Reviewer's report

Title: SLC6A3 and body mass index in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

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Reviewer: Caroline Davis

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This study examined associations among certain markers of the dopamine system - in particular for the DAT1 gene - and BMI, alcohol use, and smoking status in senior adults who took part in the Prostate Lung Colorectal and Ovarian (PLCO) Cancer Screening Trial. A strength of the study is that the authors have data on a substantial number of participants who have provided current information as well as retrospective-recall data on the variables of interest. Following are my comments about the manuscript.

1. First of all, the title of the paper is misleading/inaccurate because it only refers to the SLC6A3 gene and BMI, when the results reported in the paper relate to smoking, alcohol use, and other dopamine genetic markers.

2. In my view, the Introduction of the paper does not provide a suitable theoretical framework for the study, nor a compelling rationale for why the study variables are being examined, or how this investigation fits into the broader picture of dopamine and addictive behaviours. One example of this deficiency is the absence of a discussion of the functional significance of possessing the 9-repeat versus the 10-repeat of the DAT1. Some of this is dealt with in the Discussion section, but it would make a lot more sense to provide a sound theory and specific hypotheses at the beginning of the paper, not as a discussion piece.

3. Further to the point above, there is no clear explanation for why dopamine is important, and why the dopamine transporter specifically. Indeed, as we later learn, other dopamine genes are also relevant, but again, we are never told why these genes are being examined, instead of a host of others.

4. The authors fail to acknowledge the limitations of their data - in particular, that all the response variables are based on self-report information, and in many cases on retrospective recall that may have extend back 50 years. At the very least, given the emphasis on BMI, I would have liked to see measured height and weight at the time of assessment rather than data based on self-report.

5. With respect to the data analyses, the authors carried out a large number of statistical tests, but they don’t seem to have adjusted for this by using a correction factor for multiple comparisons.

6. There are also several more minor, editorial issues with the paper. For example: i) in the 3rd line of Background on page 3, “make” should be “makes”;
and later on, on the same page, “death of” should be “death from”; ii) on page 4, what is meant by “Smokers with high food reinforcement”? This concept needs explanation; iii) on page 9, what do the authors mean by “in a dose-dependent model”.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.

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