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Geospatial analysis of individual-based Parkinson's disease data supports a link with air pollution: A case-control study

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ABSTRACT

Background: The etiology of Parkinson's disease (PD) remains unknown. To approach the issue of PD's risk factors from a new perspective, we hypothesized that coupling the geographic distribution of PD with spatial statistics may provide new insights into environmental epidemiology research. The aim of this case-control study was to examine the spatial dependence of PD prevalence in the Canton of Geneva, Switzerland (population = 474,211).

Methods: PD cases were identified through Geneva University Hospitals, private neurologists and nursing homes medical records (n = 1115). Controls derived from a population-based study (n = 12,614) and a comprehensive population census dataset (n = 237,771). All individuals were geographically localized based on their place of residence. Spatial Getis-Ord Gi* statistics were used to identify clusters of high versus low disease prevalence. Confounder-adjustment was performed for age, sex, nationality and income. Tukey's honestly significant difference was used to determine whether nitrogen dioxide and particulate matters PM_{10} concentrations were different within PD hotspots, coldspots or neutral areas.

Results: Confounder-adjustment greatly reduced greatly the spatial association. Characteristics of the geographic space influenced PD prevalence in 6% of patients. PD hotspots were concentrated in the urban centre. There was a significant difference in mean annual nitrogen dioxide and PM_{10} levels (+3.6 μg/m3 [$p < 0.001$] and +0.63 μg/m3 [$p < 0.001$] respectively) between PD hotspots and coldspots.

Conclusion: PD prevalence exhibited a spatial dependence for a small but significant proportion of patients. A positive association was detected between PD clusters and air pollution. Our data emphasize the multifactorial nature of PD and support a link between PD and air pollution.

1. Introduction

While the etiology of Parkinson's disease (PD) remains unknown, its pathogenic mechanisms likely involve the cumulative result of a genetic vulnerability, numerous environmental insults and their interactions in the context of brain aging. A large number of epidemiological studies have identified a variety of risk and protective factors that may modulate the occurrence of PD [1–3]. Air pollution has been suggested to promote PD neuropathology [4,5]. However, epidemiological studies examining the impact of air pollution on PD occurrence have reported

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inconsistent results [6–9]. Meta-analyses found marginally significant increased risk of PD with long-term exposure to air pollution [10,11].

To approach the risk and protective factors' issue from a new perspective, we hypothesized that coupling the geographic distribution of PD using precise (non-aggregated) geospatial information with spatial statistics, may provide new insights into environmental epidemiology research. In particular, the use of non-aggregated data is likely to facilitate the identification of an interaction between disease and environment. This type of methods also avoids bias associated with the aggregation method which infers that variation at the individual level is lost. In addition, we used spatial statistics taking into account the concept of "shared environment" between individuals living in the same type of neighborhood [12], what is well adapted to PD-related investigations.

The spatial dependence of PD prevalence was explored in the Canton of Geneva, Switzerland, using an individual-based spatial analysis of data. Clusters of high and low PD prevalence were identified and compared to the distribution of environmentally relevant PD risk factors such as air pollution, drinking water supply and pesticide-associated landcovers.

2. Materials and methods

2.1. The Canton of Geneva

The Canton of Geneva has one University Hospital, several private clinics and an easy access to general practitioners and private neurologists (n = 27 in 2013). It is characterized by a well-defined urban centre surrounded by nearly a third of its territory devoted to agriculture. In 2013, 474,211 people lived in the 282.5 km^2 Canton of Geneva of which 50.1% were over the age of 40 (Cantonal Population Office). Of these, 84% lived in the urban centre.

2.2. Study population

2.2.1. Parkinson's disease cases

This research was part of a larger study aimed at determining the prevalence and incidence of degenerative and non-degenerative parkinsonism in the Canton of Geneva [13]. The study was approved by the Geneva Ethics Committee (protocol 13–019). Geneva residents who were diagnosed with PD over a 10-year study period (01.01.2003 to 31.12.2012) were identified and considered as candidates for this analysis. Patients (n = 1115) were identified through three sources: 1) All inpatients and outpatients examined at any of the Geneva University Hospitals; 2) Patients followed by private neurologists; 3) Individuals living in nursing homes.

Confirmation of PD diagnosis was ascertained by a movement disorders specialist (VF) through a detailed verification of clinical notes and imaging data. Patients were included in the study if they fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria [14]. Characteristics such as date of birth, gender, age, residential address, and whether or not they lived in a nursing home, were all recorded. Patients were excluded from the analyses if their address could not be geolocated or if their age had not been recorded. Patients living in a nursing home (n = 385) were used for the confounder adjustment, but were excluded from the spatial analyses to exclude artifactual hotspots.

2.2.2. Controls

Each year, a representative sample of the Geneva adult population is selected through an ongoing cross-sectional population-based study called the "Bus Santé" study [15] by stratifying the Canton's residential list by sex and 10-year age strata. Eligible individuals include all legal, non-institutionalized residents aged between 20 and 75. Once selected, participants undergo a standardized medical examination and complete comprehensive standardized questionnaires on various sociodemographic characteristics and risk factors for major lifestyle diseases. All participants over the age of 40 (i.e the age of the youngest PD patients in our cohort) collected from 01.01.1995 to 31.12.2014 were included in this analysis (n = 12,614). They were individually geocoded and compared to geocoded patients in order to control for the variable population density across the Canton. Only their age, sex and address were used in the adjustment procedure.

2.3. Variables

2.3.1. Geocoding

The geographic coordinates of each individual-level PD case and "Bus Santé" control were derived using the IDPADR (IDentifiant Permanent de l'ADResse), a unique and permanent street number identifier used by the Canton to manage building addresses across its territory. To do so, the participants' listed residential address was matched to the one given in the Canton's comprehensive spatial database (www.ge.ch/donnees/demarche-open-data). Each patient and "Bus Santé" control could thus be represented on a map by a point corresponding to their listed residence.

2.3.2. Demographic and socioeconomic variables

The Canton of Geneva publishes annual statistics on the demographic and socio-economic composition of the population to the statistical sub-sector level (spatial unit) also called GIREC (Groupe Interdépartemental de REprésentation Cartographique) level (Supplementary material-A). Participant sex and nationality were compared with the Geneva census population to ensure representativeness. As the "Bus Santé" study collects information on individuals younger than 75 only, we incorporated census data (n = 237,771) to match over 75 year-old patients with controls by age (Supplementary material-B). Individual level data were created from the 2013 official Canton census aggregated data from summary statistics representing each GIREC so that data could be directly compared with the individual level of PD cases (Supplementary material-C). The same method was used to adjust for other sociodemographic confounders such as nationality [16] and median income [17] which could play a role in the prevalence of PD and access to health services respectively (Supplementary material-D et -E). A total of 237,771 data points were created from the census dataset representing all individuals (including cases and controls) over the age of 40 who resided in the Canton in 2013.

2.4. Statistical analysis

2.4.1. Confounder adjustment

After standardizing confounding variables, the lme4 R library was used to fit a generalized linear mixed-effects model to the population dataset according to a binomial distribution through maximum likelihood estimation and bound by optimization by quadratic approximation. The adjustment procedure was carried out by means of a logistic mixed-effect model (Supplementary material-F). By taking the Pearson residuals (i.e. adjusted PD values), we quantified the proportion of the disease outcome that could not be explained by the four confounding risk factors (age, sex, nationality, income). The georeferenced Pearson residuals were then used for the spatial analysis whereby it is assumed that, after having adjusted for the effects of the known confounding factors, any spatial association exhibited by the residuals can be predominantly attributed to external spatially-dependent factors.

2.4.2. Spatial analysis

Getis-Ord Gi* statistics [18] were computed to identify hotspots and coldspots of PD prevalence. Getis indicators measure spatial dependence and evaluate the existence of local clusters in the spatial arrangement of a given variable (here, adjusted PD values) by comparing the sum of standardized individual values in a specified neighborhood size (or spatial lag) proportionally to the sum of individuals' adjusted PD values throughout the whole study area. Statistical significance testing was

based on a conditional randomization procedure using a sample of 999 permutations, and the Bonferroni/Sidak procedure was used to correct for multiple comparisons [19]. A hotspot refers to a statistically significant cluster of high values (i.e. an area where the adjusted PD prevalence is higher than expected at random), whereas a coldspot is a statistically significant cluster of low values where adjusted PD prevalence is lower than expected by chance. All sampling sites which are not significant are said to be neutral. Clusters shown in our study correspond to a significance level of $p < 0.05$ and a neighborhood of influence, or spatial lag of 1,000 m. In order to preserve anonymity, individual points were deleted if the cluster represented less than 3 people.

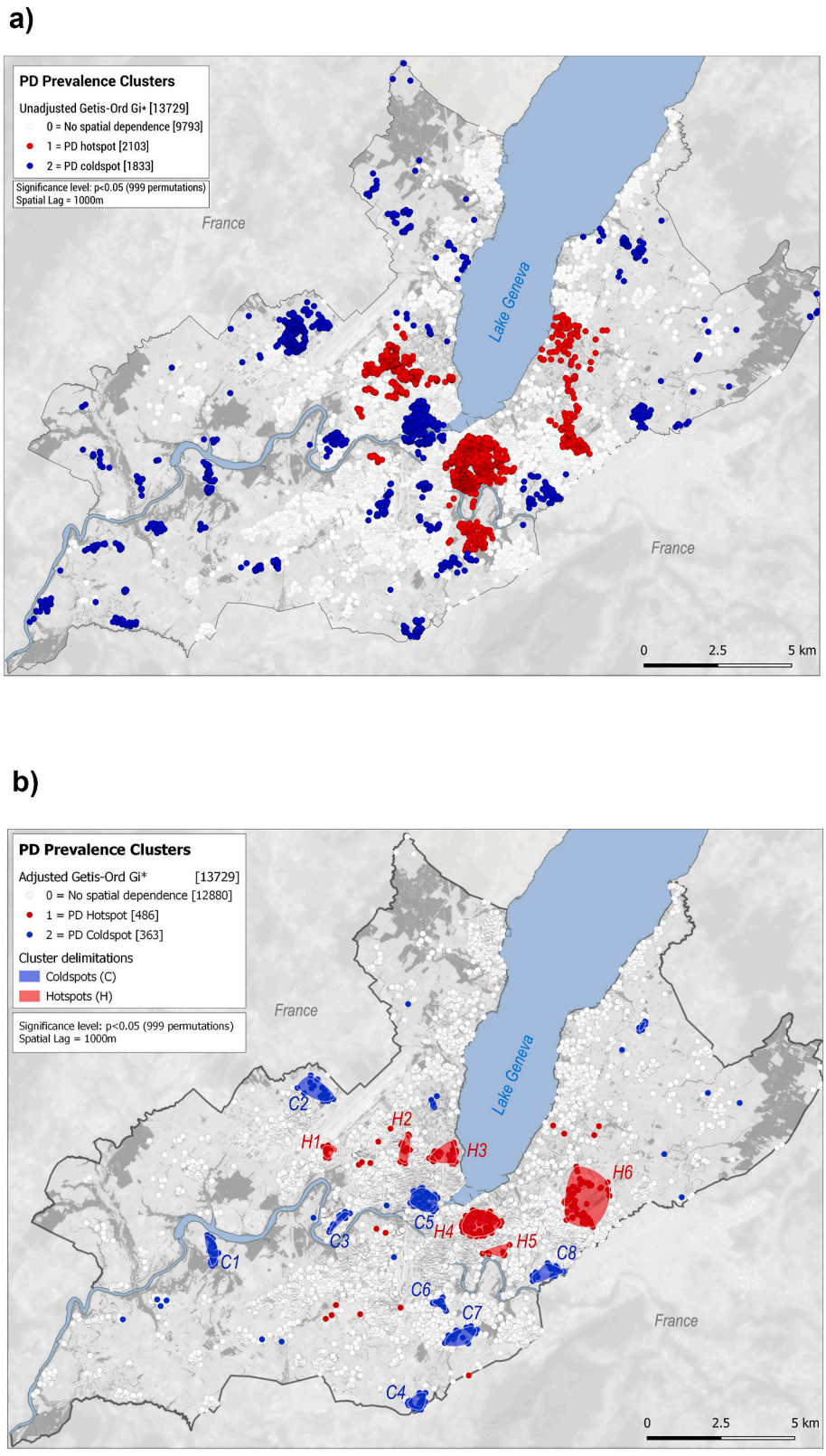

Fig. 1. Getis-Ord Gi* clusters of high and low PD prevalence in the Canton of Geneva.
Unadjusted clusters are shown in Panel A and adjusted clusters in Panel B. A red point indicates a person who lives in an area where PD is more common than expected at random (i.e. hotspot), independent of whether this person has PD or not, based upon where they live. A red point is statistically more likely to have PD than someone given by a blue point. Coldspots are given by blue points and represent areas with lower PD prevalence than expected by chance based upon where they live. PD prevalence at all other sampling locations is considered to be spatially independent and is represented by white points. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.4.3. Association with environmental covariates

2.4.3.1. Air pollution. Concentrations of dioxide nitrogen (NO2) and particulate matters (PM_{10}) were available with a spatial resolution of 10 m for the year 2010. We used a single spatial overlay function to transfer attributes from the two raster layers (NO2 and PM_{10} expressed in $\mu g/m^3$) to the point dataset of individuals. The mean NO2 and PM_{10} concentration was calculated within the three following groups: PD prevalence hotspots, coldspots, and neutral class. Finally, we used Tukey's honestly significant difference (HSD) to determine whether the means of these three groups were significantly different from each other (Supplementary material-G.a.).

2.4.3.2. Other environmental covariates. Data on drinkable water supply and pesticide-associated landcovers (Supplementary material-G.c.) are presented in Supplementary material-G.b. and G.c.). We used Tukey HSD to verify if the mean of the proportion of the disease outcome that could not be explained by the confounding risk factors, were significantly different between the four groups of drinkable water supply.

3. Results

A total of 1516 PD patients were identified. Incidence and prevalence rates are reported elsewhere [13]. Briefly, our estimates parallel European figures. Four hundred and one patients were excluded (15 because their addresses could not be geolocated, 1 because his age was not recorded, 385 because they were living in a nursing home). Eventually, 1115 PD patients were included in the spatial analysis, as were all "Bus Santé" participants over the age of 40 (n = 12,614; corresponding to 91.9% of the whole "Bus Santé" population).

3.1. Individual-level PD prevalence

The unadjusted PD prevalence clusters obtained with a 1,000 m spatial lag and a significance level of 0.05 are shown in Fig. 1A. About three quarters of individuals (patients and controls) resided in areas where PD was not geographically dependent (n = 9793; 71.3%). Conversely, 2103 individuals (15.3%) were located in regions where PD was more common than would be expected by chance (i.e. hotspots), and 1833 (13.4%) individuals resided in regions where PD was less common than would be expected by chance (i.e. coldspots). After adjustment for age, gender, Swiss nationals and neighborhood median income, the number of individuals classed as residing in regions where PD prevalence was geographically neutral increased by 3087 (n = 12,880, 93.8%) implying that a significant portion of the geographic variability observed in Fig. 1A could be explained by demographic and socioeconomic factors (Fig. 1B). PD cases tended to reside in wealthier areas ($p < 0.05$). Four hundred and eighty-six individuals (i.e. 3.5% of the whole population) resided in areas with high PD prevalence whereas 363 individuals (2.6%) lived in areas with low PD prevalence. A total of 6 hotspots and 8 coldspots were identified. They were not superimposed

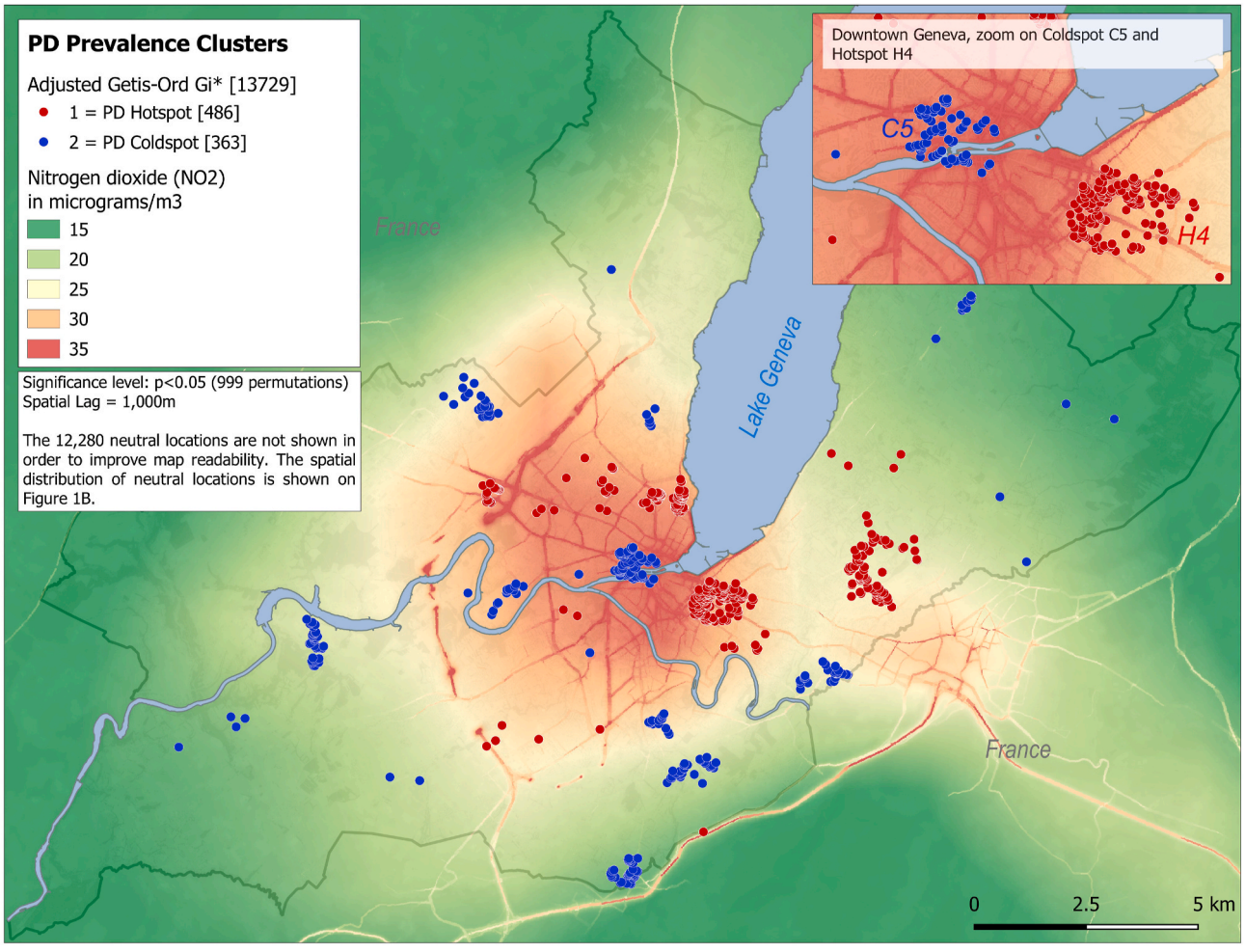

Fig. 2. Individual-level adjusted Getis-Ord Gi* clusters superimposed on the spatial distributions of atmospheric pollution.
Hotspots and coldspots are superposed on the spatial distributions of atmospheric pollution. In order to improve map readability, the 12′880 neutral locations are not shown on the map. The spatial distribution of the latter is shown on Fig. 1B.

or intermingled and did not seem to be distributed randomly throughout the Canton. Most hotspots were located in the urban environment of Geneva. Coldspots were spread over the Canton, in urban and less urban zones.

3.2. Spatial associations with hypothesized risk factors

Fig. 2 shows the individual-level clusters identified through Getis-Ord Gi* clustering superimposed on the spatial distributions of NO2 concentrations. The comparison of mean NO_2 concentration between Getis-Ord classes revealed significant differences between groups (Table 1, Suppl. Table-A and B). The NO_2 concentration was higher by 3.6 μg/m^3 ($p < 0.001$) in the adjusted hotspots than in the adjusted PD coldspots. In hotspots, the mean annual NO_2 concentration (30.25 μg/m^3) even slightly overpassed the limit authorized by the Swiss Ordinance on Air Pollution Control (OAPC) (<30 μg/m^3). The difference in NO_2 means between hotspots and coldspots for non-adjusted Getis-ord classes was smaller (3.17 μg/m^3, $p < 0.001$) also, yet significant. One coldspot (C5 as indicated in Fig. 1B) was located within an area of high level of NO2. All other coldspots were located in the countryside. In the coldspot C5, the mean NO2 concentration was 34.29 μg/m^3, i.e. 4 μg/m3 higher than the NO2 mean measured in hotspots. Despite this, the mean NO2 concentration in coldspots was 3.6 μg/m^3 lower than in hotpots. The mean NO2 concentration for all other coldspots was of 22 μg/m3.

The mean PM_{10} concentration was also significantly different between all groups (hotspot vs coldspot, hotspot vs neutral, and coldspot vs neutral) ($p < 0.001$) (Table 1, Suppl. Table C and D). The averaged PM_{10} concentration was at least 2 μg/m^3 higher than the maximum authorized by the OAPC (<20 μg/m^3) in all Getis-Ord classes. Interestingly, the mean of NO_2 and PM_{10} concentrations in all groups for adjusted and non-adjusted Getis-Ord classes showed a perfectly coherent behavior, with the highest concentrations measured in hotspots, medium concentrations in the neutral classes, and the lowest values in coldspots.

As regards to drinking water supply, no clear link was found between sources of drinkable water and PD hotspots or coldspots (Fig. 3, Supplementary material-H, Supplementary Table E and F). Regarding pesticide exposure, the hotspots did not overlap with the areas susceptible to demonstrate high values by visual inspection (Supplementary Figure, Supplementary material-H).

4. Discussion

Using an individual-level data spatial analysis employing well-established indices of spatial association and a multi-level adjustment method developed for georeferenced data, we found that 6% of patients developed PD not at random but following a spatial dependency. Clusters of high and low PD risk were identified highlighting a particular structure in the spatial distribution of PD in the Canton of Geneva. These clusters partly related to known confounders such as age, sex, nationality and income. Indeed, the number and size of clusters reduced after adjusting for these confounders, but significantly persisted at the same location. A significant positive association was detected between PD clusters and the atmospheric NO_2 and PM_{10} concentrations.

Across the PD literature, geographic approaches have rarely been used. The distribution of PD is analyzed either worldwide through metanalyses comparing prevalence and incidence between countries [20] or at the county level [21–23] through disease mapping and/or geographic correlation. These studies suggested a spatial dependence of PD. PD has been shown to be more frequent in Europe and North America compared to Africa and possibly Asia [20]. A few studies have examined the spatial patterning of PD occurrence or its spatial associations with potential risk factors [7,21,23–26]. Most of these studies used aggregated data to evaluate disease prevalence according to arbitrary political or administrative spatial units [21–23,27], further highlighting the originality of our individual approach. To the best of our knowledge, only four studies used an individual-level data spatial analysis to study the association between PD and risk factors [7,26,28,29]. A positive association was demonstrated between PD incidence and ambient exposure to organophosphate pesticides [26] as well as to ozone pollution [7]. Toro et *al.* found no clear association between ambient air pollution and PD [28] whereas Yuchi et *al* found that road proximity and air pollutants (NO2, $PM_{2.5}$) were associated with a slight

Table 1
NO2 and PM10 concentrations among the PD hotspots, coldspot and neutral areas.

NO2 concentration and adjusted PD clusters							
TUKEY HSD/KRAMER			Alpha 0.05				
Group	mean NO2 concentration μg/m3	N	ss	df	q-crit		
Neutral	28.23	12880.00	351031.64				
Hotspot	30.25	486.00	5928.43				
Coldspot	26.67	363.00	15788.86				
		13729.00	372748.94	13726	3.31		
Q Test							
Group 1	Group2	Diff-mean	Std err	q-stat	lower	upper	p-value
Neutral	Hotspot	2.03	0.17	11.90	1.46	2.59	<0.001
Neutral	Coldspot	1.55	0.20	7.93	0.90	2.20	<0.001
Hotspot	Coldspot	3.58	0.26	14.01	2.73	4.43	<0.001
PM10 concentration and adjusted PD clusters							
TUKEY HSD/KRAMER			Alpha 0.05				
Group	mean PM10 concentration μg/m3	N	ss	df	q-crit		
Coldspot	22.74	363.00	996.03				
Hotspot	23.37	486.00	471.24				
Neutral	23.00	12880.00	18604.97				
		13729.00	20072.24	13726.00	3.31		
Q Test							
Group 1	Group2	Diff-mean	Std err	q-stat	lower	upper	p-value
Coldspot	Hotspot	0.63	0.06	10.57	0.43	0.82	<0.001
Coldspot	Neutral	0.26	0.05	5.76	0.11	0.41	<0.001
Hotspot	Neutral	0.37	0.04	9.24	0.23	0.50	<0.001

Abbreviations.
Diff-mean: difference between the group means; df: degrees of freedom; N: number; NO2: dioxide nitrogen; PD: Parkinson's disease; PM: particulate matters; q-crit: threshold of the q-statistics under which the difference of the mean between the groups is not significant; q-stat: q-statistic; ss: studentized range statistic; Tukey HSD test: Tukey honestly significant difference test; Std err: standard error.

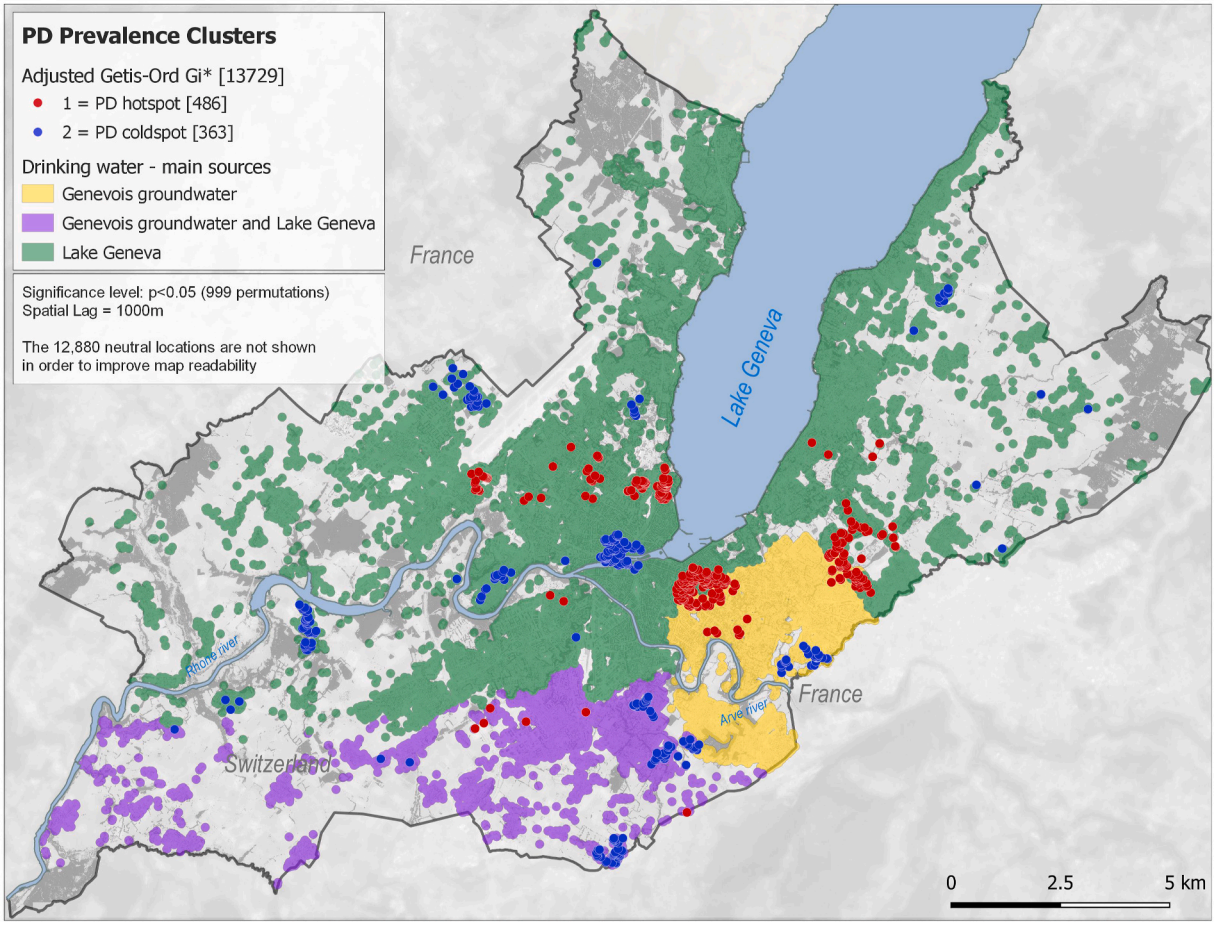

Fig. 3. Individual-level adjusted Getis-Ord Gi* clusters superimposed on the spatial distributions of water source.
In green are represented in a single merged surface all 30,048 Geneva State residential addresses supplied with drinking water from the Lake Geneva groundwater. In yellow are represented in a single merged surface all 6
787 residential addresses supplied with drinking water from the Genevois groundwater. In purple are represented all 6
422 residential addresses supplied with drinking water from the Genevois groundwater. In order to improve map readability, the 12′880 neutral locations are not shown on the map. The spatial distribution of the latter is shown on Fig. 1B. Hotspots and coldspots are superposed on groundwater areas. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

increase of PD risk [29].

We focused on the spatial dependence of PD occurrence based on local indicators of spatial autocorrelation. We found a clear association between PD hotspots and higher concentrations of NO_2 and PM_{10}. Hotspots were characterized with an annual average NO_2 slightly above the authorized value, while average PM_{10} in all classes of individuals analyzed was clearly above the legal limit. Air pollution contains a complex mixture of gases of whom NO2 and PM10 are associated with combustion sources and road traffic as their main outdoor source. As air pollution levels are higher in city centers, which has indeed been the case for the past few decades in Geneva, it is therefore coherent to find a greater proportion of individuals with PD in these areas. Recent studies found marginally significant increased risk of PD with long-term exposure to NO_2, PM_{10} [6], $PM_{2.5}$ and ozone [10,11]. It is unclear what biological mechanisms may be involved but evidence suggests that air pollution can induce neuroinflammation, elevated proinflammatory cytokines, oxidative stress, microglial activation and accumulation of α-synuclein in the brain [4,5,30]. In the Canton of Geneva, the air pollution has progressively deteriorated in recent years. Geneva authorities have finally taken measures in January 2020 to limit air pollution by banning the most polluting vehicles driving through the city centre when air pollution reaches certain levels (Stick'AIR prevention measures, https://www.ge.ch/pics-pollution-stick-air-circulation-differenciee). For the future (horizon 2030) one of the goals of canton of Geneva is to reduce 2005 reference emissions by 50% for NO2 and by 18% for PM10, considering effects due to climate change. We could therefore predict that these identified hotspots may disappear with an improvement in the air quality.

One coldspot was located within an area of high level of NO2. We have no clear explanation for this result. Given that PD is a multifactorial condition, we suspect that others factors might influence PD occurrence in this particular cluster. Air pollution might be one factor promoting PD among others. It could interact with other unfavorable factors in the hotspots highlighted by this study. In the coldspot C5, other favorable factors might be present and counteract the negative effect of air pollution effect on the occurrence of PD. A specific study on this subject would be interesting in order to discover these potential protective factors.

Our data highlights the importance of the improvement of air quality in urban areas to prevent PD and other diseases related to air pollution. It is essential to encourage urban authorities to reduce road traffic downtown, and to implement drastic plans to reduce air pollution levels in areas with a dense population or with a high number of working places. Possible future studies would include accurate exposure measurements, as currently available air pollution data are often derived from air pollution models and generalized over a territory. Local critical values are consequently smoothed by data interpolation. Others possible future studies could include the use of air sensors located close to the

residential areas of the population studied. It would also be important to identify subpopulations likely to be at higher risk for air pollution-induced diseases (genetic susceptibility or other known risk factors). Finally, it is important to acknowledge that air pollution has been identified as a key factor to improve for the prevention of disease in official public health recommendations.

Our study presents several limitations. Firstly, clusters were generated with respect to each case's known last residential address. The time spent at this address and the residential history were not known. According to the Cantonal Office of Statistics, the annual mean rate of moves within the Canton in the general population was 8.5%. However, this rate is likely much lower in the aged population as a result of the high quality of life in Switzerland. Secondly, residual confounding from alternative variables not taken into account in our study cannot be excluded. Detailed information on the type and the degree of pesticides exposure as well as smoking status were not available in the Canton. These missing risk-factors might have further reduced the size of our hotspots. However, NO2 concentration and PM10 concentration to a lesser extent, showed a significant higher mean value among the hotspots compared neutral areas and we believe that air pollution influenced PD prevalence.

In conclusion, our study constitutes one of the first individual-level geographic analysis of PD prevalence conducted in Europe. It demonstrates that PD prevalence exhibits a spatial dependence for a significant proportion of patients with the presence of prevalence clusters, independent of important socioeconomic and demographic confounders. PD prevalence hotspots were concentrated in the urban centre and were associated with atmospheric air pollution. Our findings emphasize the multifactorial nature of PD and the importance of air quality improvement in PD prevention which could be of substantial public health significance.

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Authors contributions

VF, RH, SJ, IG and PRB contributed to the conception and design of the study; VF, RH, SJ, IG, PRB, NN and MB contributed to the acquisition and analysis of data; VF, RH, SJ, IG, PRB, NN and MB contributed to drafting the text and preparing the figures.

Data availability statement

Ethical approval precludes the data being used for another purpose or being provided to researchers who have not signed the appropriate confidentiality agreement, per the local Canton of Geneva Ethics Committee.

Declaration of competing interest

The authors have no financial disclosures and no conflicts of interest concerning the research related to the manuscript.

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List of abbreviations

G	Genevois groundwater
GIREC	Groupe Interdépartemental de REprésentation Cartographique
IDPADR	IDentifiant Permanent de l'ADResse
LG	Lake Geneva
LGG	mixed Lake Geneva and Genevois
NO2	dioxide nitrogen
OAPC	Ordinance on Air Pollution Control
PD	Parkinson's disease
PM	particulate matters
SIG	Industrial Services of Geneva
U	Undefined

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.12.013.

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