PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between second-hand smoke exposure and hypertension in never smokers: a cross sectional survey using data from Korean National Health and Nutritional Examination Survey V, 2010-2012
AUTHORS	Park, Young Sik; Lee, Chang-Hoon; Kim, Yu-Il; Ahn, Chul Min; Kim, Ju Ock; Park, Ju-Heon; Lee, Sang-Haak; Kim, Jae Yeol; Chun, Eun Mi; Jung, Tae-Hoon; Yoo, Kwang-Ha

VERSION 1 – REVIEW

REVIEWER	Ulrich Keil, MD, MPH, PhD, Professor Emeritus Institute of Epidemiology and Social Medicine University of Münster Germany
REVIEW RETURNED	25-Jan-2018

GENERAL COMMENTS	The manuscript on SHS exposure and hypertension is important, because so far data on the association between SHS exposure and hypertension are scarce and a causal relationship between the two has not yet been established. This is different from the established causal relationships between SHS exposure and CHD and Stroke, respectively. The cross sectional study design does not allow to establish a causal relationship but in a field where data are so scarce the finding of an association between SHS exposure and hypertension is an advancement and merits reporting. However, I do not understand why the authors have analysed only the data of female never smokers. At least the reasons brought forward in the discussion section for the exclusion of male never smokers are not convincing to me. The authors claim that the proportion of male never smokers was 20,2 % of total never smokers which means according to my calculations that the number of male never smokers should be above 2000 in this data set. This figure may be too small to produce statistically significant results but analysing the data of male never smokers might show some trends, especially when the authors look at the mean SBP and DBP values (figure 2). Epidemiology gains a lot from comparisons between men and women and therefore I would like to see the baseline characteristics according to SHS exposure categories for women and for men in Table 1. A comparison of the results for women with those for men may shed some more light on the subject. In addition, some reasoning in the discussion section for the exclusion of male never smokers are not clear to me. E.g." We thought that the small

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	proportion of male never smokers would not represent the nationwide population" . Why this argument when on the other hand the authors claim that their data come from a nationwide population survey, representative of the population of South Korea? " Another consideration was interaction. Smoking could influence cardiovascular disease due to sex-dependent biologic effect." But how should we learn more about this topic when we exclude the data of male never smokers? I would not like to see a combined analysis of male and female data (looking for interactions) but separate analyses for men and women modeled on the analyses for women presented in this manuscript. After this general comment I will go through the manuscript page by page making suggestions for corrections,clarifications and improvements: page 1, the second part of the title should read: " a cross sectional survey using data from the Korean National Health and Nutrition Examination Survey V, 2010-2012." page 3, abstract, Participants: describe the selection process with a few more words. page 3, line 27, "And we calculated mean systolic and diastolic blood pressure values according to SHS exposure." line 37, Adjusted mean systolic and diastolic blood pressure values in the.....were significantly elevated in group III by 2,3 and 1,7 mmHg respectively. page 4, line 17, ...and measure the differences of systolic and diastolic blood pressure means by different SHS exposure groups. page 6, line 50, Definition of hypertension: This definition is clear but later in the manuscript it is said that female never smokers were analysed who did not have hypertension diagnosed by a physician or were on anti-hypertensive medications. What was the definition of the outcome variable hypertension in the analyses? page 7, line 5, The measurement of BP has been described elsewhere. line 7, ...after at least 5 minutes rest in a sitting position, BP.... line 24, In model 1, the only co-variable was age, while in model 2, multiple covariates such as age, body mass index(BMI).....and serum total chelesterol were included and adjusted for. In addition we compared SBP and DBP means between groups, again adjusting for covariates. line 36 see my previous question about the definition of hypertension. Please clarify. page 8, line 16, and socioeconomic status was evenly distributed by SHS exposure groups. line 20, The participants in group I were older than those in the two other groups....line 29, the prevalence of diabetes were significantly different between the three SHS exposure groups. page 9, Discussion, line 20, using a well designed nationwide survey. line 22, ...we calculated the difference in mean systolic and diastolic BP between group I and III by 2,3 and 1,7 mmHg, respectively. line 29, increase in body weight. line 53, Plasma cotinine?? level..... page 10, line 16-31: What about measuring CO with a Smokerlyser? line 42, ...we included various potential confounding factors,.... Further comments to the discussion section are to be found in the beginning of my review. Table 1. Weight, height, BP, BMI, etc. are all given as mean values but this is not indicated in the table. All other variables are given as percentages (%). If this is clearly indicated behind the variables hypertension, diabetes mellitus, etc. the many % signs behind the figures can be spared=deleted.

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	Table 2 is simple and clear. Both tables should also contain the respective figures for male never smokers if the authors agree with my suggestions and my reasoning. Figures 1 and 2 are fine with me. Again I would also like to see the respective results for men. References: ok

REVIEWER	Markus Juonala University of Turku, Finland
REVIEW RETURNED	26-Feb-2018

GENERAL COMMENTS	This paper examines the association between questionnaire-based evaluation of passive smoke exposure and hypertension. Specific comments: 1) Abstract: It shoud be mentioned that the main results are adjusted for several possible confounding factors. 2) Methods: Details of the assessement of all the variables used in the analyses, i.e. also the variables adjusted for, should be included in the Methods. 3) Results / analyses. There might be some collinearity issues in the multivariable analyses, as e.g. weight, height and waist circumference are all included, as well as both education and occupation. 4) Limitations: Study focused only on females, because so few males were never smokers. I would suggest analysing also male data, the interpretation might then be just as authors assume, but it would be useful to have that data available.

VERSION 1 – AUTHOR RESPONSE

Response to Editor comments
- Please edit the title - it should not be declarative.
Response) We modified the title according to editor's and 1st reviewer's comment. And as we mentioned above, we included the male population. So we omitted the mention of female in the title. The final title is "The association between second-hand smoke exposure and hypertension in never smokers: a cross sectional survey using data from Korean National Health and Nutritional Examination Survey V, 2010-2012"

- Did you have a study protocol for this study?
Response) We have no study protocol published or displayed at web sites, but we have a protocol shared by authors. (in Korean).

- Did you do any analysis before you planned the research question or after?
Response) We did analysis after we planned the research question.

- Please include figure legends at the end of your main manuscript.
Response) We moved the figure legends at the end of main manuscript. Because we added the male population, so we added more description.

- Please combine your Figures 2A and 2B into one to have a single file figure and make sure that they have a resolution of at least 300 dpi. Figures in PDF, DOCUMENT, EXCEL and POWER POINT format are not acceptable. Note: If you can't convert your figure into one, kindly renumber the figure legends into Figure 1, Figure 2, etc.
Response) We combined 2A, 2B, 2C & 2D into a single JPG file, which resolution was about 300 DPI.

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Reviewer #1
Response) According to reviewer's suggestion, we included all population of KNHANES V. The total study population is 10, 532 (female 8,987 and male 1,545) and did analysis for female and male separately. We added their baseline characteristics in Table 1, the results of model 1 and 2 in Table 2. Also, the adjusted mean SBP and DBP were shown in Figure 2 (presented below, A and B for female, C and D for male).

page 1, the second part of the title should read: " a cross sectional survey using data from the Korean National Health and Nutrition Examination Survey V, 2010-2012."
Response) We modified the title according to reviewer's comment.
"The association between second-hand smoke exposure and hypertension in never smokers: a cross sectional survey using data from Korean National Health and Nutritional Examination Survey V, 2010-2012"

page 3, abstract, Participants: describe the selection process with a few more words.
Response) We added some words for selection process,
"We selected never smokers aged over 20 years who answered the question about the SHS exposure."

page 3, line 27, "And we calculated mean systolic and diastolic blood pressure values according to SHS exposure." line 37, Adjusted mean systolic and diastolic blood pressure values in the.....were significantly elevated in group III by 2,3 and 1,7 mmHg respectively.
Response) We modified sentences according to reviewer's correction.

page 4, line 17, ...and measure the differences of systolic and diastolic blood pressure means by different SHS exposure groups.
Response) We modified sentences according to reviewer's correction.

page 6, line 50, Definition of hypertension: This definition is clear but later in the manuscript it is said that female never smokers were analysed who did not have hypertension diagnosed by a physician or were on anti-hypertensive medications. What was the definition of the outcome variable hypertension in the analyses?
Response) We are sorry to confuse you. We described the definition of hypertension in method section,
"if one or more of the criteria below were met,
1) Diagnosed by physician
2) Using anti-hypertensive medications
3) SBP ≥140mmHg
4) DBP ≥90mmHg
"
To determine if SHS exposure is associated with hypertension (the main outcome), we surely applied this criteria as the definition of hypertension. (Table 2) However, to evaluate the relationship between SHS exposure and mean SBP or DBP, the analysis was limited to population who were not taking antihypertensive medication because anti-hypertensive treatment could be a bias. (Figure 2)

To avoid confusion, wee omitted the sentence "who had not been diagnosed with hypertension by their doctors (in the abstract)", "had not been diagnosed with hypertension by their physician (in the

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statistical analysis section)" and "previous diagnosis of hypertension (Legend of Figure 2)" in the revised manuscript.

page 7, line 5, The measurement of BP has been described elsewhere.
Response) We modified sentences according to reviewer's correction.

line 7, ...after at least 5 minutes rest in a sitting position, BP....
Response) We modified sentences according to reviewer's correction.

line 24, In model 1, the only co-variable was age, while in model 2, multiple covariates such as age, body mass index(BMI).....and serum total chelesterol were included and adjusted for. In addition we compared SBP and DBP means between groups, again adjusting for covariates.
Response) We modified sentences according to reviewer's correction.

line 36 see my previous question about the definition of hypertension. Please clarify.
Response) As mentioned above, we deleted the sentence "who had not been diagnosed with hypertension by their doctors (in the abstract)", "had not been diagnosed with hypertension by their physician (in the statistical analysis section)" and "previous diagnosis of hypertension (Legend of Figure 2)".

page 8, line 16, and socioeconomic status was evenly distributed by SHS exposure groups.
Response) We modified sentences according to reviewer's correction.

line 20, The participants in group I were older than those in the two other groups....
Response) We modified sentences according to reviewer's correction.

line 29, the prevalence of diabetes were significantly different between the three SHS exposure groups.
Response) We modified sentences according to reviewer's correction.

page 9, Discussion, line 20, using a well designed nationwide survey.
Response) We modified sentences according to reviewer's correction.

line 22, ...we calculated the difference in mean systolic and diastolic BP between group I and III by 2,3 and 1,7 mmHg, respectively.
Response) We modified sentences according to reviewer's correction.

line 29, increase in body weight.
Response) We modified sentences according to reviewer's correction.

line 53, Plasma cotinine?? level.....
Response) According to the cited article (Ref. 21), serum nicotine level is correct. The table 2 showed the results from Ref. 21. In the manuscript, serum nicotine was miscited as a plasma nicotine. So, we replaced 'plasma' with 'serum'.

(Ref. 21: Argacha JF, Adamopoulos D, Gujic M, et al. Acute effects of passive smoking on peripheral vascular function. Hypertension 2008;51:1506-11.)

page 10, line 16-31: What about measuring CO with a Smokerlyser?
Response) We agree with reviewer's opinion. There are several biomarkers for evaluation of smoking. Most common used biomarker is serum or urine cotinine, because of its long half-life. Compare to cotinine, CO method is very easy, but the half-life is very short, about 5 hours. In the literature review,

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CO method was used for evaluation of stop smoking and serum or urine cotinine was used for evaluation of SHS exposure. In KNHANES data, only urine cotinine were measured for small population (1959/10532, 18.6%).

line 42, ...we included various potential confounding factors,....
Response) We modified sentences according to reviewer's correction.

Further comments to the discussion section are to be found in the beginning of my review.
Response) We made a paragraph about male group in discussion section.
"The association between hypertension and SHS exposure was observed only in female group. We postulated three possibilities. First, male never smokers were younger than female who never smoked (39.9±0.5 vs. 47.7±0.3 yearsThe influence of smoking exposure on BP could be limited in younger men.15 Second, smoking exposure could influence cardiovascular disease due to sex-dependent biologic effect.16 Third, the low statistical power due to small sample size could affect results. In our dataset, the proportion of male never smokers was only 19.4% of total male population aged over 20 years. Although we did not achieve statistically significant results in male group, the trend was confirmed, and it could support the biologic effect between SHS exposure and blood pressure."

Table 1. Weight, height, BP, BMI, etc. are all given as mean values but this is not indicated in the table. All other variables are given as percentages (%). If this is clearly indicated behind the variables hypertension, diabetes mellitus, etc. the many % signs behind the figures can be spared=deleted.
Response) According to reviewer's comment, we added the mention of "The data were presented as mean±standard error in continuous variables and % in categorical variables." below the table 1.

Table 2 is simple and clear. Both tables should also contain the respective figures for male never smokers if the authors agree with my suggestions and my reasoning.
Response) We added the results of male population in Table 2.

Figures 1 and 2 are fine with me. Again I would also like to see the respective results for men.
Response) We added the data of male in Figure 1 and 2.

References: ok
Response) Thank you for your check

Reviewer #2
1) Abstract: It shoud be mentioned that the main results are adjusted for several possible confounding factors.
Response) According to reviewer's comment, we added some phrases in the abstract, Primary and secondary measurement section.
"We investigated the association between SHS exposure and hypertension by using multivariate analysis. And we evaluated the mean systolic and diastolic blood pressure values according to SHS exposure after adjusting for possible confounding factors. All analyzes were carried out by female and male, separately."

2) Methods: Details of the assessement of all the variables used in the analyses, i.e. also the variables adjusted for, shoul be included in the Methods.
Response) Thank you for your comment.
In the statistical analysis section of Method, we described the model 1 and 2. The detailed confounding covariates were listed there. We found there were errors in the selection of covariates

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and those were corrected. (instead of BMI and DM, height, weight and fasting glucose were selected as covariates).

3) Results / analyses. There might be some collinearity issues in the multivariable analyses, as e.g. weight, height and waist circumference are all included, as well as both education and occupation.
Response) Thank you for good advice. However, there were no significant collinearity. First, we evaluated the collinearity between weight, height and waist circumference. All VIF values are less than 10. The detailed numbers are shown below. Because we analyzed female and male separately, so the VIF values were also presented separately.

	Female	Male
Weight vs. WC	2.57	2.83
Height vs. WC	1.01	1.00
Height vs. Weight	1.13	1.29

Because education and occupation are categorical variables, so we check various methods for collinearity. We present more detailed data about that. First, we calculated VIF value between education and occupation, and the value is 1.09 for female and 1.18 for male. Second is interaction model. The combination of two variables are 28 (education variable has 4, occupation has 7), so we made new binary categorical variable for education (Elementary~middle school vs. high school ~ above high school) and occupation (employed vs. unemployed). We calculated the interaction value using model 2. The P values are 0.658 (female) 0.258 (male). Both are more than 0.005.

Third, we calculated adjusted OR for hypertension ("≥ 2hr/day" of model 2) with or without these variables (below table).

	aOR in female	aOR in male
Current model	1.50 (1.10-2.04)	0.93 (0.52-1.68)
w/o occupation	1.41 (1.06-1.89)	1.12 (0.62-2.01)
w/o education	1.53 (1.13-2.09)	0.96 (0.54-1.73)
w/o occupation and education	1.48 (1.12-1.97)	1.21 (0.68-2.15)

Finally, we excluded the collinearity between education and occupation.

4) Limitations: Study focused only on females, because so few males were never smokers. I would suggest analysing also male data, the interpretation might then be just as authors assume, but it would be useful to have that data available.
Response) According to reviewer's suggestion, we added the data of male population.

VERSION 2 – REVIEW

REVIEWER	Markus Juonala University of Turku, Finland
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	No further comments

REVIEWER	Ulrich Keil, MD, MPH, PhD, Professor Emeritus Institute of Epidemiology and Social Medicine University of Muenster Germany
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	Thank you for following the suggestion to also analyse the male

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	never smokers of the Korean National Health Survey. This makes the paper more complete, although the analyses on the male population of never smokers are not statistically significant. But the mean SBP and DBP values show a tendency for higher values in groups II and III compared to group I. I have a number of smaller comments, which may also fall in the rubric of language editing. This is why the editors should also deal with my suggestions. page 3, line 31, All analyses were stratified by women and men. page 3. line 42, ...associated with group III than group I in women... page 3, line 44, and diastolic blood pressure values in women who were not taking antihypertensive medication..... page 4, line 17, ...and measured the differences... page 4, line 28, ...could not conclude a causal relationsship.... page 7, line 7, ...at least 5 minutes rest in a sitting position,..... page 7, line 24, ...the association between SHS exposure and hypertension.... page 8, quite often female should be replaced by women and male by men page 8, line 55, I would replace the last sentence by the following words: But in men no statistically significant differences were seen. page 9, lines 16 and 18, In men we observed a tendency toward higher mean systolic and diastolic BP values in groups II and III versus group I or compared to group I. page 9, line 50, We postulate three possibilities. page 9, line 52, The influence of SHS exposure.....Second, SHS exposure could influence.... page 10, line 14, ...of systolic and diastolic BP was the same,.... page 11, line 31,.....could not conclude a causal relationship.... page 11, line 53, factors related to hypertension.... page 12, line 13, ...could also contribute to the development of hypertension. Table 2. again the heading should be women and men instead of female and male Perhaps a few words on Model 2b for men are warranted. While model 1a shows results similar to model 1a for women, although not statistically significant, model 2b shows weird results, obviously because of the many co-variables in the model and the small numbers involved.

VERSION 2 – AUTHOR RESPONSE

According to reviewer's correction, 'female' and 'male' were replaced by women and men in the manuscript and figure 1, figure 2, table 1 and table 2.

page 3, line 31, All analyses were stratified by women and men.
Response) We modified the sentence according to reviewer's correction.

page 3. line 42, ...associated with group III than group I in women...
Response: We modified the sentence according to reviewer's correction.

page 3, line 44, and diastolic blood pressure values in women who were not taking antihypertensive medication.....
Response: We modified the sentence according to reviewer's correction.

page 4, line 17, ...and measured the differences...

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Response: We modified the sentence according to reviewer's correction.

page 4, line 28, ...could not conclude a causal relationsship....
Response: We modified the sentence according to reviewer's correction.

page 7, line 7, ...at least 5 minutes rest in a sitting position,.....
Response: We modified the sentence according to reviewer's correction.

page 7, line 24, ...the association between SHS exposure and hypertension....
Response: We modified the sentence according to reviewer's correction.

page 8, quite often female should be replaced by women and male by men
Response: We modified the sentence according to reviewer's correction.

page 8, line 55, I would replace the last sentence by the following words: But in men no statistically significant differences were seen.
Response) We replaced the sentence according to reviewer's suggestion.

page 9, lines 16 and 18, In men we observed a tendency toward higher mean systolic and diastolic BP values in groups II and III versus group I or compared to group I.
Response) We modified the sentence according to reviewer's correction.

page 9, line 50, We postulate three possibilities.
Response) We modified the sentence according to reviewer's correction.

page 9, line 52, The influence of SHS exposure.....Second, SHS exposure could influence....
Response) We modified the sentence according to reviewer's correction.

page 10, line 14, ...of systolic and diastolic BP was the same,....
Response) We modified the sentence according to reviewer's correction.

page 11, line 31,.....could not conclude a causal relationship....
Response) We modified the sentence according to reviewer's correction.

page 11, line 53, factors related to hypertension....
Response) We modified the sentence according to reviewer's correction.

page 12, line 13, ...could also contribute to the development of hypertension.
Response) We modified the sentence according to reviewer's correction.

Table 2. again the heading should be women and men instead of female and male
Response) We modified the sentence according to reviewer's correction, the headings of Table 1 and 2 were modified. Also, these words were changed in Figure 1 and 2 including Figure 2 legend.

Perhaps a few words on Model 2b for men are warranted. While model 1a shows results similar to model 1a for women, although not statistically significant, model 2b shows weird results, obviously because of the many co-variables in the model and the small numbers involved.
Response) According to reviewer's suggestion, we added that comments in the discussion section (2nd paragraph).
"We postulate three possibilities. First, …… Third, there could be some limitations of statistical model 2 for men because of the many co-variables and the small numbers involved. The low …. "

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