Reviewer's report

Title: Modification by hemochromatosis gene polymorphisms of the association between traffic-related air pollution and cognition in older men: a prospective cohort study

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Reviewer: Erin Semmens

Reviewer's report:

This paper describes a hypothesis-driven investigation of the potential modification by HFE polymorphisms of traffic-related air pollution effects on cognitive performance in older men. The writing is clear, and the study is an interesting extension of published work. Studies of air pollution effects on central nervous system function are relatively new, and this work provides some insight into the mechanisms underlying the associations observed in several large epidemiologic investigations. Below are issues to consider and address.

Major Compulsory Revisions
None

Minor Essential Revisions

1) Background, paragraph 2: Briefly summarizing the other work that has been done examining the effects of air pollution exposure on the brain would provide a stronger public health motivation for conducting the work described.

2) Methods, Cognitive testing: Although described in the previously reported analysis, please discuss the clinical significance of an MMSE score # 25.

3) Methods, Statistical Methods, paragraph 2, sentence 2: “Using separate models for each analysis…” Please clarify that “each analysis” refers to each SNP and to each cognitive outcome (i.e., the cognitive z-score and the MMSE score).

4) Methods, Statistical Methods, paragraph 2: It would be helpful to report what statistical test was performed and what threshold was used to define significance of interactions between BC and HFE SNPs.

5) Results, paragraph 2: Although the authors touch on this in the last sentence of the paragraph, it would be helpful to more explicitly report results for statistical tests of interaction, which should then be referenced again in the Discussion. The fact that significant associations were observed between BC and both the cognitive z-score and low MMSE score in those lacking an HFE C282Y variant is intriguing. However, while it is important not to over-emphasize a p-value, the fact that the interaction was not statistically significant in any case deserves mentioning.
Discretionary Revisions

1) Please provide a more detailed discussion of how the exposure metric of interest was selected. If baseline cognitive tests occurred sometime between 1996 and 2007, then exposure estimated for the year preceding the baseline assessment could conceivably stretch over more than 10 years. How did concentrations change over time? If they changed substantially or differentially, how might this have affected results? Were any other metrics used to define long-term exposure to BC (e.g. choosing mean exposure during a fixed calendar year for everyone)?

2) Discussion, paragraph 1: Would the authors provide some context for what “strong adverse associations” mean? For example, the effect of BC exposure on cognition in those lacking the C282Y variant was similar to that observed with an x year increase in age or y years additional education.

3) If performed, please mention results of analyses examining how HFE SNPs might modify the effects of long-term BC exposure on cognitive trajectories over time in those who had multiple cognitive assessments.

Level of interest: An article of importance in its field

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.