Reviewer’s report

Title: Low level maternal smoking and infant birthweight reduction: genetic contributions of GSTT1 and GSTM1 polymorphisms

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Reviewer: Xinguang Chen

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Overall, the data reported in this study is unique and interesting to the readers of BMC-Pregnancy and Child Birth. Findings of this study add additional evidence on the interplay among two key GST genes and maternal smoking on birth weight of children with data collected from a decent study sample. However, a number of key issues must be addressed before the paper can be considered for publication.

Major Compulsory Revisions

Abstract: Information related to method part is included in the background part (e.g. sample size, specific genes to be examined). Method part needs to be streamlined and revised to include key information (e.g., sample, analytical method). Conclusion part also needs to be revised. The effect of the two genes on birth weight has been reported in a number of studies, findings of this study provide additional data supporting previous findings.

Introduction section

Need more through literature study – data relating GSTM1, GSTT1, prenatal and post natal tobacco exposure and birth weight and related developmental measures (lung growth) have been reported (e.g., Chen et al, 2011, Environmental Research; Lee et al, 2010, Environmental health perspective; to name a few). The authors need to review and abstract findings, including both positive and negative, from all related studies to demonstrate the need for their study. Almost all reported studies around this topic area have examined the interplay among all the related genes and tobacco exposure on outcome variables if sample size is allowed. A relatively larger sample is the strength of this study, but the authors did not make this part standing out.

Methods Section

More information is needed regarding the study cohort. How the study subjects were defined and selected? For which population is this sample representative? What is the refusal rate? “STREGA” is not defined.

Description of variable measurement is problematic. Measurement of maternal smoking is poorly defined. It is unclear how “light smoker” was defined. No measurement of smoking BEFORE pregnancy was found. Exposure to environmental smoking (particularly husband smoking) was not included. Birth weight is not an exposure variable but was included under the subheading
“Exposure Assessment”. This reviewer is looking for a well organized section on variable assessment, including outcome variable, genetic variables, variables for tobacco exposure, and other control variables.

Genotype frequency is part of the statistical analysis, but it was treated not as statistical analysis (the first sentence in the statistical analysis section on page 7).

Results Section

Missing data which are obvious but are not indicated in any of the tables or text. The reasons and impact of missing data on the study findings should be added and discussed as limitation. The authors also need to report genetic equilibrium analysis (e.g., Hardy-Weinberg equilibrium analysis) to ensure the appropriateness of the genotyping results. Reporting the results regarding genotypes and quitting smoking is highly distractively. This is a totally different area (see paper by Chen and Woodcroft, 2009, Nicotine and Tobacco Research), and could not be adequately addressed in this study. Several variables not significantly associated with birth weight were included in both Table 1 and Table 2; but a number of key variables included in the regression analysis were not included in Table 1. The headings for Table 2 and Table 3 are insufficient; consider revision to including information about the analytical method, sample size, and type of results, etc.

Discussion Section

The key finding of this study is the significant gene-gene interaction as presented in Table 3, but has caught attention of the authors. Findings of this study as reported in the paper appears to indicate no significant interaction between either of the two genes and maternal smoking on birth weight (none of the interaction terms was significant after the main effect was included). This section is gone off line again at the beginning to include other factors rather than genes, maternal smoking and birth weight. When discussion about GST gene and maternal smoking, the authors only cited one study [9], ignoring a number of other studies, such as the one by Chen and Woodcroft, 2009. Most part presented in the discussion section should be moved to the Introduction section to demonstrate the significance of the current study, particularly those with inconsistent results regarding GST genes, maternal smoking and child birth weight.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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