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: Beate Ritz

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This is an interesting paper exploring possible gene-environment interactions building upon an earlier report published by the same authors in which they found that black carbon (BC) estimates of traffic pollution from a spatiotemporal land use regression model for the greater Boston area in 1995 were associated with cognitive function in elderly men from the Normative Aging Study (NAS). The candidate gene they identified for this purpose is the hemochromatosis gene (HFE) which had previously been found to modify short term air pollution effects on cardiovascular outcomes in the NAS. The authors provide appropriate biologic justification for selecting this gene that acts in inflammatory and oxidative stress pathways hypothesized to also influence cognitive decline in the elderly. The paper is well written and the results clearly presented and discussed.

Major revisions:

1) The main issue with this paper is whether one is inclined to agree with the authors interpretation that their results suggest and interaction between the variant polymorphism in HFE and BC exposure since the 95% CI of the variant estimate for both the total cognitive score and the low scoring on the MMSE overlap largely with the wild type estimates and CIs and the p-values for interaction are 0.2 and 0.11 which would not be considered formally statistically significant. Thus the authors should at least comment on their use of the term ‘suggest’. The lack of a negative association in variant carriers is however intriguing and worthwhile to be noted.

2) The authors describe using “all” cognitive tests conducted for each person in multiple waves of testing, i.e. baseline and follow-up exams. They seem to have standardized results to the baseline test score, but it is unclear whether or how they used multiple tests per person. Is it correct that the beta they present represents a rate of cognitive decline? This should be stated more clearly. Also, how would this work if there was only one test result available i.e. the one from baseline?

3) In their original paper the authors explicitly addressed potential confounding by lead since traffic-related exposures were a primary source of lead exposure in the era of leaded gasoline. Even though this did seem to change main effects for total cognition in the previous paper it by more than 10%, thus, why did they choose to not adjust for lead exposure in the GxE analyses presented here?
4) Are the betas and ORs presented in tables 2 and 3 from two different models, i.e. are they indeed then marginal rather than main effects? The p-value for interaction - I presume - is from a model with both an interaction term and both main effects in the same model. I don’t understand the sentence in the ‘stat method section’ that states “Using separate models for each analysis, we then evaluated the main effects of each HFE SNP on cognition and the potential for effect modification of the black carbon cognition association by HFE SNPs using multiplicative interaction terms.” What is meant by separate models? Stratified analyses? Also they state that “As the current dataset excludes participants from the previously reported analyses [2] who lacked valid HFE genotyping, we also reproduced the previously reported main effect models in this reduced dataset.” How can these be ‘main effects’ previously reported when there were no interactions tested, i.e. shouldn’t this be marginal effects then?

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'