

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Passive smoking and Chronic Obstructive Pulmonary Disease. Cross-sectional analysis of data from the Health Survey for England.
AUTHORS	Jordan, Rachel; Cheng, Kar Keung; Miller, Martin; Adab, Peymane

VERSION 1 - REVIEW

REVIEWER	David Mannino CDC
REVIEW RETURNED	11-May-2011

GENERAL COMMENTS	<p>The authors provide an analysis of the Health Survey for England to examine the relation between reported passive emoke exposure and measures of lung function impairment (COPD defined using the LLN,GOLD, and NICE criteria). They find a modest effect- but this strengthens with the inclusion of respiratory symptoms.</p> <p>Major Comments:</p> <p>Exclusions - The authors excluded subjects reporting "asthma" from the analysis. I would strongly advise that they be included (or- at a minimum a supplemental table be included that includes subjects with asthma). I would also include an asthma history as a covariate in this model. In most of may analyses, what is called "asthma" is associated with smoking (and smoke exposure) and is also a pretty strong predictor for the presence of lung function impairment (ORs in the 4-6 range).</p> <p>Exclusion - No spirometry - A substantial number of subjects were excluded because of lack of spirometry. In my experience, these tend to be older and sicker individuals. I would suggest that Table 1 be replicated (again- perhaps as a supplemental table or tables) comparing the included to the excluded for each year and the total!</p> <p>GOLD and NICE definitions - I believe the authors should replicate Tables 2, 3 and 4 for the GOLD and NICE definitions for inclusion in the supplement.</p> <p>Minor comments :</p> <p>I would use the term "modified GOLD" as this was a prebronchodilator measure. Do not know if NICE is pre or post- but that may have to be described as "modified" also.</p> <p>Optional comment:</p> <p>The current analysis includes "restricted" subjects as normal (using either the LLN or the GOLD/NICE criteria). I'd be curious as to what</p>
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	happens to the results if these are excluded from the normals (or what happens if they are included as a separate outcome?)
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REVIEWER	Dr. Sandra Baldacci Researcher, Pulmonary Environmental Epidemiology Unit, CNR Institute of Clinical Physiology Pisa Italy I declare that I have no competing interests
REVIEW RETURNED	31-May-2011

THE STUDY	There are some important aspects concerning study design and sampling criteria which have to be clarified and that, at the moment, are affecting all the framework of the study. For further details, please consider the attached file.
RESULTS & CONCLUSIONS	In Results section the same problems already affecting the Methods section are present (see the attached file).
REPORTING & ETHICS	CONSORT (Consolidated Standards of Reporting Trials) is not considered since the paper doesn't deal with a trial. No note on informed consent or ethical approval has been mentioned.
GENERAL COMMENTS	<p>In the last twenty years, several epidemiological studies carried out worldwide, have collected significant evidences about the relationship between passive smoking and health. In fact, ETS, besides a relevant activity in cancerogenesis, appears to influence the development of other respiratory and cardiovascular diseases. In this connection, the present study also addresses this still appealing topic of public health interest.</p> <p>On the other hand, in respect to active smoking, the importance of the detrimental effects of ETS is less known, due to the fact that ETS effects have been mainly investigated in paediatric samples. On the contrary, in this case, the authors report their data on the association between passive smoking exposure and the presence of COPD, evaluated by different methods, in adults participating in large Health Surveys for England.</p> <p>However, the paper includes a number of shortcomings to be faced.</p> <ol style="list-style-type: none"> 1. Study design and sampling criteria are not well defined. For the sake of clearness, it should be reported in the "Methods" section if each survey involves a different population sample or if there are subjects who participated in more than one survey. In other words, are data from the three samples of 1995, 1996 and 2001 completely independent? Because, if this is not the case, the assumptions of independence, on which ordinary regression models are based, fall away. In case of dependent samples (paired data), intraclass correlation should be performed, and, on the basis of the result of this one, a suitable model should be used. 2. As before mentioned, data structure is crucial, it affects statistical planning and results. For this reason, if the three samples involve subjects participating in more than one survey, a longitudinal approach could be advisable, e.g. generalized estimating equation (GEE) regression models for, at the most, three observations (1995, 1996, 2001). Above all, also in case of independent data, combining the three samples appears a little risky, the single survey could be linked to a few unconsidered factors which could affect the outcome; adjustment of regression models by this

	<p>categorical variable (1995 survey, 1996 survey and 2001 survey) could bypass this problem.</p> <ol style="list-style-type: none"> 3. Airway obstruction criterion (LLN) is not immediately comprehensible. 4. Environmental Tobacco Smoke (ETS) has been defined as the smoke which non smokers are exposed to when they are in an indoor environment with smokers; thus the effect of passive smokers should be investigated in the nonsmokers subsample. Since a large combined sample has been utilized, analyses could be limited to non smokers as in Table 3. 5. Even if the current paper has not the suitable requirements in order to evaluate the role of passive smoking in COPD causation, statistical analyses could produce more robust results/associations if a lifetime indicator of chronic passive smoking exposure was utilized instead of current exposure indicator. 6. The lack of objective biomarkers for measuring passive smoking exposure is not a problem, as many previous published papers on this topic have utilized subjective reliable ETS indicators but taking into account number of hours, number of smokers or, at least, place of exposure such as at home, at work or in other places. However, this paper utilizes a very generic ETS indicator: is it possible to define a more meaningful passive smoking indicator? 7. Always in order to better elucidate "Methods" section: in the "Outcomes" part, the specific questions should be reported for each item considered in the analyses. 8. It should be useful to provide further details on questionnaire/interview characteristics; for example: is it a standardized questionnaire already used in previous studies or was it created ex novo? 9. References would be checked in order to eliminate possible inaccuracies. <p>Specific comments:</p> <ol style="list-style-type: none"> 1. Abstract: in the "Design" section LLN has to be written in full; more information should be provided about the research tool (questionnaire). The "Results" part is not clear; while the same results are better described in the Key messages. 2. Introduction: in the 2nd paragraph (line 6 to 8), before mentioning the role of passive smoking in the aetiology of COPD, the impact of this exposure source in the general population should be emphasized. Reference of Simoni et al. (Respir Med 2007, 101, 531-538) concerning the association between ETS and respiratory symptoms/disease could be useful for further literature comparisons. In the last paragraph, the problem of misclassification of exposed subjects should be considered. 3. "Methods" section is insufficient and needs of integrations and clarifications as before mentioned. It has to be provided details on sampling method i.e. size of eligible subjects, strata used in multistage stratified random sampling. As regards "Questionnaire and procedures" section, which were longstanding illnesses asked? As regards "Outcomes" section, it is important to define GOLD (to write in full) and NICE (to write in full) criteria even if they are present in Table 1 legend. Bronchitis is not a symptom. As regards the
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	<p>presence of clinically significant COPD, which symptoms were included in this diagnostic label: all the mentioned symptoms or only those specifically related to COPD. As regards “Statistical analyses” section, what do you mean with “by year”? please, specify. Why have you considered only age, sex and smoking status as confounders? What about the other important risk factors for COPD as socioeconomic status, occupational exposure, outdoor pollution?</p> <p>4. “Results”: once again, are all the 18817 subject different?</p> <p>5. “Discussion”: interpretation of trends obtained separately in the three surveys are missing. At the end of the first paragraph, the reported comparison is not clear. It is mentioned a probable reduction of passive smoking exposure, due to the introduction of bans to smoking in public places: when did these bans occur? during the surveys period? Could be the comment about “smaller numbers (and therefore increased uncertainty) among never smokers” expanded? A few references would be added when “published excess risks of passive smoking on heart disease, lung cancer and asthma” are reported.</p> <p>6. Table 1: in the title “patients” should be substituted with “subjects” as the study samples have been selected from the general population.</p>
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VERSION 1 – AUTHOR RESPONSE

Passive smoking and COPD: response to referees

Referee 1: David Mannino

1. As requested we have now included in an additional analysis subjects reporting asthma (Table 5), with history of asthma as a covariate.
2. In Table 1 we have now included an additional column which allows readers to assess the differences between included and excluded participants.
3. We have now created a new Table 4 which displays the effect of NICE and GOLD criteria on the association between passive smoking and COPD among never smokers .
4. Minor: The term “modified” GOLD has now been used to describe post-bronchodilator values; NICE has only recently required post-bronchodilator spirometry.
5. Optional: we decided not to explore the effect of “restricted” subjects as this is a different question which should probably be covered in a separate paper.

Referee 2: Sandra Baldacci

Informed consent/ethical approval: this is not required as the Health Survey for England data is already publicly available.

1. Study design and sampling criteria: we have clarified in the methods section that the survey is conducted independently each year.
2. In order to mitigate against the potential problems of combining the data we have now included a term for “year of study” in the regression model for the analyses.
3. LLN: the description of LLN has been further clarified in the methods.
4. Limit analysis to non-smokers: In Table 2 we have retained the ever smoking participants as well as including a column specifically for never smokers; despite the reasonable sample size, the effects are non-significant among never smokers and leaving in the ever smokers allows the patterns of

effect to be seen. In subsequent tables we have restricted to never smokers as the definition of COPD becomes more specific.

5. Lifetime indicator of passive smoking exposure: unfortunately this is not available in the HSE dataset.

6. Unfortunately there are no other suitable measures of passive smoking exposure.

7. Outcomes: the outcome section has been re-ordered to reflect the reported analyses.

8. Further details are now provided on the questionnaire in the methods section.

9. The references have now been checked again.

Specific comments

1. Abstract: LLN has now been written in full and the results section improved.

2. Introduction:

The role of passive smoking has been re-ordered to describe its association with other diseases first. The reference of Simoni et al has now been included.

The potential problem of misclassification among smokers has now been mentioned.

3. Methods:

Sampling: now given in more detail.

Longstanding illnesses: this is now removed as not necessary.

Outcomes/bronchitis/symptoms: Now clarified in the methods section.

By year: the statistical section has now been reworded.

Confounders: we have now included a measure of socioeconomic status as a potential confounder in analyses containing all participants; among never smokers the “socioeconomic” covariate did not improve the statistical model and was therefore omitted. Unfortunately there is no good measure of occupational exposure or outdoor air pollution. This is revised in the statistical methods section.

4. Results: as now mentioned in the methods section we have clarified that all participants are independent

5. Discussion: We have now mentioned trends by year and reworded the first paragraph. The dates of the public smoking bans in relation to the surveys has now been clarified – they occurred after data collection. A few references have been added regarding excess risks of passive smoking as requested.

6. Table 1: “Patients” has been replaced with “participants” throughout.

VERSION 2 - REVIEW

REVIEWER	<i>Dave Mannino</i>
REVIEW RETURNED	29-Jun-2011

GENERAL COMMENTS	My prior concerns have been addressed! Very nice revision!
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REVIEWER	<i>Sandra Baldacci</i>
REVIEW RETURNED	18-Jul-2011

THE STUDY	A few last methodological aspects remain to be clarified. For further details, please consider the attached file.
GENERAL COMMENTS	The description of LLN continues to be not very clear. The following is a possible suggestion to improve this definition: METHODS:In this way, participants with pre-bronchodilator FEV1/FVC values below the LLN (ie the lowest 5% of the healthy never smoking Population that fall outside the limit represented by the predicted value minus 1.645-times the standard error of the estimate (SEE)) were classified as having obstructive airways disease.

	<p>To see: Comparison of the Prevalence of Chronic Obstructive Pulmonary Disease Diagnosed by Lower Limit of Normal and Fixed Ratio Criteria. Yong Il Hwang et al. J Korean Med Sci 2009; 24: 621-6</p> <p>A few discrepancies, in terminology used for symptoms, are still present, comparing “Questionnaire and procedures” and “Outcomes”. Definition of a few symptoms remains too generic: regular sputum, frequent symptoms of winter bronchitis or wheeze...What do you mean for “regular”, “frequent” or “symptoms of winter bronchitis”?</p> <p>reference n. 15 has still to be corrected in an author’ name and year of publication.</p>
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VERSION 2 – AUTHOR RESPONSE

Passive smoking and COPD: response to referees version 2

Referee 1: David Mannino

No comments to address!

Referee 2: Sandra Baldacci

3. We have improved the LLN description in the methods section as requested; this was adjusted/approved by Dr Martin Miller (co-author) who is one of the key authors of the ATS/ERS spirometry standards.

7. The questions used to elicit the symptoms in the questionnaire have now been detailed and the outcomes section clarified as requested.

9. Reference 15 has now been amended as requested.