PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of smoke-free legislation on fetal, infant, and child health: a systematic review and meta-analysis protocol
AUTHORS	Been, Jasper; Nurmatov, Ulugbek; van Schayck, Onno; Sheikh, Aziz

VERSION 1 - REVIEW

REVIEWER	Dr Daniel F Mackay, Senior Lecturer in Public Health, Institute of Health and Wellbeing, University of Glasgow SCOTLAND
REVIEW RETURNED	27-Nov-2012

GENERAL COMMENTS	ABSTRACT Page 2, 43-44: The decision as to whether to use fixed or random effects is not one that should be taken on the basis of the heterogeneity that is found-it should be stated apriori. The fact that the potential studies to be included in the review come from different countries have different study designs implies implicitly that they have not been conducted under similar conditions therefore random effects has to be the choice of analysis. Failing that a compromise would be a mixed model-this can be done using the R software or WinBugs. 48: You also need to present subgroup analysis by coverage of ban ..... you mention intervention type...is this the same thing? If so, for clarity, I would state "coverage of ban" rather than intervention. 49: You may not be able to formally assess publication bias. If the outcome measures are ORs then it is well known that Eggers test is biased under such circumstances. To get round this using Peters/Harbord Begg etc will require the numbers of exposed not exposed which I'm sure that not all papers will present. INTRO: 31: First sentence is conjecture....need a ref here...or delete last 6 words. 48: Preterm deliveries showed a significant drop in the Scottish paper. Delete "possibly" as it isn't correct. Results either (i) show or (ii) do NOT show a reduction in an outcome. It can't be "possibly" - that option doesn't make sense in the context of a meta analysis. METHODS: 41-42: *Why* are you excluding these types of studies? In my

	opinion they should go in to the meta analysis as these effects can be controlled for and analysed as a sub-group analysis. In my opinion you are being far too selective at this stage and you need to be careful here. I have no problem with types of studies being included as long as the method of meta analysis takes their characteristics into account in the reporting of the results. There is no mention of meta regression ....this can and should be done. Why are you excluding studies that present their findings as ORs? This would seem strange to a wide readership and warrants some form of explanation in the text. Medication use: are you going to report results as does-response? More detail is needed for these choices. There is no mention of the software to be used. I'm assuming this will be Stata? Or.....? SEARCH STRATEGY: There is no mention of secondhand tobacco smoke or ETS in your search terms. Why? Most child "exposure" is through SHS and/or ETS .....seems odd not to include them !

REVIEWER	Dr Jo Leonardi-Bee Associate Professor of Medical Statistics University of Nottingham UK No competing interests
REVIEW RETURNED	06-Dec-2012

GENERAL COMMENTS	The authors plan to conduct a systematic review and meta-analysis to assess the impact of smoke free legislation on fetal, infant, and child outcomes. The protocol is well written, and I only have a few comments for the authors to clarify/address: 1. for some outcomes, the included studies may have used definitions which are different to those stated in the protocol; how will the authors deal with this inconsistency between the studies? 2. the authors will investigate an extremely comprehensive list of outcomes, I am concerned that given the tight time line, this will not be achievable 3. the authors have not mentioned contacted the authors of included studies to clarify any ambiguities or lack of detail in the methods or results. I think it is important that they do this 4. what was the rationale for including asthma as the primary outcome for child? 5. how will be authors identify experts to consult to identify further studies? 6. how do the authors plan to identify unpublished non-RCTs, only

	lists of trial registers are provided 7. will a meta-analysis be performed irrespective of the I squared value? Or only where there isn't extreme heterogeneity between the studies, for example, I squared<75% 8. The authors state they will only include studies in a meta-analysis if the results have been adjusted for maternal or parental smoking - could this introduce bias? I would prefer for all studies to be included, and then a sensitivity analysis to be performed to exclude the studies which have not adjusted for this confounder 9. the authors have stated they will conduct subgroup/sensitivity analyses based on patient level characteristics. The authors need to be aware of the issue of ecological fallacy, and summary data meta-analysis is not the optimum method for looking at patient level characteristics 10. what is the definition of 'sufficient' for the number of studies to be included in a meta-analysis before an assessment of publication bias is made 11. the authors need to clarify which model they will choose when multiple adjusted models are presented in the papers. will they choose the most adjusted model?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Dr Daniel F Mackay)

ABSTRACT
Page 2, 43-44: The decision as to whether to use fixed or random effects is not one that should be taken on the basis of the heterogeneity that is found-it should be stated apriori. The fact that the potential studies to be included in the review come from different countries have different study designs implies implicitly that they have not been conducted under similar conditions therefore random effects has to be the choice of analysis. Failing that a compromise would be a mixed model-this can be done using the R software or WinBugs.

RESPONSE: We agree that given the expected diversity in population and study characteristics, a fixed effects model is unlikely to be appropriate for any of the meta-analyses that might be undertaken. Therefore according to the suggestion of the reviewer, we have decided to apply a random-effects model to all analyses. This has been altered in the protocol (page 8, ‘Data analysis’, 1st paragraph). We will keep the heterogeneity assessments as these will generate valuable information about the degree of heterogeneity and as such may influence interpretation of the results.

48: You also need to present subgroup analysis by coverage of ban ..... you mention intervention type...is this the same thing? If so, for clarity, I would state "coverage of ban" rather than intervention.

RESPONSE: Indeed ‘intervention type’ as stated in the abstract refers to the proposed sensitity analysis of coverage of the ban (comprehensive vs. site-specific). We agree that this designation may be subject to various interpretations and have therefore substituted it by ‘coverage of ban’ as suggested (page 2, ‘Methods’, 2nd paragraph).

49: You may not be able to formally assess publication bias. If the outcome measures are ORs then it is well known that Eggers test is biased under such circumstances. To get round this using Peters/Harbord Begg etc will require the numbers of exposed not exposed which I'm sure that not all papers will present.

RESPONSE: We agree with the reviewer that formal assessments of publication bias may not always

be possible given the expected range of outcome variables and potential lack of reporting of relevant numbers required for the analyses. We have now acknowledged this in the protocol (page 9, 2nd paragraph).

INTRO:
31: First sentence is conjecture....need a ref here...or delete last 6 words.

RESPONSE: We feel it is important to acknowledge that adverse outcomes associated with second hand smoke exposure may have their origin before birth, and have therefore added references here (page 3, 3rd paragraph).

48: Preterm deliveries showed a significant drop in the Scottish paper. Delete "possibly" as it isn't correct. Results either (i) show or (ii) do NOT show a reduction in an outcome. It can't be "possibly" - that option doesn't make sense in the context of a meta analysis.

RESPONSE: We agree with the reviewer and have rephrased this sentence (page 3, 3rd paragraph).

METHODS:
41-42: *Why* are you excluding these types of studies? In my opinion they should go in to the meta analysis as these effects can be controlled for and analysed as a sub-group analysis. In my opinion you are being far too selective at this stage and you need to be careful here. I have no problem with types of studies being included as long as the method of meta analysis takes their characteristics into account in the reporting of the results.

RESPONSE: We appreciate the concern raised by the reviewer. Our rationale for performing this review is to identify the evidence and knowledge gaps with regard to the effectiveness of smoke-free legislation to improve fetal, infants, and child health, with the ultimate goal to formulate policy recommendations based on our findings. This closely relates to the approach of the Cochrane EPOC group, whom in their guidelines strongly disencourage the inclusion study designs other than the ones stated in our review given the difficulty to attribute causation from such studies. We realise that part of the available evidence may therefore be disregarded, however this is for the benefit of the higher level of evidence identified and the strength of any recommendations based on them. We have tried to strnegthen the justification of our decision in the protocol (page 4, ‘Types of studies’).

There is no mention of meta regression ....this can and should be done.

RESPONSE: Meta-regression can be a valuable tool to explore modulatory effects of continuous or categorical covariates on the effect estimate in meta-analysis. However, our proposed sensitivity analyses do not include continuous or categorical variables that would be suitable for exploration through meta-regression, which is why we have chosen not to describe this option in our protocol.

Why are you excluding studies that present their findings as ORs? This would seem strange to a wide readership and warrants some form of explanation in the text.

RESPONSE: We are not planning to exclude studies that present their data in ORs. We realise that our formulation may be erroneously interpreted as exclusive and have rephrased this (page 5, 1st paragraph).

Medication use: are you going to report results as dose-response? More detail is needed for these choices.

RESPONSE: Medication use or prescription is mentioned as a possible tool to define presence of a

diagnosis (e.g. inhaled corticosteroid use as a surrogate for asthma). We will not consider investigating any dose-effect relationships. This has been rephrased (page 5, 1st paragraph).

There is no mention of the software to be used. I'm assuming this will be Stata? Or.....?

RESPONSE: We will indeed make use of the Stata statistical software. This has now been acknowledged in the protocol (page 9, 2nd paragraph).

SEARCH STRATEGY:
There is no mention of secondhand tobacco smoke or ETS in your search terms. Why? Most child "exposure" is through SHS and/or ETS .....seems odd not to include them !

RESPONSE: We see how it may seem odd not to include these central terms in our search strategy. However, it must be noted how terms like ‘second hand (tobacco) smoke’ and ‘environmental (tobacco) smoke’ all include either ‘smoke’, ‘smoking’, or ‘tobacco’. Therefore despite not including terms such as ‘environmental’ and ‘second hand’ in our search strategy, their combinations with smoke-related terms will ensure that they are picked up by our search strategy (e.g. lines 1-5 in appendix 1). Feedback provided by our librarian involved in developing the search strategy confirms the inclusiveness of our strategy.

Reviewer 2 (Dr Jo Leonardi-Bee):

The authors plan to conduct a systematic review and meta-analysis to assess the impact of smoke free legislation on fetal, infant, and child outcomes. The protocol is well written, and I only have a few comments for the authors to clarify/address:

1. for some outcomes, the included studies may have used definitions which are different to those stated in the protocol; how will the authors deal with this inconsistency between the studies?

RESPONSE: We acknowledge that our outcome definitions may not fit all outcomes used in potentially relevant studies. We have added a section on how we will handle these potential differences (page 6, 2nd paragraph).

2. the authors will investigate an extremely comprehensive list of outcomes, I am concerned that given the tight time line, this will not be achievable

RESPONSE: We value this concern. In order to obtain a comprehensive estimate of the effect of smoke-free legislation on fetal, infant, and child health we feel it is important that all the diagnoses proposed are included in the search strategy. Therefore, given the concern about the timeline we have decided to extend the timeline by three months (page 9, ‘Timeline’). We are confident that we will be able to deliver this work within the proposed time period.

3. the authors have not mentioned contacted the authors of included studies to clarify any ambiguities or lack of detail in the methods or results. I think it is important that they do this

RESPONSE: We agree that it is important that authors of eligible studies are contacted in case of ambiguities, and we have made it more explicit that we are planning to do so (page 7, ‘Data extraction’, 1st paragraph).

4. what was the rationale for including asthma as the primary outcome for child?

RESPONSE: Similar to the other two primary outcomes, the rationale for including asthma as a primary outcome is based on 1. the magnitude of its disease burden in paediatric medicine, 2. its well recognised important association with antenatal and postnatal second hand smoke exposure, 3. the recognised association between smoke-free legislation and a reduction in asthma-associated health care use in at least one high quality study. We have now acknowledged this in the protocol (page 5, 1st paragraph).

5. how will be authors identify experts to consult to identify further studies?

RESPONSE: We will approach experts that have made significant recent contributions to the field of (prevention of) SHS exposure and/or SHS exposure-associated effects on paediatric health.

6. how do the authors plan to identify unpublished non-RCTs, only lists of trial registers are provided

RESPONSE: As the reviewer will be aware, proper registration of unpublished and ongoing observational research is currently underdeveloped. Several clinical trial registries such as ClinicalTrials.gov now also allow for observational designs to be registered. Furthermore, it is increasingly seen as good practice to publish protocols for high standard observational research in advance in peer-reviewed journals. Observational study protocols published through either of these means will be picked up by our search strategy. We have deliberately chosen not to include conference abstracts in our search strategy because selection of potentially relevant conferences and exclusion of others introduces bias and furthermore it is impossible to perform quality assessment on research reported in abstract form only.

7. will a meta-analysis be performed irrespective of the I squared value? Or only where there isn't extreme heterogeneity between the studies, for example, I squared<75%

RESPONSE: We plan to use a random effects model for any meta-analysis to deal with heterogeneity. In addition we agree it is reasonable to define an I-square cut-off above which no meta-analysis will be undertaken, and have added this to our protocol (page 8, 'Data analysis').

8. The authors state they will only include studies in a meta-analysis if the results have been adjusted for maternal or parental smoking - could this introduce bias? I would prefer for all studies to be included, and then a sensitivity analysis to be performed to exclude the studies which have not adjusted for this confounder

RESPONSE: This restriction only applies to meta-analyses of adjusted effect estimates as described in the protocol, not to all meta-analyses planned. For adjusted effect estimates, we feel maternal / parental smoking is the most important confounder, although not all studies may have included this variable in their multivariate analyses. To avoid any bias that may be introduced we have omitted this restriction and added it as a sensitivity analysis to the adjusted meta-analyses, as suggested (page 8, last paragraph).

9. the authors have stated they will conduct subgroup/sensitivity analyses based on patient level characteristics. The authors need to be aware of the issue of ecological fallacy, and summary data meta-analysis is not the optimum method for looking at patient level characteristics

RESPONSE: Ecological fallacy is potentially an important issue indeed. At this stage, we are not planning any individual level patient data meta-analyses, which might solve part of this issue. We will refrain from performing meta-regression in which ecological fallacy is a concern particularly. We merely need to interpret our findings in the light of potential ecological fallacy. Where possible, we will compare results from aggregate subgroup analyses obtained by meta-analysis with similar subgroup

analyses performed in individual studies. However, we should be aware that ecological fallacy may also be an issue in individual ecological studies. This will certainly be discussed in the eventual paper reporting the results although we do not see a place for this discussion in the current protocol.

10. what is the definition of 'sufficient' for the number of studies to be included in a meta-analysis before an assessment of publication bias is made

RESPONSE: We will perform a formal assessment of publication bias when ten or more studies are included in a single meta-analysis. This has been added to the protocol (page 9, 2nd paragraph).

11. the authors need to clarify which model they will choose when multiple adjusted models are presented in the papers. will they choose the most adjusted model?

RESPONSE: For meta-analyses of adjusted effect estimates we will indeed select for inclusion the most adjusted model when papers present several models. This has now been acknowledged in the protocol (page 8, 'Data analysis', 1st paragraph).

VERSION 2 – REVIEW

REVIEWER	Jo Leonardi-Bee Associate Professor in Medical Statistics University of Nottingham UK I have no competing interests with this protocol
REVIEW RETURNED	15-Jan-2013

GENERAL COMMENTS	The authors have addressed all of the questions, and the protocol is now fine for publication