## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Assessing tobacco smoke exposure in pregnancy from self-report, urinary cotinine and NNAL: a validation study using the New Hampshire Birth Cohort Study |
| **AUTHORS** | Peacock, Janet; Palys, Thomas; Halchenko, Yuliya; Sayarath, Vicki; Takigawa, Cindy; Murphy, Sharon; Peterson, Lisa; Baker, Emily; Karagas, Margaret R. |

## VERSION 1 – REVIEW

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| **REVIEWER** | Ekblad, Mikael<br>Turku University Hospital |
| **REVIEW RETURNED** | 24-Aug-2021 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review this manuscript titled: “Self-reported smoking, cotinine and NNAL levels in pregnancy and outcome of pregnancy in the New Hampshire Birth Cohort Study”. They observed high concordance between self-complete questionnaire smoking data and urinary cotinine and NNAL in a birth cohort with a low prevalence of smoking. This study is exceptionally conducted and written. The results are presented clearly.<br><br>I have only minor comments regarding the manuscript.<br><br>Page 5, row 12-14: “Criteria for eligibility -- the use of a private, unregulated water system (e.g., private well) at home”. Did I understand correctly, the study included only women who had unregulated water system at home? Or was this an exclusion criteria?<br><br>Page 9, row 15-16: “Just over one percent of women (n=17) reported being active smokers, but their biomarker levels were very low.” I would wish the authors would mention in the discussion about the known individual differences in nicotine metabolism, which is one of the limitations if only cotinine verification of smoking is used to determine smoking exposure (not the case of this study). |

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| **REVIEWER** | Nawi, Azmawati Mohammed<br>Universiti Kebangsaan Malaysia, Department of Community Health |
| **REVIEW RETURNED** | 13-Sep-2021 |

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| **GENERAL COMMENTS** | 1. Abstract: The objective in the abstract mention the interaction with the environment exposures..does the analysis was done?.<br><br>2. Introduction:<br>The manuscript is well written however there was no clear justification of the research needs. What is the main use of both |

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| | biomarkers later on? as the prevalence of smokers among pregnant women was low.<br><br>2. Discussion: Needs to add the mechanism of smoking and its effect on pregnancy outcome (fetal outcome). Please add other limitations especially on recall bias.<br><br>3. Please add suggestions based on your findings |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Dr. Mikael Ekblad, Turku University Hospital
Comments to the Author:
Thank you for the opportunity to review this manuscript titled: “Self-reported smoking, cotinine and NNAL levels in pregnancy and outcome of pregnancy in the New Hampshire Birth Cohort Study”. They observed high concordance between self-complete questionnaire smoking data and urinary cotinine and NNAL in a birth cohort with a low prevalence of smoking. This study is exceptionally conducted and written. The results are presented clearly.

*Thank you for these positive comments.*

I have only minor comments regarding the manuscript.

Page 5, row 12-14: “Criteria for eligibility -- the use of a private, unregulated water system (e.g., private well) at home”. Did I understand correctly, the study included only women who had unregulated water system at home? Or was this an exclusion criteria?

*This was one of the inclusion criteria for the birth cohort – we have clarified the wording for this.*

Page 9, row 15-16: “Just over one percent of women (n=17) reported being active smokers, but their biomarker levels were very low.” I would wish the authors would mention in the discussion about the known individual differences in nicotine metabolism, which is one of the limitations if only cotinine verification of smoking is used to determine smoking exposure (not the case of this study).

*Yes it is true cotinine levels may be influenced by metabolism, although it is primarily individual differences in cotinine metabolism not nicotine metabolism that influence cotinine levels (1,2). The two primary enzymes that metabolize cotinine are CYP2A6 and UGT2B10. Deletions in either one of these genes will have a significant influence on cotinine levels, however the effect of variants with a modest impact on metabolism or even smokers heterozygous for these deletions will have a much less pronounced impact. A 25% reduction in cotinine was observed in one study of White smokers with reduced metabolism CYP2A6 alleles, a reduction in cotinine of this magnitude would not affect the classification of these individuals as smokers or not (2). A deletion in UGT2B10 is relatively common in African Americans and CYP2A6 variants are most abundant in Asian populations (3), the participants in our study are 97% White so it is unlikely metabolism has a significant influence on differences in cotinine levels across this population. A non-daily low level of smoking or the temporary abstinence from smoking and the collection of a spot urine sample at a single time during pregnancy is likely the reason for the low level of cotinine in these self-reported smokers. this conclusion is added to the discussion.*

*1. Sipe CJ, Koopmeiners JS, Donny EC, Hatsukami DK, Murphy SE. UGT2B10 genotype influences serum cotinine levels and is a primary determinant of higher cotinine in African American smokers. Cancer Epidemiol Biomarkers Prev 2020;29(8):1673-8 doi 10.1158/1055-9965.EPI-20-0203.*
*2. Zhu AZ, Renner CC, Hatsukami DK, Swan GE, Lerman C, Benowitz NL, et al. The ability of plasma cotinine to predict nicotine and carcinogen exposure is altered by differences in CYP2A6: the influence of genetics, race, and sex. Cancer Epidemiol Biomarkers Prev 2013;22(4):708-18.*

*3. Park SL, Tiirikainen MI, Patel YM, Wilkens LR, Stram DO, Le Marchand L, et al. Genetic determinants of CYP2A6 activity across racial/ethnic groups with different risks of lung cancer and effect on their smoking intensity. Carcinogenesis 2016;37(3):269-79.*

Reviewer: 2
Dr. Azmawati Mohammed Nawi, Universiti Kebangsaan Malaysia
Comments to the Author:

1. Abstract: The objective in the abstract mention the interaction with the environment exposures..does the analysis was done?.

*We apologize that our wording of the abstract (objectives) was ambiguous in this respect and we have removed the mention of 'interaction' to remedy this.*

2. Introduction:
The manuscript is well written however there was no clear justification of the research needs. What is the main use of both biomarkers later on? as the prevalence of smokers among pregnant women was low.

*We thank the reviewer for these comments for which we have re-worded the relevant paragraph to clarify our aims as indicated below:*

*"The New Hampshire Birth Cohort Study is a large ongoing prospective study from USA with lower smoking prevalence than has been evaluated historically and that has obtained detailed self-reported smoking data and urinary cotinine/NNAL levels. We sought to establish biomarker cut-offs for smoking and SHS exposure and to validate the use of self-reported smoking against the biomarkers to extend the knowledge base for the utility of NNAL. We hypothesized that NNAL would be strongly positively correlated with cotinine and that the two biomarkers would be similarly predictive of smoking and SHS, and that self-reported smoking would be shown to be reliable."*

2. Discussion: Needs to add the mechanism of smoking and its effect on pregnancy outcome (fetal outcome). Please add other limitations especially on recall bias.

*We thank the reviewer for this suggestion and have added a sentence at the beginning of the discussion regarding the mechanisms through which smoking impacts the mother and fetus.*

*"Tobacco smoke contains many constituents including nicotine and carbon monoxide which are known to adversely affect the mother and fetus through vasoconstriction (nicotine) and hypoxia (carbon monoxide)[19] and hence the accurate assessment of tobacco smoke exposure in pregnancy is critical."*

*We have added a sentence to the discussion about recall bias as follows:*

*"Most of our self-reported smoking questions were related to current habit and so were not subject to recall bias but we did enquire about SHS exposure pre-conception and so those responses may have been affected by errors in recall."*

2. Please add suggestions based on your findings

*We have changed our final section to suggestions rather than conclusions, as previously and now say:*

*" We suggest on the basis of this relatively recent pregnancy cohort of USA women from rural Northern New England that either detailed self-completed questionnaire smoking data or biomarker data from may be used in further analyses of the effects of tobacco smoke on health outcomes in*

*children. We further suggest that cotinine levels rather than NNAL levels be used to detect SHS exposure.“*