Reviewer's report

Title: Road proximity, air pollution, noise, green space and neurologic disease incidence: A population-based cohort study

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Reviewer: Beate Ritz

Reviewer's report:

This is a very well conducted cohort/nested case controls study of multiple environmental factors (proximity to roadways, noise, air pollution and greenness) and several important neurological outcomes in the elderly. This study is based on a very strong resource i.e. the Canadian health care system that allows identifying diseased individuals from a health care database that covers almost everyone and also has access to extensive data to model the exposures of interest well for this population. The comparison of the satellite derived air pollution and land use regression results is interesting and another strength, as suggests that local contrasts in pollution levels (micro- rather than national scale derived estimates of exposure) and sources are the most important contributors to the outcomes in the Vancouver environment. Overall this is a strong study and the manuscript is well written.

Comments

- None of these diseases are treated in hospitals until late in disease and some are not even very treatable (AD and NAD) and treatment information may not be a great tool to identify cases early; but according to the validation studies conducted in Canada the procedures used in this study to identify cases electronically from the medical records have good sensitivity and excellent specificity. However, would this also include age at onset? Especially for such insidious diseases as AD and PD the prodromal stage is very long and they may come to the attention of the medical system (and especially hospitals) relatively late depending on patient characteristics and attitudes. For example, the median age of onset of PD of 72 years is older than the median age otherwise reported in population-based studies of about 68 years. Hence, the environmental measures may not reflect exposures prior to disease onset unless individuals have a very low frequency of moving. Also, during disease progression these disorders are disabling and the patients may choose to move to accommodate their diseases - thus the exposure measures could include exposures after changes in residence to accommodate worsening of the disorder rather than exposures that are contributing to the disease onset. I would like the authors to consider and discuss this issue and possibly provide some additional information on how much the exposure measures do indeed reflect long term exposures prior to disease onset.

- It may be less confusing to avoid referring to cases and controls in the results section when the analyses are for the cohort i.e. when referring to NAD and PD results. On the
other hand please avoid saying "in the cohorts of AD and MS" since these were analyzed with a nested case control approach

- To point out in the results that cases and non-cases differed (for NAD and PD) in terms of age and comorbidities while this is not the case for AD and MS is trivial as the controls were matched to cases by age for the later but not former; please consider rewording this.

- The authors point out the co-morbidity differences between cases and non-cases for NAD and PD but not AD and MS, but from table 1 and 2 it is clear that this is solely due to age i.e. the cohorts are not age matched or adjusted while the nested case control samples are. Please either adjust for age in the cohort or do not point out such comorbidity differences as currently done.

- Do results vary by gender (given the preponderance of different outcomes in either males (PD) or females (AD and MS) or by major races (e.g. PD is reported to be less common among Asians ; Vancouver has a large Asian population - is race information only available at the neighborhood levels as well?)

- Please remind the reader which covariates in table 1 are measured at the neighborhood level and not individual

- What is the influence of living in high rise buildings (with air filtration etc) - is there a way to explore this in sensitivity analyses excluding certain neighborhoods with a high proportion of high rises?

- Why not use a cut-off for noise rather than a linear model, such as 65 dB and ≥ 65 dB and nighttime noise as <55 dB and ≥55 dB since the effect of noise on the outcomes may not necessarily be linear. Also, how common is the use of noise protecting windows in Vancouver near major roadways?

- In Table 5, it seems that the interquartile range used to generate the estimates is taken from cases of each disease rather than from the non-cases or controls? This is different from the usual recommended use of the control population exposure distribution as the reference; what was the reason for using case exposures? Also, why not use one IQR for the whole population (or all non-cases) instead - this would allow comparing the results more validly across diseases; using one IQR will probably change little but still it would allow for more valid comparisons.

- In Table 5, please also list which confounding variable were included in the models, this information can also go into a footnote.

- Please explain whether you controlled for comorbidities such as diabetes and CVD or stroke in all models including the NAD model. These diseases might be mediators on the pathway to NAD i.e. would also be caused by air pollution or noise exposures and
contribute to NAD, hence it might not be appropriate to adjust for them. Do results change if these covariates are not included in the NAD models?

- The increase in AD risk with greenness seems rather strange and needs an explanation. Furthermore, not only is greenness positively associated with AD and MS but also seems to confound the air pollution estimates for these diseases. Would it be possible to check whether the distribution of cases for these two outcomes with a relatively small N is different across the city compared with cases of NAD and PD?

- I do not understand the conclusion that AD was linked to air pollution while MS was not when all effect estimates for AD and air pollutants were less than one or very close to one while for MS there is a large and even statistically significant effect for PM2.5 (when controlling for greenness [OR= 1.43 (1.09-1.97)]).

- Would the authors have any explanation for the fact road proximity is a better - i.e. more consistent - predictor of the outcomes than most of the air pollutants?

Minor point:

- Page 30 table 3 has a typo in the last column and row, visible minority is 21.74 not 11.74; there is another mistake for NAD and highways&lt;150m in table 2 page 28; it should read under cases 12.9 and not 22.9%. It seems that the lengthy tables need some additional scrutiny for typos.

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