson e uso de agrotóxicos em áreas urbanas e não urbanas do Brasil

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**How to cite:** Santos ASE, Krawczyk N, Parks CG, Asmus CFI, Câmara VM, Lima J, Meyer A. Parkinson's disease hospitalization rates and pesticide use in urban and non-urban regions of Brazil. *Cad Saúde Colet*, 2021;29(4):496-508. <https://doi.org/10.1590/1414-462X202129040236>

### Abstract

**Background:** Few studies have evaluated the role played by pesticide exposure in the development of Parkinson's disease (PD) in Brazil. **Objective:** This study aimed to investigate the association between pesticide use and PD hospitalization in Brazilian micro-regions. **Method:** Pesticide expenditure per capita in 1985 and PD hospitalization rates (HR) from 1997 to 2007 were calculated for all 552 Brazilian micro-regions. The Spearman's correlation test was used to compare pesticide expenditure and PD HR by sex, age, and urban and non-urban micro-regions. Micro-regions were grouped according to the quintiles of pesticide expenditure. PD HR ratios (HRR) were calculated to compare PD HR across the quintiles of pesticide expenditure. **Results:** Moderate correlation ( $r=0.518$ ;  $p<0.001$ ) between PD HR in non-urban micro-regions and pesticide expenditure was observed. In non-urban areas, compared with micro-regions of the first quintile of pesticide use, PD HRR ranged from 1.70 to 5.90 in micro-regions of higher pesticide use. In general, regardless of sex and age, the higher the use of pesticides, the greater the magnitude of PD HRR. **Conclusion:** Our results suggest that pesticide use is associated with PD in Brazil, especially in non-urban areas where pesticides are used more intensively.

**Keywords:** pesticides; Parkinson's disease; environmental health; hospitalizations; Brazil

### Resumo

**Introdução:** Poucos estudos avaliaram os efeitos da exposição a agrotóxicos sobre a doença de Parkinson (DP) no Brasil. **Objetivo:** Este estudo teve por objetivo investigar essa associação em microrregiões brasileiras. **Método:** As taxas de hospitalização (TH) por DP de 1997 a 2007 e os gastos per capita com agrotóxicos em 1985 foram calculados para todas as 552 microrregiões brasileiras. O coeficiente de correlação de Spearman foi utilizado para verificar relação entre as variáveis. Foi calculada a razão de TH (RTH) por DP entre quintis de gastos com agrotóxicos em microrregiões urbanas e não urbanas, usando o 1º quintil como referência. **Resultados:** Uma moderada correlação ( $r = 0,518$ ;  $p < 0,001$ ) foi observada entre as TH por DP em microrregiões não urbanas e gastos com agrotóxicos. As associações entre gastos com agrotóxicos e RTH por DP foram maiores nas microrregiões não urbanas. Comparadas às microrregiões

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Financial support: none.

Conflict of interests: nothing to declare.

Received on: June 28, 2019. Accepted on: Aug. 10, 2020



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do 1º quintil, as TH por DP foram de 1,70 a 5,90 vezes maiores nas demais microrregiões. Foi observada uma relação dose-reposta entre as TH por PD e os quintis de uso de agrotóxicos, independentemente de sexo e idade. **Conclusão:** Nossos resultados sugerem que o uso de agrotóxicos pode estar associado à DP no Brasil, especialmente em áreas não urbanas, onde o uso é mais intenso.

**Palavras-chave:** agrotóxicos; doença de Parkinson; saúde ambiental; hospitalizações; Brasil

## INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disorder<sup>1</sup>. The common motor symptoms of PD, such as bradykinesia, tremor, rigidity and postural instability, are related to the degeneration of dopaminergic neurons in the nigrostriatal pathway in the midbrain<sup>2</sup>. PD incidence in the United States (US) and European countries ranges from 8/100,000 to 18/100,000<sup>3</sup>. Sex differences have also been observed in Western populations, where PD incidence is higher among males<sup>4</sup>. There is no data on PD incidence in Brazil, but the estimated prevalence is around 3%, which is higher than that observed in the US, Europe, and Asia (108/100,000 to 1600/100,000)<sup>5-7</sup>.

According to the World Health Organization (WHO)<sup>8</sup>, PD and other neurodegenerative diseases together may surpass cancer and become the second most common cause of death by 2040. Aging is an important risk factor for PD, and the incidence of this disease gradually increases in older age groups<sup>8-10</sup>. Brazil has been experiencing a demographic transition, with declining fertility and birth rates and fast population aging<sup>11</sup>, which is expected to increase the number of PD cases and their costs to the public health system<sup>12,13</sup>.

Lifestyle, aging, and environmental factors are associated with the increasing trend of PD incidence<sup>14-17</sup>. Two meta-analyses have supported the positive association between occupational exposure to different pesticide classes and PD<sup>18,19</sup>. Evidence of the association between specific pesticides and PD is limited to the herbicide *paraquat*, the insecticide *rotenone*, and the fungicide *maneb*<sup>19,20</sup>. Regarding environmental exposure to pesticides, a recent meta-analysis found a positive association between rural living, farming activities, and well-water consumption and PD<sup>21</sup>.

The use of pesticides in Brazil has substantially increased in the past two decades, with a growth rate of 163% in the 1990s, followed by an increase of 190% in the 2000s<sup>22-24</sup>. This increase led Brazil to the first position of pesticide use in the world in 2009<sup>22,23</sup>. The use of pesticides at such high levels and without proper training has raised concerns about the long-term health effects on Brazilian agricultural workers and exposed communities. Several studies have investigated the association of pesticides with health outcomes among Brazilian agricultural workers, including cancer and reproductive and mood disorders<sup>25-27</sup>. However, research on pesticides and PD in Brazil is limited to small retrospective studies<sup>28-30</sup>. In this study, we aimed to expand the literature on this theme by investigating the association between pesticide expenditures and PD hospitalization rates (HR) across a national sample of urban and non-urban regions in Brazil.

## METHOD

### Study design

We carried out an ecological study using data from the 1985 per capita expenditure on pesticides in each Brazilian micro-region as surrogate measures of population exposure to these toxins. Expenditure data were compared to PD HR in the same micro-regions between 1997 and 2007. We used the 1985 per capita expenditure on pesticides as a surrogate measure of population exposure to pesticides and the PD HR between 1997 and 2007 to guarantee the temporal sequence between exposure and effects. The Brazilian Institute of Geography and Statistics (IBGE) defines micro-regions as groups of adjacent municipalities that have similar socioeconomic characteristics. We conducted separate analyses for 52 urban and 500 non-urban micro-regions. Urban status was based on the IBGE definition.

## Pesticide expenditure data

Data on pesticide expenditure in each Brazilian farm were obtained from the Agricultural Census of 1985. Farm pesticide expenditures were then pooled within each micro-region and converted to US dollars (USD) based on the average currency conversion rate in July 1985. The total pesticide expenditure, in USD, for each micro-region was then divided by the number of inhabitants in the same year to obtain the per capita expenditure on pesticides for each micro-region. The use of the 1985 Agricultural Census data on pesticide expenditure relies on the fact that PD is a chronic illness with a long latency period, and the environmental exposures that may increase the risk of PD can occur decades before the onset of signs and symptoms. Thus, to investigate the association of pesticide use with PD HR in Brazil between 1997 and 2007, data on pesticide use available in the 1985 Agricultural Census were used to calculate the microregions' per capita pesticide expenditures. This allowed us to observe a difference of at least 10 years between exposure (1985) and outcome (1997-2007). Although there are three more recent Brazilian agricultural censuses, pesticide use data from two of them (2006 and 2017) could not have been used because exposure would have occurred after the disease outcome (1997-2007 PD HR), and data from the 1996 census would not have allowed observation of the long latency period of PD.

## Hospitalization data

Hospital admissions due to PD (ICD-10: G20) that occurred between 01 January 1997 and 31 December 2007 among individuals aged  $\geq 20$  years were retrieved from the Brazilian Hospital Information System for each micro-region. PD HR were calculated using the total number of hospital admissions between 1997 and 2007 divided by the mid-interval population (2002), multiplied by 100,000 for each micro-region. PD HR were stratified by age (20-49, 50-69, and  $\geq 70$ ) and sex. The hospitalization data used in the present study are publicly available through the Brazilian Public Health System Information Technology (IT) Department<sup>31</sup> and, therefore, did not require Institutional Review Board (IRB) review.

## Hospitalization rate ratios (HRR)

The Spearman's rank correlation coefficient between per capita pesticide expenditure and HR was calculated for each age and sex stratum. All micro-regions (separated into urban and non-urban) were grouped based on the quintiles of per capita pesticide expenditure, and HR were calculated for each quintile. The HRR were then obtained by dividing the HR of each quintile by the HR of the first quintile, which was used as the reference group. The HRR and their 95% confidence intervals (95% CI) were stratified by age and sex.

## RESULTS

Table 1 provides a description of the per capita expenditure on pesticides in Brazilian urban and non-urban micro-regions in 1985 and the Spearman's rank correlation coefficients between per capita pesticide expenditures and PD HR according to age and sex. Per capita pesticide expenditure was 4 times higher in non-urban than in urban micro-regions. Correlation coefficients between per capita pesticide expenditure and PD HR were highest for non-urban ( $r=0.518$ ) and lowest in urban ( $r=0.372$ ) micro-regions. When the analysis was restricted to non-urban micro-regions, older groups showed higher correlation coefficients ( $r=0.485$ ), though no differences were observed according to sex.

Table 2 presents the HRR for PD stratified by age and micro-region status to the population using pesticide expenditure data from 1985. Overall, for all ages, in urban and non-urban micro-regions, quintiles with higher pesticide expenditure presented higher PD HR than the reference quintile. However, in urban micro-regions, the highest HRR was observed in the 4th quintile. Non-urban micro-regions exhibited the highest PD HRR in all quintiles compared with urban micro-regions, with a consistent rise in PD HRR as quintiles increase in per capita pesticide expenditure. In the edge age groups (20-49 and  $\geq 70$ ), a significant difference in PD

**Table 1.** Correlation between pesticide expenditure per capita in Brazilian micro-regions in 1985 and PD hospitalization rates from 1997 to 2007

	<b>Urban micro-regions (52)</b>	<b>Non-urban micro-regions (500)</b>	<b>All micro-regions (552)</b>
<b>Year</b>	<b>1985</b>		
<b>Population</b>	54,747,410	76,891,862	131,639,272
<b>Sales (USD)</b>	190,972.27	1,182,961.47	1,373,933.74
<b>Per capita expenditure on pesticides</b>	0.003	0.012	0.008
<b>Spearman's rank correlation coefficient</b>	<b>N</b>	<b>r</b>	<b>p</b>
<b>All micro-regions</b>	552	0.496	<0.001
<b>Urban micro-regions</b>	52	0.372	0.007
<b>Non-urban micro-regions</b>	500	0.518	<0.001
<b>Non-urban micro-regions by age</b>			
<b>20-49 years</b>	500	0.368	<0.001
<b>50-69 years</b>	500	0.425	<0.001
<b>≥70 years</b>	500	0.485	<0.001
<b>Non-urban micro-regions by sex</b>			
<b>Men</b>	500	0.500	<0.001
<b>Women</b>	500	0.479	<0.001

HRR could already be observed by the 3rd quintile, which has a PD HRR over two times that of micro-regions in the lowest quintile. By the 5th quintile, the HRR for PD were up to 4 to 6 times higher.

The HRR for PD stratified by age and micro-region status to male according to 1985 pesticide expenditure quintiles are presented in Table 3. In the urban micro-regions, males showed higher PD HRR in the 4th quintile compared with the 5th quintile, especially for the edge age groups (20-49 and ≥70). Differences in the magnitude of PD HRR for males between urban and non-urban micro-regions were observed for all quintiles analyzed, with PD HRR being the highest in non-urban micro-regions. Non-urban micro-regions showed a gradual shift towards higher PD HRR with increasing pesticide expenditure. Edge age groups showed the highest PD HRR in the top quintiles, in particular in the 5th quintile, where the increase was five times higher than in the 1st quintile.

When the PD HRR for females was stratified by age in urban micro-regions, an increased PD HRR was observed in the 4th quintile compared with the 1st quintile, mainly for the 50-69 and ≥70 age groups. In the 5th quintile for females, the PD HRR was lower than that in the 4th quintile. Non-urban regions showed a dose-response-like pattern with an increase in the PD HRR across pesticide expenditure quintiles compared with the reference quintile. By the 5th quintile, the PD HRR were up to 5 to 7 times that of micro-regions in the reference quintile. (Table 4).

**Table 2.** Hospitalization rates (HR) and hospitalization rate ratios (HRR) for PD between 1997 and 2007 according to the quintiles of pesticide expenditure in urban and non-urban Brazilian micro-regions in 1985 stratified by age

Micro-region	N	20-49 years			50-69 years			≥70 years			Total		
		HR	HRR (95% CI)	N	HR	HRR (95% CI)	N	HR	HRR (95% CI)	N	HR	HRR (95% CI)	
<b>Urban</b>													
1st quintile	219	1.19	Reference	778	15.71	Reference	1045	69.41	Reference	2042	8.23	Reference	
2nd quintile	67	1.11	0.93 (0.71-1.22)	260	18.55	1.18 (1.03-1.36)	268	70.31	1.01 (0.88-1.16)	595	7.60	0.92 (0.84-1.01)	
3rd quintile	76	1.46	1.23 (0.95-1.59)	300	21.94	1.40 (1.22-1.60)	366	97.73	1.41 (1.25-1.58)	742	10.70	1.30 (1.20-1.41)	
4th quintile	76	2.06	1.72 (1.33-2.24)	287	30.93	1.97 (1.72-2.25)	409	162.70	2.34 (2.09-2.63)	772	15.84	1.92 (1.77-2.09)	
5th quintile	38	1.56	1.31 (0.93-1.84)	198	26.93	1.71 (1.47-2.00)	241	104.60	1.50 (1.31-1.73)	477	14.01	1.70 (1.54-1.88)	
<b>Non-urban</b>													
1st quintile	62	0.70	Reference	279	11.87	Reference	291	40.03	Reference	632	5.30	Reference	
2nd quintile	97	1.18	1.69 (1.23-2.32)	399	16.95	1.42 (1.23-1.66)	526	65.01	1.62 (1.41-1.87)	1022	9.00	1.70 (1.54-1.87)	
3rd quintile	198	2.52	3.59 (2.70-4.78)	574	25.48	2.15 (1.86-2.48)	775	107.00	2.67 (2.34-3.06)	1547	14.27	2.69 (2.45-2.95)	
4th quintile	226	2.62	3.74 (2.82-4.95)	784	30.32	2.55 (2.23-2.93)	1242	152.8	3.82 (3.36-4.34)	2252	18.73	3.53 (3.23-3.86)	
5th quintile	274	3.75	5.38 (4.06-7.05)	1220	53.95	4.55 (3.99-5.18)	1711	251.00	6.27 (5.54-7.10)	3205	31.26	5.90 (5.41-6.42)	

95%CI = 95% confidence interval

**Table 3.** Hospitalization rates (HR) and hospitalization rate ratios (HRR) for PD between 1997 and 2007 according to the quintiles of pesticide expenditure in urban and non-urban Brazilian micro-regions in 1985 for males and stratified by age

Micro-region	20-49 years			50-69 years			≥70 years			Total		
	N	HR	HRR (95% CI)	N	HR	HRR (95% CI)	N	HR	HRR (95% CI)	N	HR	HRR (95% CI)
<b>Urban</b>												
1st quintile	128	1.47	Reference	486	22.03	Reference	475	83.95	Reference	1089	9.48	Reference
2nd quintile	37	1.27	0.86 (0.60-1.25)	156	24.16	1.10 (0.92-1.31)	150	99.17	1.18 (0.98-1.42)	343	9.25	0.97 (0.86-1.10)
3rd quintile	37	1.47	1.00 (0.69-1.44)	170	26.66	1.21 (1.02-1.44)	183	123.30	1.45 (1.24-1.74)	390	11.79	1.24 (1.11-1.40)
4th quintile	44	2.42	1.65 (1.17-2.32)	154	34.44	1.56 (1.30-1.87)	191	178.31	2.12 (1.80-2.51)	389	16.39	1.73 (1.54-1.94)
5th quintile	24	1.99	1.35 (0.87-2.09)	120	33.95	1.54 (1.26-1.88)	116	116.30	1.38 (1.13-1.70)	260	15.65	1.65 (1.44-1.89)
<b>Non-urban</b>												
1st quintile	31	0.70	Reference	148	12.88	Reference	151	44.61	Reference	330	5.59	Reference
2nd quintile	50	1.24	1.77 (1.13-2.77)	202	18.08	1.40 (1.14-1.74)	290	77.68	1.74 (1.43-2.12)	542	9.82	1.76 (1.53-2.01)
3rd quintile	78	1.99	2.85 (1.88-4.32)	302	27.66	2.15 (1.76-2.61)	382	115.2	2.58 (2.14-3.12)	762	14.31	2.56 (2.25-2.91)
4th quintile	102	2.36	3.37 (2.25-5.03)	419	33.13	2.57 (2.13-3.10)	593	159.1	3.56 (2.98-4.26)	1114	18.71	3.35 (2.96-3.78)
5th quintile	140	3.83	5.45 (3.69-8.04)	660	59.12	4.59 (3.84-5.48)	756	242.1	5.43 (4.56-6.46)	1556	30.58	5.47 (4.86-6.16)

**Table 4.** Hospitalization rates (HR) and hospitalization rate ratios (HRR) for PD between 1997 and 2007 according to the quintiles of pesticide expenditure in urban and non-urban Brazilian micro-regions in 1985 for females and stratified by age

	20-49 years			50 - 69 years			≥70 years			Total		
	N	HR	HRR (95% CI)	N	HR	HRR (95% CI)	N	HR	HRR (95% CI)	N	HR	HRR (95% CI)
<b>Urban</b>												
1st quintile	91	0.94	Reference	292	10.64	Reference	569	60.64	Reference	952	7.14	Reference
2nd quintile	30	0.96	1.01 (0.67-1.53)	104	13.76	1.29 (1.03-1.62)	118	51.32	0.85 (0.69-1.03)	252	6.11	0.86 (0.74-0.98)
3rd quintile	39	1.46	1.55 (1.06-2.25)	130	17.81	1.67 (1.36-2.06)	183	80.94	1.33 (1.13-1.58)	352	9.71	1.36 (1.20-1.54)
4th quintile	32	1.71	1.81 (1.21-2.70)	133	27.66	2.60 (2.12-3.19)	218	151.2	2.50 (2.13-2.91)	383	15.31	2.14 (1.90-2.41)
5th quintile	14	1.14	1.21 (0.69-2.12)	78	20.43	1.92 (1.50-2.47)	125	95.66	1.58 (1.30-1.91)	217	12.45	1.74 (1.50-2.02)
<b>Non-urban</b>												
1st quintile	31	0.70	Reference	131	10.90	Reference	140	36.04	Reference	302	5.02	Reference
2nd quintile	47	1.13	1.61 (1.03-2.54)	197	15.92	1.46 (1.17-1.82)	236	54.15	1.50 (1.22-1.85)	480	8.23	1.64 (1.42-1.89)
3rd quintile	120	3.03	4.33 (2.92-6.43)	272	23.42	2.15 (1.74-2.65)	393	100.20	2.78 (2.29-3.37)	785	14.24	2.84 (2.49-3.24)
4th quintile	124	2.88	4.11 (2.77-6.09)	365	27.63	2.53 (2.08-3.10)	649	147.60	4.09 (3.41-4.91)	1138	18.75	3.74 (3.29-4.24)
5th quintile	134	3.67	5.24 (3.55-7.75)	560	48.90	4.49 (3.71-5.43)	955	258.50	7.17 (6.01-8.56)	1649	31.93	6.36 (5.63-7.19)

## DISCUSSION

Our study showed an association between per capita pesticide expenditure and HR for PD in Brazil. The correlation between pesticide expenditure and PD HR was highest in non-urban micro-regions, and the regions with higher pesticide expenditures experienced higher PD HR with a pronounced increasing gradient of HR with increasing pesticide expenditure in non-urban micro-regions. Although we were not able to evaluate direct exposure to pesticides in hospitalized individuals, people living in regions with heavier pesticide consumption may experience higher environmental or occupational exposure. Therefore, these results also corroborate findings of other studies that observed positive associations between environmental or occupational pesticide exposure and PD<sup>32,33</sup>.

A meta-analysis found a summary risk ratio (sRR) of 1.62 (95% CI=1.40-1.88) for PD in case-control, cohort, and cross-sectional studies assessing occupational and non-occupational exposure to pesticides. In addition, studies based on job-title exposure have reported higher risks estimates (RR=2.5; 95% CI=1.50-4.10) than studies based on self-reported exposure (RR=1.5; 95% CI=1.30-1.80)<sup>34</sup>. Increased risk of PD has also been associated with exposure to the insecticides *chlorpyrifos* and *rotenone*, the fungicides *maneb* and *mancozeb*, and the herbicide *paraquat* in the states of Texas and California, USA<sup>35-37</sup>. Some studies also have suggested possible associations of PD risk with exposure to hexachlorocyclohexane<sup>38,39</sup>. In Brazil, the use of these pesticides has been reported since the 1960s, but it was not possible to estimate the amount used in the micro-regions assessed in 1985<sup>40-43</sup>.

Our results also suggest that, in non-urban micro-regions, PD was associated with pesticide expenditure even in the lower age groups. Whereas a diagnostic code for PD suggests a clinical judgment, misdiagnosis of early PD onset sometimes occurs due to the absence of some classic PD symptoms found in older individuals<sup>44</sup>. While PD affects mostly people over the age of 60<sup>45</sup>, positive correlations between pesticide exposure and early PD onset have previously been observed<sup>46,47</sup>. Our results support these findings and suggest that early PD and pesticide exposure be further investigated.

Our analyses of urban micro-regions showed that PD HR, in general, rose in the quintiles with higher pesticide expenditure, but they dropped in the last quintiles, which showed the highest pesticide expenditure. This unexpected drop in the magnitude of the HRR observed for the 5th quintiles may reflect differences in the distribution of other risk factors for PD not evaluated in this study, including exposure to solvents, head traumas, air pollution<sup>48-51</sup>, and several other possible confounders related to the distribution and grouping strategies of Brazilian municipalities into urban micro-regions.

Brazilian cities with high industrial activities and human development indexes (HDI) are often defined as urban even when they present high levels of agricultural activity. Moreover, pesticides are also heavily used in urban areas of Brazil to control vector-borne diseases such as dengue, malaria, leishmaniasis, and Chagas disease<sup>52,53</sup>. As pesticides play an important role in pest control and even in regular gardening activities in urban areas, they should also be considered as a possible risk factor for some pesticide-related diseases, such as PD, in these areas<sup>54</sup>. Some studies have suggested positive associations between PD and exposure to the insecticides *malathion* and hexachlorocyclohexane<sup>38,55</sup>. The Brazilian vector control program in the 1980s and 90s indicated the use of these specific insecticides for the control of dengue and malaria mosquitoes<sup>56-58</sup>.

Hospitalizations may be influenced by the disease prevalence (PD prevalence is higher in males), access to health care and treatment, disease severity, comorbidities, and socioeconomic and cultural disparities<sup>59</sup>. Sex differences in PD HR were partially observed in our study. In urban areas, men consistently had higher PD HR compared with women in all quintiles of pesticide use. Accordingly, men also showed higher PD HR in non-urban areas compared with women, but less consistently. These results might be related to the lack of adjustment for variables associated with HR such as disease severity, comorbidities and socioeconomic and cultural disparities that affect men and women differentially<sup>60-62</sup>.

Brazilian rural areas have a significant dependence on public health facilities, insufficient number of health professionals, and weak health infrastructure. Thus, differences in medical



assistance between urban and non-urban micro-regions may have an impact on PD HR. However, we believe that this difference in access to health services may not have had an influence on the association between PD and pesticide exposure, as we do not believe that access to health care would have changed across the quintiles of pesticide use in Brazil.

It is important to stress that there is no consensus on the association between pesticide exposure and PD in the literature, although most of the evidence points to that direction<sup>21</sup>. Measurement of population exposure is crucial to precisely estimate the magnitude of the association between PD and pesticide use<sup>32</sup>. In our study, the lack of information regarding specific classes and types of pesticides used (insecticides, herbicides, fungicides, etc.) did not allow us to perform a more detailed analysis of the relationship between specific pesticides and PD. Despite this limitation, the different types of crops found in each studied quintile of pesticide expenditure suggest differences in the types of pesticides used among them. In 1985, in terms of planted area in the five studied quintiles, rice, corn, and coffee were always among the five most common crops, regardless of the quintile. In addition, soybean was also among the most common crops in four of these quintiles (2nd, 3rd, 4th, and 5th). Cassava, sugar cane, and beans were the fifth most common crop depending on the specific quintile. On the other hand, recent reports from the Brazilian Institute of Environmental and Renewable Natural Resources (IBAMA) show small variations in the five most commonly sold pesticides in the five Brazilian regions between 2009 and 2018<sup>63</sup>. Comparing these two years, glyphosate and 2,4-D were among the five most commonly commercialized pesticides in all Brazilian regions in both 2009 and 2018. The third most common pesticide used in all Brazilian regions in 2009 was the herbicide *atrazine*, while in 2018, the fungicide *mancozeb* took its place. The fourth and fifth most used pesticides varied in each of the Brazilian regions and the two compared years. In 2009, these places were taken by the fungicides *carbendazim*, sulfur, copper, *mancozeb* and thiophanate-methyl, the herbicide *picloram*, and the insecticides *malathion* and *methamidophos*. On the other hand, in 2018, the fungicides sulfur and copper, the herbicides *picloram*, *paraquat*, triclopyr-butotyl, and *atrazine*, and the insecticides acephate and *malathion* took these positions.

The nature of this ecological analysis imposes some limitations to our results, as the associations observed at the micro-region level may not reflect the true individual relationship of exposure to pesticides and PD. Another limitation to this study is that we were unable to verify whether expenditure on pesticides in a micro-region correlates with pesticide use in that micro-region, as pesticides may be purchased in a certain region, due to a more competitive price, but actually be used in another. In addition, there is no data on specific pesticides used in each Brazilian municipality. Data on specific crops cultivated in Brazilian municipality could be used as a proxy to estimate pesticide use in Brazil. However, considering the 5,570 municipalities in Brazil, it would have been challenging to describe the types of crops cultivated in each of these micro-regions. Furthermore, due to difficulty in determining PD diagnosis<sup>64</sup>, misdiagnosis may lead to underestimation of HR.

Despite these limitations, the use of a large database in this study has enabled a robust evaluation of the data. To ensure that exposure to these pesticides would have occurred before PD development, diagnosis, and hospitalization, we used data on per capita pesticide expenditure in 1985. Data on pesticide use in each Brazilian municipality are provided by the Brazilian agricultural censuses. In that sense, there are four of these censuses with pesticide use data so far: 1985, 1996, 2006, and 2017. It is our best understanding that to ensure temporality between exposure and outcome, the 1985 pesticide use data are more appropriate than those of the other censuses. In addition, although we agree that there has been an exponential growth in pesticide use in Brazil, the variation in per capita pesticide expenditure across Brazilian municipalities, and consequently micro-regions, has not change significantly over time, which is confirmed by the high correlation between per capita pesticide expenditures in Brazil in 1985, 1996, and 2006 (data not shown). Finally, since the mid-1990s, the amount and types of pesticides used in Brazil have increased dramatically<sup>24</sup>. The use of glyphosate, for instance, has increased exponentially since the 2000s. In fact, Brazil has become one of the top consumers of this chemical in the world<sup>65,66</sup>. Since environmental exposure may occur decades

before the onset of PD signs and symptoms, the effect of pesticide consumption in more recent years may play a role in the development of PD and, therefore, in PD HR, in the coming years.

The results of this study corroborate the hypothesis that the use of pesticides may be associated with an increased risk of PD. The findings also suggest that the relationship between pesticide consumption and PD HR is higher and more gradual in non-urban micro-regions. Pesticide use in Brazil is a significant public health concern due to its potential long-term effects of environmental and occupational exposure. Our results support that there is a relationship between PD, a chronic neurodegenerative disease, and pesticide exposure; however, further high-quality studies are required to prove this association.

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