Reviewer’s report

Title: Spatial distribution of Parkinson's disease mortality in Spain, 1989-1998, as a guide for focused aetiological research or health-care intervention.

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Reviewer: Denis Zmirou-Navier

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This paper aims to raise hypotheses as to possible causes of high or low incidence of mortality associated with Parkinson’s disease at a city level, in Spain, by a spatial statistical analysis of Parkinson’s disease (PD) mortality. Age and sex standardized mortality ratios and municipal relative risks derived from an autoregressive model are exhibited and their spatial patterns are analysed in conjunction with two other sources of data: (i) province wide statistics of usage of levodopa, a drug prescribed for the treatment of Parkinson’s symptoms, as a means to evaluate the spatial distribution of diagnoses of the disease; and (ii) the European EPER registry of highly polluting industries.

Strong disparities in the spatial distribution of PD mortality are shown, with a somewhat north-south declining gradient, equally observed for both genders. Cities with high mortality rates are said to frequently host EPER industries (located within 2 km from the city centroïd). The spatial pattern of levodopa usage tends to resemble that of PD mortality, leading the authors to dismiss an important role of PD under-ascertainment in explaining their findings. As a consequence, some emphasis is put on the hypothesis of historical industrial emissions as a contributing factor to PD incidence and mortality, a hypothesis the authors suggest to explore with focused studies. Unexplained spatial discrepancies also give ground to the proposal of intervention studies to improve PD diagnosis and treatment.

This is a well written paper that makes usage of existing data with appropriate statistical analysis to raise interesting hypotheses that may warrant further investigation. However, there are some limitations that preclude publication in its present status.

Major Compulsory Revisions

- Table 2 exhibits municipalities where 10 or more PD deaths have been observed and “high” RRs. Cities where EPER facilities are located are also shown. Table 3 presents, to the contrary, cities with “low” RRs; it does not parallel table 2 in that no mention is made of cities with EPER industries. Now the text suggests that there are some (Gibraltar, for instance, or in the province of Huelva – p10, second paragraph). This discrepant presentation unduly emphasizes an association between “high RR cities” and EPER sites, with no formal statistical testing.
Minor Essential Revisions

- The second sentence of the abstract is unclear: “Undiagnosis of PD at death ... during life”.

- The Background section of the paper introduces the current state of evidence regarding possible links between PD and exposure to chemical substances. Essentially, papers dealing with pesticides usage are quoted. It is unclear how this relates to the analysis that is conducted in the paper where EPER data relate to industrial emissions (by air, water or production of waste). The rationale for the study of this association is better explained in the discussion section. The authors might want to justify more clearly their case in the introduction.

- In the Discussion section, it is suggested (p10, second para) that “Such features might indicate that environmental pollutants causing cancer and parkinsonism are different in nature, or that latency periods for environmentally-induced parkinsonism in the Province of Tarragona are shorter than those for cancer”. The latter statement is weak. One important underlying assumption in the study is that of spatial stability of the population (low between provinces and between cities migration; see discretionary revisions). Hence, that some cities in the province of Tarragona with EPER industries do not share the same pattern of cancer and PD incidence is not likely to be explained by different latency periods.

- Also, in the Discussion, the authors state that (p10, last para) “In contrast, a few of the above-mentioned towns with high mortality deserve particular attention because they were located in areas of low industrial activity and low PD mortality ...”. This is inaccurate. Registration of a given facility in the EPER database is compulsory when a certain emission threshold is exceeded, for a limited number of pollutants. The thresholds are rather high. Now, one might well encounter areas where there is a concentration of small to medium size industries, none attaining the threshold for any single pollutant. In such a case, there could be a substantial level of environmental pollution due to industries, while none is in the EPER database. In the analysis conducted in the paper, such a city would be inappropriately cited as of “low industrial activity”. I reckon that the authors cannot identify such situations using their source of information, but caution is warranted when interpreting the findings.

Discretionary Revisions

- Discussion (p 9, last sentence): this sentence is difficult to understand. Further, why is the issue restricted to the sole city of Tarragona?

- Discussion (p10, second para): the authors suggest that lower mortality in Benidorm and in the Canary Islands might be influenced by the immigration from aged European residents. Along the same line they also might want to elaborate here about inner Spain migration patterns: might some findings of this study be affected by specific internal migration patterns?

- Discussion (p 11, first para): this sentence is too long and difficult to understand
- Conclusion: add one term in the sentence “... reported provincial mortality and levodopa USAGE, with municipal …”
- Correct the typo in Authors contributions: « wioth”

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests