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

Version: 1 Date: 27 November 2012

Reviewer: C. Arden Pope

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Major comments:

1. This paper used data from over 600 participants of the VA normative Aging Study. Traffic related air pollution exposure was estimated by estimating black carbon (BC) using a land use regression model. In a previous paper they reported that traffic related exposure was associated with measures of cognition. In this paper the evaluated whether or not this association was modified by hemochromatosis gene polymorphisms. They found that the adverse BC-cognition association appeared to be modified by the HFE C282Y but not the HFE H63D genotype. These somewhat suggestive results are interesting and potentially important.

2. The paper is succinctly written and the analysis is conducted by a well-respected research team with relevant experience.

3. The paper is well-motivated and is a natural extension of the previously reported work that found adverse BC-cognition associations and effect modification for cardiovascular disease outcomes and polymorphisms in the hemochromatosis gene. The paper also provides some discussion of proposed biological mechanisms.

4. In general, the weakest aspect of the paper is, although well motivated, the actual results are not highly compelling. Given that the statistical inference of an adverse association was at best marginally significant, given that there are multiple testing issues, and given that the results are not fully consistent with presumed priors, the results are mostly only suggestive. In fairness, the authors do not severely oversell the results and the statement that this finding and the proposed biological mechanism require confirmation is certainly true.

5. In the background a brief discussion of the background and importance of HFE polymorphisms (including relevance outside of the air pollution literature, with key cites) would be helpful.

Minor comments:

1. Page 4, 1st paragraph, line 2. “there are many reasons why we may . . . “ Suggest “there are many reasons to be interested. . . “


4. Page 12, line 7. Redundant use of the word “directly”.

**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.