Author's response to reviews

Title: Exposure to tobacco smoke based on urinary cotinine levels among Israeli smoking and nonsmoking adults: a cross-sectional analysis of the first Israeli biomonitoring study

Authors:

Hagai Levine (tohagai@bezeqint.net)
Tamar Berman (tamar.berman@moh.health.gov.il)
Rebecca Goldsmith (rivka.goldsmith@moh.health.gov.il)
Thomas Göen (Thomas.Goen@ipasum.med.uni-erlangen.de)
Judith Spungen (jhspungen@gmail.com)
Lena Novack (novack@bgu.ac.il)
Yona Amitai (yonaamitai89@gmail.com)
Tamar Shohat (tamar.shohat@icdc.health.gov.il)
Itamar Grotto (itamar.grotto@MOH.HEALTH.GOV.IL)

Version: 2 Date: 28 November 2013

Author's response to reviews: see over
To

BMC Public Health Editorial

Please find enclosed our revised manuscript 1202371383103923 – “Exposure to tobacco smoke based on urinary cotinine levels among Israeli smoking and nonsmoking adults: a cross-sectional analysis of the first Israeli biomonitoring study”.

The following point-by-point “Response to Reviewers” indicates our response (in bold font) to the reviewers’ helpful and constructive comments and describes changes made in the manuscript. As required, all modifications were marked in the revised paper.

We hope you find our revised paper now acceptable for publication. We thank you for your consideration and look forward to your positive reply.

Sincerely yours,

Hagai Levine, MD, MPH (On behalf of all authors)
Faculty member, Hebrew University-Hadassah Braun School of Public Health and Community Medicine, Ein Kerem, Jerusalem, Israel
Response to Reviewer 1:
Reviewer's report
Title: Exposure to environmental tobacco smoke based on urinary cotinine levels among Israeli nonsmoking adults: a cross-sectional study of the first Israeli biomonitoring study
Version: 1 Date: 7 October 2013
Reviewer: Gideon St.Helen
Reviewer's report:
General comment:
The manuscript by Levine and colleagues describes data from the first Israeli Biomonitoring Study and focuses on measurements of urine cotinine among self-reported nonsmokers to characterize their exposure to secondhand smoke. The Israeli Biomonitoring Study is a cross-sectional study and seeks to measure exposure to environmental pollutants in a representative sample of the Israeli population, secondhand smoke being one of these environmental pollutants. The authors found “widespread and high” secondhand smoke exposure based on high proportions of >LOD urine cotinine. Comparisons with smokers are also presented in the study with results as to be expected. The data are presented in the context of a national smoke-free legislation which is about to go into effect. Therefore this study will serve as an important benchmark from which the effectiveness of the smoke-free air law will be assessed periodically. Given that the data are from a larger study which was not specifically designed for the objectives of the manuscript under review, the manuscript has some limitations that are not readily address but may not be fatal. Of note, the authors present the study as a nationally representative sample of the population. Although the study protocol was designed to sample in a nationally representative manner, this was not achieved (as noted in the limitations). Further, the sample size is relatively small and was non-randomized. In addition, it is not clear to what extent subjects did not misclassify their smoking status. While 5 “nonsmokers” with urine cotinine >150 ng/mL were omitted, several other subjects had urine cotinine that exceeded 50 ng/mL, the well accepted discriminator of smokers and non-smokers, and self-identified smokers had urine cotinine levels that were characteristic of nonsmokers. It would have been helpful if there was information on time since last cigarette among “smokers” or time since last exposure to SHS among “non-smokers”. This would have allowed for better discussion of higher than usual cotinine among “nonsmokers” or lower than usual cotinine among “smokers”. Further, it wasn’t clear whether unhealthy individuals, pregnant women, or drug users were included or excluded in the study, all factors that affect biomarker levels. Despite these limitations and minor comments below, the manuscript is of importance in the field of tobacco control. Biomonitoring is an important element in assessing the effectiveness of smoke-free air laws and this study presents data that form the foundation of future assessments.

We referred to all these general comments and improved the manuscript accordingly, as detailed in the specific comments, including additional sensitivity analysis.
Specific comments (All minor essential revisions)

Abstract
1. The abstract is clear, well-written, and summarizes the results of the study very well.
   -Thanks.
2. The results justify the conclusions made
   -Thanks.

Background:
3. The term secondhand smoke (SHS) is more commonly used vs. ETS.
   -We mentioned SHS as well but prefer ETS, which is also widely used.
4. First paragraph: omit the reference to thirdhand smoke. SHS and THS should not be conflated.
   -Omitted.
5. 4th paragraph, sentence starting with “Cotinine, the main metabolite”: replace “main metabolite” with “primary proximate metabolite”
   -Replaced.
6. 4th paragraph, sentence starting with “the cotinine level provide”…With a half-life of 16-18 hrs, cotinine is eliminated from the body given no further exposure to tobacco smoke in 3-4 days. So it should be mentioned that cotinine as a biomarker presents information on ongoing or recent SHS exposure instead of “over time”.
   -Corrected.
7. 5th paragraph, last line: replace “actual ETS” with “systemic exposure to ETS”
   -Corrected.
8. 6th paragraph: The Israeli smoke-free legislation is mentioned in the background but no further information is given to the reader about what this new law entails. Is it outdoors, indoors, workplaces, public places? Give more context to this new legislation and whether there currently exists any other laws in Israel relating to tobacco smoke.
   -We agree, but feel it would be more suitable to elaborate on the smoke-free legislation in the discussion. So we corrected the background and discussion accordingly.

Methods
1. Study design is well presented
2. Relatively small sample size but this cannot be corrected now
3. One weakness is the inclusion criteria. The researchers did not make health status, drug use, and pregnancy inclusion/exclusion criteria. These are known to affect drug pharmacokinetics and therefore concentration of urine cotinine levels measured. Are the results for healthy individuals?
   -Following this comment, this issue is now further elaborated in the manuscript: “Participants were not targeted for specific health status”.
4. There’s a weakness with the questionnaire item on smoking status. “Do you currently smoke”? What does “currently” mean? Current smoking is often identified by the question, “have you smoked in the past 30 days?” This is a better question than what was asked in this manuscript.
   -We agree and will aim to use this wording in future studies.
5. Stat analysis: analyses done are appropriate.
   -Good.
6. “using the lognormal distribution” does this mean that biomarker concentrations were logtransformed before stat analyses? May be better to state the latter.
   - This sentence refers to some comparisons using the t-test procedure for ratio using the lognormal distribution. The main analysis was for cotinine level above LOQ (binary outcome, so nothing can be log-transformed here). Hence, wouldn’t be correct to state the latter.
7. I don’t see the need to include fruits and vegetables in this analysis. It has been established that any potential nicotine from these is negligible to say the least. Spearman correlations are not appropriate here if you want to assess whether eating fruits and vegetables affect cotinine levels. It should be included as a covariate in regression models. I am not certain whether this was done in the multivariate analyses. If yes, make it clearer.
   -We agree. Following the reviewer’s suggestion, we omitted this analysis from methods and results. As Reviewer 3 suggested, we further discussed the negligible contribution of dietary sources to nicotine/cotinine exposure.
8. A cutpoint of >150 ng/mL urine cotinine is a very high cutpoint to discriminate smokers from nonsmokers. This is based on an older study. Why wasn’t 50 ng/mL (µg/L) used instead as a discriminator?
   - Following the reviewer’s comment we conducted and added to the revised manuscript a sensitivity analysis using a cut-off point of 50, which led to further exclusion of 5 participants (with cotinine levels between 50-150). Results were overall similar as added as last sentence of the results section.
   We had thought thoroughly on this point prior to analysis, and different cut-off points are legitimate. A cut-off point of 150 is very specific to detect hidden active smokers, but not very sensitive. If we used a cut-off point of 50 we would be able to exclude more hidden smokers but on the other side might falsely exclude passive smokers and lose power. We decided to have more specificity to detect hidden active smokers.
Results
9. 3rd paragraph: striking difference is followed by borderline statistical significance. This is contradictory.
   -We agree and corrected the sentence accordingly.
10. Not always clear which cut-point is being referred to at times (<1 or <4 µg/L). Be clearer.
   -We agree and re-organized the paragraph.
Discussion
1. 2nd paragraph: The statement “findings validate self-reported smoking status”: this is not altogether supported given the 5 self-identified nonsmokers omitted due to really high cotinine as well as several nonsmokers with >50 ng/mL and “smokers” with really low cotinine levels. Why is the urine cotinine of smokers <LOD? Is there any data on time from last cigarette? The authors should address these discrepancies in self-report and cotinine levels.
We agree with this limitation and following the reviewer’s comment, omitted the statement as well as addressed this issue in the limitation paragraph: “Another limitation is the possibility of that cotinine levels found in our nonsmoking population derived not only from ETS, but, in some cases, from misclassification of smoking status or use of Nicotine replacement therapy as a source of exposure. We minimized this possibility by exclusion of those with cotinine levels >150 µg/g and by our sensitivity analysis (excluding cotinine levels >50 µg/g). Unfortunately, we did not collect data on time elapsed since last cigarette smoked among self-reported smokers which might explain why some self-reported smokers (which did not smoke recently) had relatively low urinary cotinine levels as well as the higher smoking rate in our study population compared to the general Israeli adult population. Self-reported smoking status is considered valid; especially for those aged 20 and above [37], so it is unlikely that misclassification by smoking status significantly affected our results”. We clarified that all smokers had urinary cotinine levels above LOD.

2. The authors state “This observation gives further evidence to harmful effects of this common habit” in reference to water pipes. The data presented does not allow the authors to make this conclusion. Measurement of cotinine does not necessarily indicate harmful effects.

- The reviewer is correct. The sentence was re-phrased: “This observation gives further evidence to the addictive potential of this common habit in our population”.

Conclusion

1. Despite the limitations of the study in terms of sample size, representativeness, discrepancies with self-reported smoking status, the data presented support the conclusions made.

- We wish to specially thank the reviewer for the insightful review which was very helpful in improving the manuscript.

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 have no competing interests to declare.
Response to Reviewer 2:
Reviewer's report
Title: Exposure to environmental tobacco smoke based on urinary cotinine levels among Israeli nonsmoking adults: a cross-sectional study of the first Israeli biomonitoring study
Version: 1 Date: 14 October 2013
Reviewer: Emilia Zainal Abidin
Reviewer's report:
This paper presents results from the Israeli Biomonitoring Study among 250 adults focusing on ETS exposure prior to the implementation of SFL in 2011. Urinary samples were collected among smoking and non-smoking adults along with information from questionnaire (interview-based) using the door-to-door method. The authors analysed urinary cotinine using GC-MS method, a gold-standard robust method. Results were presented in Geometric Means and 2 cut-off points >1 ug/ml and >4 ug/ml. The participants of this study also were requested to complete the 24-hour dietary recall questionnaire. The outcome of this study was expected to be used as a baseline data to support the implementation of SFL in 2012.
This is an important work in the field of tobacco control and smoke-free legislation study. This study is also interesting and unique in terms of the results from participants who smoke water-pipes, which is not common in Asia.
Some points for suggestions to be considered by the authors.
- We thank the reviewer for her kind words and valuable comments which were helpful in improving the manuscript.
Please make your review as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:
- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
1. - Minor Essential Revisions
a. Title and Abstract page
- Background paragraph – the purpose of this study was to examine current levels of ETS among non-smoking Israeli adults – I find this confusing since there were both smoking and non-smoking adults in the results – suggest to rephrase
- The reviewer is correct and we rephrased (“smoking and nonsmoking adults”) the title, abstract and background section accordingly.
- Methods paragraph – active smoking characteristics – implying that they are smokers – suggest to rephrase. Were there any questions on ETS exposure hours posed for non-smokers?
-We corrected to “active smoking status” as suggested by the reviewer. Unfortunately, there was no question on ETS exposure as mentioned in the limitation paragraph.
b. Background
- 3rd paragraph – 1st sentence add reference.
-We shortened the background and omitted this sentence.
- 2nd sentence Smoking rates across sex and ethnicity needs to be rephrased, i.e. highest were among Arab males etc.
-Rephrased.
- 3rd sentence – previous efforts to reduce ETS in public spaces has been only partially successful – please explain further as in discussion it was mentioned that SFL were implemented in 2012
-This sentence was rephrased. After careful consideration we think it would aid the reader if we relate in-depth to the legislation in the discussion.
- 6th paragraph – non-smoking Israeli adults – rephrased as the comment for abstract above.
-Rephrased.
c. Methods – study design, setting and participants
- 1st paragraph – 1st and 2nd sentence needs to be rephrased as the sentence did not mention that this paper/study makes up a part of a larger study clearly. Also aims need to be stated specifically
-The reviewer is correct and we rephrased accordingly as well as added references to our previous publications.
- 2nd paragraph – eligible population included adults aged 20 to 74 years old. Also explain why is this age group selected.
-An explanation was added: “aiming to represent the Israeli non-institutionalized adult population”.
- 2nd paragraph – within each area, recruitment was done by knocking on doors and interviewing those who met the inclusion criteria...As the homes were selected on a random basis, please mention it here
-Unfortunately, we don’t think we can call this method random, as explained in the limitation paragraph.
- …this was documented…suggest to lose this sentence
-Omitted.
- Data sources and variables – 1st paragraph - , and were carried out in Hebrew and Arabic..suggest to be deleted
-Deleted.
- 2nd sentence we excluded from the non-smokers group 4 individuals with null questionnaire responses for smoking status and 5 participants with creatinine adjusted cotinine concentrations - This is repetitive, is present in results - suggest either place the sentence here or in results, although I would prefer it to be in results.
-We agree, omitted here, described in results.
- Statistical methods – 3rd paragraph – Would suggest that the comparison with the Canadian Human Biomonitoring Study be included in the discussion part
instead of in the methods or results (as this result was presented in text not table)
-Omitted from results. We think this analysis should still be mentioned in the methods.
d. Results
- Would be ideal if all three tables were mentioned in text or mentioned in parenthesis (according to journal’s format)
-Corrected.
- 5th paragraph – suggest to be placed in discussion
-We agree and moved it to the discussion.
e. Discussion
- 4th paragraph – 2nd sentence consider rephrasing
-Rephrased.
- 5th paragraph – more tolerance to work ETS – exposure at work
-Corrected.
- 6th paragraph – Need to consider this paragraph, would suggest to shorten its length and delete the last sentence
-Shortened and last sentence deleted.
2. - Discretionary Revisions
a. Background
- 5th paragraph – 1st sentence Knowledge, Attitudes and Practices survey – GATS from WHO? Would be ideal if it is explained here
-The paragraph was shortened to avoid diverting the reader's attention.
b. Methods – study design, setting and participants
- 3rd paragraph – after this sentence…participation in the study was voluntary…..suggest to be deleted.
-Deleted.
- 2nd paragraph – 1st sentence how about recreational smokers?
-As stated: “of any kind”.
c. Discussion
- 2nd paragraph – authors might consider including the GM across frequency of smoking in one of the latter paragraph as it might be of interest for others
-In line with previous comments of the reviewer, we added data on cotinine levels by smoking frequency to the results and changed the manuscript accordingly.
- 3rd paragraph – in our study all nonsmokers had levels of urinary cotinine above LOD…
-Corrected.
- 3rd paragraph. In this study, a moderate correlation….consider replacing with in the and replacing saliva cotinine levels with salivary cotinine levels
-Corrected.
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests
Response to Reviewer 3:

Reviewer's report
Title: Exposure to environmental tobacco smoke based on urinary cotinine levels among Israeli nonsmoking adults: a cross-sectional study of the first Israeli biomonitoring study
Version: 1
Date: 25 October 2013
Reviewer: Alexander Stiby

Reviewer's report:
Major Compulsory Revisions
1. Methods are not clear. Limit of detection and limit of quantification need to have clear definitions. Smoker/non smoker is addressed purely on self-report but cotinine levels should also be used, using the active smoking cut-off.
-We made some amendments to the methods section to make it clearer for the reader. We added clear definitions of limit of detection and limit of quantification: “Limit of detection and limit of quantification were calculated based on a signal-to-noise ratio of 1 to 3 and 1 to 6, respectively”. It is not correct that nonsmoking status was addressed purely on self-report. In reference to active smoking cut-off, we used urinary cotinine cut-off of >150µg/g to exclude nonsmokers with additional sensitivity analysis with cut-off of >50µg/g.
2. The use of the phrase ‘statistical significance’ should not be used as using the cut-off of p<0.05 is arbitrary.
-We changed the phrase, when needed (“borderline”).
3. The methods discuss showing OR's but these are not presented in the results.
-We refer the reviewer to the last (now second to last) paragraph of the results.
4. Results are discussed in the results section for the association between fruit and vegetable consumption on adjusted cotinine levels among non smokers. These results are not presented in any of the tables.
-As another reviewer suggested, we omitted this part from the results and methods sections.
5. Data is discussed in discussion section which is not presented in the article.
-As another reviewer suggested, we added the data on cotinine levels by smoking frequency to the results.
6. The sample size is very small to be making conclusions, this would be to be extensively addressed in the discussion.
-In addition to addressing this issue in the limitation paragraph, we added to the opening paragraph of the discussion: “Despite limited power due to small sample size”. However, from a statistical point of view, it is not true to state that a sample size of ~250 is too small to make conclusions.
7. Discussion needs to address other sources of cotinine.
-We added a detailed discussion on the possibility of other sources of cotinine in the limitation paragraph.

Minor Essential Revisions
1. A more complete breakdown of the numbers from the Israeli Biomonitoring
Study are required. Also, a description of the potential sample size, why was it only 300 individuals when the study looks into 20 cities?

-20 multiply by 15 equals 300, as explained in the methods. We added references to the Israeli biomonitoring study.

2. Bracket missing when describing education in the methods.
   -Corrected

3. Units need to be included for age in the results.
   -Added, where needed.

4. Conclusion is miss-spelt.
   -Corrected.

5. Tables need to be able to stand alone, therefore need a description/legend.
   -There is a description for each table. Following the reviewer's comment, legends were extended, as needed.

6. Quality of figure needs to be increased, also the description need to be extended to be able to stand alone.
   -Description extended. We would appreciate editorial help in increasing the quality of the figure, if needed.

Discretionary Revisions

1. Very recent study, 'Stiby et al. (2013)' would be useful in the background literature.
   -We tried, but did not find where this would fit as our study was among adult population while the study mentioned, authored by the reviewer, was among children. We are currently conducting a study among children and would be glad to cite the reviewer's publication in the future.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being Published
   -We further edited the language.

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

Declaration of competing interests:
I declare I have no competing interests.