PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	SECONDHAND TOBACCO SMOKE EXPOSURE AMONG CHILDREN UNDER 5 YEARS OLD; QUESTIONNAIRES VERSUS COTININE BIOMARKERS: A COHORT STUDY
AUTHORS	Mourino, Nerea; Pérez-Ríos, Mónica; Santiago-Perez, Maria Isolina; Lanphear, Bruce; Yolton, Kimberly; Braun, Joseph M

VERSION 1 – REVIEW

REVIEWER	Cheung Yee Tak Derek The University of Hong Kong, Hong Kong
REVIEW RETURNED	06-Nov-2020

GENERAL COMMENTS	Use of mother-reported SHS exposure as gold standard to identify the cut-points of SHS, and subsequently examine the concordance in SHS exposure between mother-reported and serum cotinine is problematic. The authors have mentioned the reporting bias and low reliability of mother-reported SHS exposure. Since the prevalence of mother-reported SHS exposure was much lower than that derived from serum cotinine using LOD, the cut-points would be surely increased using ROC method. Also, other essential factors of children SHS cotinine level were not adequately reported, such as paternal smoking, tobacco consumption level, whether home smoking is allowed. SHS exposure included children who were exposed in any setting ever, sometimes or seldom, without any specification of time and duration. Such definition is too broad and not justified.

REVIEWER	Ajith Alagiyawanna Health Promotion Bureau, Ministry of Health Sri Lanka
REVIEW RETURNED	07-Nov-2020

GENERAL COMMENTS	Good piece of work

REVIEWER	Yoonsang Kim NORC at the University of Chicago, USA
REVIEW RETURNED	11-Mar-2021

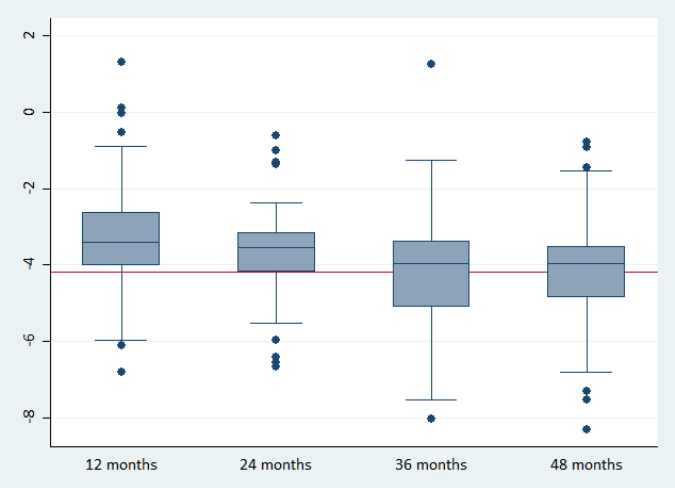
GENERAL COMMENTS	Here are my specific comments about the methods: 1. 468 agreed to participate, and 389 remained in the study until the birth of their child. And some study participants dropped after the birth of their child, resulting in 51% of attrition rate. What were the main reasons for dropping out? Also, the attrition rate of children differs from the attrition rate of mothers.

	2. “The optimal serum cotinine cut-points at each age were the concentrations at which the difference between sensitivity and specificity was minimum.” What’s the rationale of this approach? Why not use the maximum average of sensitivity and specificity to find the optimal cut-points? Or F1 score (harmonic mean of sensitivity and positive predictive value) as frequently used in informatics and computer science? 3. ICC was calculated for children with complete data. Would it be possibly biased because children with intermittent missing or who dropped out were excluded?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Yee Tak Derek Cheung, The University of Hong Kong
Comments to the Author:
Use of mother-reported SHS exposure as gold standard to identify the cut-points of SHS, and subsequently examine the concordance in SHS exposure between mother-reported and serum cotinine is problematic. The authors have mentioned the reporting bias and low reliability of mother-reported SHS exposure. Since the prevalence of mother-reported SHS exposure was much lower than that derived from serum cotinine using LOD, the cut-points would be surely increased using ROC method.

We agree with the reviewer that self-report is not a true gold standard. However, our intention was to use concordance as another way of validating the discriminatory capacity of the ROC curve, not to compare both information sources themselves. With respect to the concordance between prevalence based on mother self-reported and the cotinine assay limit of detection (LOD), we believe that such low kappa values cannot be due only to the mother's underreporting, thus highlighting the inappropriateness of using that cut-point. The cut-points may be slightly overestimated, but in view of the box-plots that we have prepared for the reviewer (see below), we do not think that the overestimation is excessive.



The figure shows the cotinine concentration (log) at 4 points in time in children not exposed to secondhand tobacco smoke (SHS) according to the mother: these children have measurable cotinine concentrations at all 4 follow-up periods, and their mother always declared that they were not exposed. Although they are the same mothers who maintain the same statement over time, that the child was not exposed, the cotinine concentration of the children is decreasing. Thus, the same cut-point at all ages (the one derived from the assay LOD) cannot be adequate, because this drop is unlikely to be due to misclassification of self-reported SHS by the mother. This, while the thresholds are likely semi-quantitative, demonstrates the need to consider alternative thresholds in future studies.

According with these data we have added this sentence in the discussion: *"…*re-classified as SHS exposed. *Our results (data not shown) show that among the children whose mothers declared that they were not smokers at the 4 follow-up periods and that the children were not exposed to SHS, the cotinine concentration decreased as age increased. This decrease is unlikely to be due to misclassification of self-reported SHS by the mother."*

Also, other essential factors of children SHS cotinine level was not adequately reported, such as paternal smoking, tobacco consumption level, whether home smoking is allowed.

SHS exposure included children who were exposed in any setting ever, sometimes or seldom, without any specification of time and duration. Such definition is too broad and not justified.

We agree that the definition as it was included in the manuscript is broad. However, the questions were more specific, and we have provided the specific definition in the methods.

*"*Each child was classified as exposed if the mother reported either being a smoker or living with a smoker who smokes at home or if the mother reported that her child was exposed to SHS *in the car or in other homes and places (such as grandmother´s home or daycare)*. Otherwise, we classified children as unexposed."

We agree that we lack more refined measures of exposure duration, and we have added this as a limitation to the discussion.

"We lacked information about the duration of exposure to SHS, which could have been used to provide more valid and reliable cotinine thresholds. "

Reviewer: 2
Dr. Amaap Alagiyawanna, Ministry of Health Sri Lanka
Comments to the Author:
Good piece of work

Thank you for the positive feedback on our manuscript.

Reviewer: 3
Dr. Yoonsang Kim, National Opinion Research Center
Comments to the Author:
Here are my specific comments about the methods:
1. 468 agreed to participate, and 389 remained in the study until the birth of their child. And some study participants dropped after the birth of their child, resulting in 51% of attrition rate. What were the

main reasons for dropping out? Also, the attrition rate of children differs from the attrition rate of mothers.

After initial enrollment, 67 women dropped out during the study "run in" phase, which gave participants the chance to discuss the study with their families before fully committing to participating. This is often done in randomized controlled trials of pharmaceuticals or medical devices to ensure that committed participants are enrolled. While, we do not have the specific reasons for them dropping out, we have invited them to participate in our two most recent study visits at ages 8 and 12 years.

Generally, the sociodemographic composition of the analytic sample in the first four years of life is similar to the baseline sample. This information is detailed in Supplementary Table 1.

Additional details regarding enrollment and attrition has been added: "…or radiation therapy. *From March 2003 to January 2006, we recruited 468 pregnant women living in a five county region of the Cincinnati, OH metropolitan area (Butler, Clermont, Hamilton, and Warren counties) and Northern Kentucky (Campbell county) to participate in a longitudinal pregnancy and birth cohort study. Sixty-seven women dropped out in pregnancy during the run-in phase of a randomized controlled trial of residential lead and injury hazard controls nested within the cohort. From 2003 to 2014, we conducted up to 11 in-person follow-up visits on 410 eligible children (390 singletons and 10 twin sets) at the delivery hospital, our study clinic, or participant's homes when children where approximately 1 day, 4 weeks, and 1, 2, 3, 4, 5, and 8 years of age; follow-up rates ranged from 94% (age 4 weeks) to 48% (age 4 years).* A detailed…"

2. "The optimal serum cotinine cut-points at each age were the concentrations at which the difference between sensitivity and specificity was minimum." What's the rationale of this approach? Why not use the maximum average of sensitivity and specificity to find the optimal cut-points? Or F1 score (harmonic mean of sensitivity and positive predictive value) as frequently used in informatics and computer science?

We are aware that there are various methods to optimize such cut-points. We tested the 3 criteria most often used in biostatistics: maximizing the Youden index, the identification of the point on the curve with minimum distance from the left-upper corner of the unit square, and minimizing the difference between sensitivity and specificity. Reassuringly, all three methods provided similar results. Taking into account that our objective was to find a cut- point that maximized both sensitivity and specificity, to minimize misclassification either as exposed or unexposed based on cotinine concentration, we chose the third approach.

To clarify our approach, we have included the following text in the manuscript.

"Also, while different methods are available to identify the optimal serum cotinine cut-points, we have chosen the one that minimizes the difference between sensitivity and specificity since our objective

was to minimize misclassification of exposed or unexposed based on cotinine concentration; the differences between the methods were negligible."

3. ICC was calculated for children with complete data. Would it be possibly biased because children with intermittent missing or who dropped out were excluded?

While possible, we do not believe that this bias is present. When calculating the ICC with measurements up to 36 months, for which we have data from 121 children, the ICC changes negligibly relative to the ICC obtained from using different combinations of measures.

If only the measurements at 12 and 24 months (169 children) are considered, the ICC increases slightly, but part of this increase may be due to the fact that correlation is only calculated between two more temporally proximal measurements, and the correlation tends to decrease as the number of measurements increases, likely reflecting the increasing time between measures.

Here are the data obtained:

ICC reported in the manuscript (n = 71 children): 0.72 (0.63 - 0.80)

ICC for measurements at 12, 24 and 36 months (n = 121 children): 0.73 (0.64 - 0.81)

ICC for measurements at 12 and 24 months (n = 169 children): 0.79 (0.72 - 0.84)

Also, Spearman Rank Correlations were calculated:

rho for measurements at 12, 24, 36 and 48 months (n = 71 children):

	12 months	24 months	36 months	48 months
12 months	1			
24 months	0.7741	1		
36 months	0.6243	0.6912	1	
48 months	0.685	0.768	0.6689	1

rho for measurements at 12, 24 and 36 months (n = 121 children): 0.73 (0.64 - 0.81)

	12 months	24 months	36 months
12 months	1		
24 months	0.7711	1	
36 months	0.6636	0.7339	1

rho for measurements at 12 and 24 months (n = 169 children): 0.7710

VERSION 2 – REVIEW

REVIEWER	Yoonsang Kim NORC at the University of Chicago, USA
REVIEW RETURNED	04-May-2021

GENERAL COMMENTS	The authors addressed my comment about the method used to find the optimal serum cotinine cut-points in Discussion/limitation. I don't think this is a limitation. I'd suggest moving the description to Methods. In response to my third comment about ICC, the authors described "ICC reported in the manuscript (n=71 children): 0.72 (0.63-0.80). However, in the manuscript, it says "the ICC between repeated serum cotinine concentrations (analysis restricted to 73 children with cotinine measures at 12, 24, 36 and 48 months) was 0.72." Was the n 71 or 73? Please update it with the correct number.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3:
Dr. Yoonsang Kim, National Opinion Research Center

Comments to the Author:

The authors addressed my comment about the method used to find the optimal serum cotinine cut-points in Discussion/limitation. I don't think this is a limitation. I'd suggest moving the description to Methods.

We agree with the reviewer that data about the method used to find the optimal serum cotinine cut-points is not a limitation in itself so we have removed the previous sentence from the discussion section and added the following description in the methods section (statistical analysis):

"There are various methods to optimize cotinine cut-points. We tested the three criteria most often used in biostatistics: maximizing the Youden index, the identification of the point on the curve with minimum distance from the left-upper corner of the unit square, and minimizing the difference between sensitivity and specificity; while the three methods provided similar results, we chose the third approach to be able to identify the optimal age-specific cut-point which maximizes both

sensitivity and specificity, to minimize misclassification either as exposed or unexposed based on cotinine concentrations".

In response to my third comment about ICC, the authors described "ICC reported in the manuscript (n=71 children): 0.72 (0.63-0.80). However, in the manuscript, it says "the ICC between repeated serum cotinine concentrations (analysis restricted to 73 children with cotinine measures at 12, 24, 36 and 48 months) was 0.72." Was the n 71 or 73? Please update it with the correct number.

We thank the reviewer for noticing the inconsistency in the number of children to whom the analysis was restricted. We have updated the data in the new version:

"The ICC between repeated serum cotinine concentrations (analysis restricted to 71 children with cotinine measures at 12, 24, 36 and 48 months) was 0.72…"