

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Smoking and Atherosclerotic Cardiovascular Disease Risk in Young Men: The Korean Life Course Health Study
<b>AUTHORS</b>	Jee, Yongho; Jung, Keum Ji; Lee, Sunmi; Back, Joung Hwan; Jee, Sun Ha; Cho, Sung-il

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Giuseppe Gorini ISPRO, Florence, Italy
<b>REVIEW RETURNED</b>	31-Jul-2018

<b>GENERAL COMMENTS</b>	<p>This interesting study examined the association between smoking and the development of atherosclerotic cardiovascular diseases (ASCVD) in a cohort of more than 100,000 Korean young men followed up for 23 years.</p> <ol style="list-style-type: none"><li>1. Introduction: at page 5, line 15 there is in brackets: "(WHO)": does it mean the first reference? Please, erase "(WHO)", and add at least one reference.</li><li>2. Results: at page 11, line 17, when Authors wrote about the Hazard Ratio relating to IHD of ex-smokers, the P value in brackets is wrong. It is not &lt;0.001, but it is =0.8567, according to Table 2.</li><li>3. Figure 3: the D is not reported in the fourth graph in the Figure 3, regarding years of smoking and stroke.</li><li>4. Figure 3: I strongly suggest to add two more graphs in Figure 3 (E and F), showing the Risk Ratios for ASCVD by cigarette smoked per day and by years of smoking.</li><li>5. Figure 4: I recommend to add another graph (the C one), where you can show the Risk Ratios for ASCVD by quintiles of total cholesterol.</li><li>6. Table 3: Please, erase the row with "Physical activity". If you have no data regarding prevalence of physical activity, it's better not to mention it, instead of reporting "??". You can add one sentence in the results section where you explain that you had no figures on physical activity prevalence, and therefore it was no possible to calculate PAR for this protective factor.</li><li>7. Discussion: at page 13, line 47 you reported that ...."the risk of IHD lasts for an unknown period, while the high risk for ASCVD decreases after smoking cessation." I strongly suggest to add three references to your reference list This article previously showed this important result: A. Lightwood &amp; Glantz. Circulation, 1997 (<a href="https://www.ahajournals.org/doi/10.1161/circ.96.4.1089">https://www.ahajournals.org/doi/10.1161/circ.96.4.1089</a> ) B. Nurses'Health Study (only women): (<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879642/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879642/</a> ) C. Cancer Prevention Study II: <a href="http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.482.5541&amp;rep=rep1&amp;type=pdf">http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.482.5541&amp;rep=rep1&amp;type=pdf</a></li></ol>
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	8. Conclusions: at page 14, line 49, you began a sentence with "And". Please, change this way: "Moreover, the association was no modified..."
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<b>REVIEWER</b>	Viktor Hamrefors Lund University, Sweden.
<b>REVIEW RETURNED</b>	29-Aug-2018

<b>GENERAL COMMENTS</b>	<p>In this study the authors examine the effect of smoking on the risk of atherosclerotic cardiovascular disease. They report that smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD.</p> <p>The results are clearly presented and even if not surprising or very novel, they add to the important knowledge of the meaning of cardiovascular risk factors in young subjects.</p> <p>Comments/concerns:</p> <ol style="list-style-type: none"> <li>1. Abstract: Only men were examined, which should be stated already in the objective.</li> <li>2. It is reported that only 10 % of the Korean population was covered by the insurance system in 1992-94 and thus could be included in the current study analysis. Do the authors have any data for comparison of the 90 % that were not included at the time? Regardless, the authors should comment on the low and non-random coverage and potential selection bias induced by this.</li> <li>3. The authors report 23 years of follow-up, however this seems to be the whole follow-up period from 1992(-94) to 2015. What was the median follow-up time in the cohort?</li> <li>4. In the results section the authors report 78 % hypertension, which must be an inverse typo since the proportion in Table 1 is 22 %. Anyway, 22 % is still a very high accounting for the young age of the subjects at baseline. Since the authors use the argument of low prevalence of non-smoking risk factors as a rationale for their study they should comment on the high proportion of hypertensive subjects.</li> <li>5. The proportion of current smokers (&gt; 60 %) at baseline is very high. What is the current smoking rate in Korea? Furthermore, since regular medical check-ups were done the authors should have data on those who quit smoking during follow-up? What was the association in subjects that quit smoking within, say 10 years, from the baseline screening?</li> <li>6. In connection with point 5: Based on the young age at baseline, it is not surprising that ex-smoking was not a significant risk factor - this should be added in the discussion.</li> <li>7. Did the authors look specifically for associations between smoking and ASCVD mortality? If not these analyses may be worth adding to the manuscript.</li> </ol>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Giuseppe Gorini

Institution and Country: ISPRO, Florence, Italy

Please state any competing interests or state 'None declared': None to declare

Response: Okay, we stated as "None to declare" in the conflict of interest part.

Please leave your comments for the authors below

This interesting study examined the association between smoking and the development of atherosclerotic cardiovascular diseases (ASCVD) in a cohort of more than 100,000 Korean young men followed up for 23 years.

1. Introduction: at page 5, line 15 there is in brackets: "(WHO)": does it mean the first reference? Please, erase "(WHO)", and add at least one reference.

Response: Thank you for comments. We modified to the form of BMJ reference style.

2. Results: at page 11, line 17, when Authors wrote about the Hazard Ratio relating to IHD of ex-smokers, the P value in brackets is wrong. It is not  $<0.001$ , but it is  $=0.8567$ , according to Table 2.

Response: In the revised version, we have corrected the point you noted.

3. Figure 3: the D is not reported in the fourth graph in the Figure 3, regarding years of smoking and stroke.

Response: In the revised version, we confirmed the figure and added figures for ASCVD.

4. Figure 3: I strongly suggest to add two more graphs in Figure 3 (E and F), showing the Risk Ratios for ASCVD by cigarette smoked per day and by years of smoking.

Response: Thank you for your comment; we added tables showing the Risk Ratios for ASCVD by cigarette smoked per day and by years of smoking (Figure 3-E, 3-F).

5. Figure 4: I recommend to add another graph (the C one), where you can show the Risk Ratios for ASCVD by quintiles of total cholesterol.

Response: Thank you for your comment; we added a table showing the Risk Ratios for ASCVD by quartiles of total cholesterol (Figure 4-C).

6. Table 3: Please, erase the row with "Physical activity". If you have no data regarding prevalence of physical activity, it's better not to mention it, instead of reporting "??". You can add one sentence in the results section where you explain that you had no figures on physical activity prevalence, and therefore it was no possible to calculate PAR for this protective factor.

Response: In the revised version, we added PAR for Physical activity.

7. Discussion: at page 13, line 47 you reported that ...."the risk of IHD lasts for an unknown period, while the high risk for ASCVD decreases after smoking cessation." I strongly suggest to add three references to your reference list This article previously showed this important result:

A. Lightwood & Glantz. *Circulation*, 1997 (<https://www.ahajournals.org/doi/10.1161/circ.96.4.1089> )

B. Nurses'Health Study (only women): (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879642/> )

C. Cancer Prevention Study II:

<http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.482.5541&rep=rep1&type=pdf>

Response: Thank you for introducing good references. We have added the following discussion in the revised manuscript.

Previous studies shown that reducing adult smoking pays more immediate dividends, both in terms of health improvements and cost savings (Lightwood et al., 1997). In particular, most of the excess risk of vascular mortality due to smoking in women may be eliminated rapidly upon cessation and within 20 years for lung diseases. (Kenfield et al., 2008). Although it is too late smoking cessation, cancer diagnosis itself may cause smoking cessation (Westmaas et al., 2015).

References:

Lightwood JM, Glantz SA. Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. *Circulation*. 1997 Aug 19;96(4):1089-96.

Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and smoking cessation in relation to mortality in women. *JAMA*. 2008 May 7;299(17):2037-47. doi: 10.1001/jama.299.17.2037.

Westmaas JL, Newton CC, Stevens VL, Flanders WD, Gapstur SM, Jacobs EJ. Does a Recent Cancer Diagnosis Predict Smoking Cessation? An Analysis From a Large Prospective US Cohort.

*J Clin Oncol*. 2015 May 20;33(15):1647-52. doi: 10.1200/JCO.2014.58.3088. Epub 2015 Apr 20.

8. Conclusions: at page 14, line 49, you began a sentence with "And". Please, change this way: "Moreover, the association was no modified..."

Response: Thank you for your comment, we changed the sentence as you recommended.

Reviewer: 2

Reviewer Name: Viktor Hamrefors

Institution and Country: Lund University, Sweden.

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

In this study the authors examine the effect of smoking on the risk of atherosclerotic cardiovascular disease. They report that smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD.

The results are clearly presented and even if not surprising or very novel, they add to the important knowledge of the meaning of cardiovascular risk factors in young subjects.

Comments/concerns:

1. Abstract: Only men were examined, which should be stated already in the objective.

Response: Thank you for your comment we added the word 'men' in the sentence at the objective part.

2. It is reported that only 10 % of the Korean population was covered by the insurance system in 1992-94 and thus could be included in the current study analysis. Do the authors have any data for comparison of the 90 % that were not included at the time? Regardless, the authors should comment on the low and non-random coverage and potential selection bias induced by this.

Response: Thank you for your valuable suggestions. In the revision, we added the limitation in the discussion.

3. The authors report 23 years of follow-up, however this seems to be the whole follow-up period from 1992(-94) to 2015. What was the median follow-up time in the cohort?

Response: The mean follow-up time was 22.8 years and median follow-up time was 24.0 years because most people are still young and the incidence or mortality rate is still low.

4. In the results section the authors report 78 % hypertension, which must be an inverse typo since the proportion in Table 1 is 22 %. Anyway, 22 % is still a very high accounting for the young age of the subjects at baseline. Since the authors use the argument of low prevalence of non-smoking risk factors as a rationale for their study they should comment on the high proportion of hypertensive subjects.

Response: Thanks for the good comments. In revisions, we corrected the prevalence of hypertension.

5. The proportion of current smokers (> 60 %) at baseline is very high. What is the current smoking rate in Korea? Furthermore, since regular medical check-ups were done the authors should have data on those who quit smoking during follow-up? What was the association in subjects that quit smoking within, say 10 years, from the baseline screening?

Response: Korea's adult smoking rate is currently around 40%. The subjects of this study received a medical examination every two years. In 2002, 10 years later, the smoking rate dropped to 36%. As of 1992, a systematic analysis of smokers after 10 years in smokers will be needed in the next study.

6. In connection with point 5: Based on the young age at baseline, it is not surprising that ex-smoking was not a significant risk factor - this should be added in the discussion.

Response: I totally agree. In this study, the risk of heart disease in past smokers was not significant. These findings can be interpreted in two ways. First, it can be an effect on quitting smoking. Second, Even if young people aged 20-29 quit smoking, they did not have a long period of life-time cigarette smoking, which obviously did not have to do with the increased risk of heart disease. It is the part that needs to be studied further. I added this part to the discussion.

7. Did the authors look specifically for associations between smoking and ASCVD mortality? If not these analyses may be worth adding to the manuscript.

Response: In this study, the number of deaths due to ASCVD was 306 only (90 IHD and 126 total stroke). It is a small number to build a model, so I want to study smoking and death after tracking for several more years. Thank you.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Giuseppe Gorini ISPRO
<b>REVIEW RETURNED</b>	09-Oct-2018

<b>GENERAL COMMENTS</b>	<p>Please, there is one thing to change: the reference 27 (Westmaas et al.)</p> <p>One of the reviewers suggested to cite results of one of the biggest US cohorts on smoking and mortality, the Cancer Prevention Study II (CPSII), and suggested to cite the chapter 4 of the US National Cancer Institute Tobacco Control Monograph n.8 (you can find it here:  <a href="https://cancercontrol.cancer.gov/brp/tcrb/monographs/8/index.html">https://cancercontrol.cancer.gov/brp/tcrb/monographs/8/index.html</a> ).</p> <p>So, erase, please the Westmaas et al. article, in the reference list, and add this chapter on results in the CPSII cohort. Results of CPSII are very similar to those collected in the Nurses' Health Study, and involved both men and women.</p> <p>So, you could write only one comment for both studies (Nurses' health study, and CPSII study), saying that ..... "most of the excess risk of vascular mortality due to smoking may be eliminated rapidly upon cessation and within 20 years for lung diseases".</p> <p>The comment on smoking cessation after a cancer diagnosis from the Westmaas, et al.'s reference,) does not fit with comments on this article.</p>
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<b>REVIEWER</b>	Viktor Hamrefors Lund University, Malmö, Sweden
<b>REVIEW RETURNED</b>	11-Oct-2018

<b>GENERAL COMMENTS</b>	<p>The authors have responded well to most of my questions, however there are still some unaddressed issues that should be clarified and/or corrected:</p> <p>*The following question (copied from previous review) has not been addressed by the authors despite being said so in their reply (results still say 78 % hypertension). Moreover, the high prevalence of hypertension (22 %) has not been commented upon in the discussion: "In the results section the authors report 78 % hypertension, which must be an inverse typo since the proportion in Table 1 is 22 %. Anyway, 22 % is still a very high accounting for the young age of the subjects at baseline. Since the authors use the argument of low prevalence of non-smoking risk factors as a rationale for their study they should comment on the high proportion of hypertensive subjects."</p> <p>* May I ask the authors to clarify their reply to the following question? Do the authors mean that analyses in subjects that quit smoking is the subject of an upcoming study?</p> <p>Response: Korea's adult smoking rate is currently around 40%. The subjects of this study received a medical examination every two years. In 2002, 10 years later, the smoking rate dropped to 36%. As of 1992, a systematic analysis of smokers after 10 years in smokers will be needed in the next study."</p> <p>*The added section in the discussion about former smokers is important, however the authors may try to improve the language in order to be more clear what they mean here.</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Giuseppe Gorini

Institution and Country: ISPRO

Please state any competing interests or state 'None declared': none to declare

Response: Thank you; we stated as 'None declared' in the conflict of interests section.

Please leave your comments for the authors below

Please, there is one thing to change: the reference 27 (Westmaas et al.)

One of the reviewers suggested to cite results of one of the biggest US cohorts on smoking and mortality, the Cancer Prevention Study II (CPSII), and suggested to cite the chapter 4 of the US National Cancer Institute Tobacco Control Monograph n.8 (you can find it here: <https://cancercontrol.cancer.gov/brp/tcrb/monographs/8/index.html> ).

So, erase, please the Westmaas et al. article, in the reference list, and add this chapter on results in the CPSII cohort. Results of CPSII are very similar to those collected in the Nurses' Health Study, and involved both men and women. So, you could write only one comment for both studies (Nurses' health study, and CPSII study), saying that ..... "most of the excess risk of vascular mortality due to smoking may be eliminated rapidly upon cessation and within 20 years for lung diseases". The comment on smoking cessation after a cancer diagnosis from the Westmaas, et al.'s reference,) does not fit with comments on this article.

Response: Thank you. We erased "Westmaas et al". article, in the reference list, and add this chapter on results in the CPSII cohort. We also added comments regarding the CPSII cohort.

Reviewer: 2

Reviewer Name: Viktor Hamrefors

Institution and Country: Lund University, Malmö, Sweden

Please state any competing interests or state 'None declared': None declared

Response: Thank you; we stated as 'None declared' in the conflict of interests section.

Please leave your comments for the authors below

The authors have responded well to most of my questions, however there are still some unaddressed issues that should be clarified and/or corrected:

\*The following question (copied from previous review) has not been addressed by the authors despite being said so in their reply (results still say 78 % hypertension).

Response: In revised manuscript, we corrected this error. It was 15.4% hypertension (Page 10).

Moreover, the high prevalence of hypertension (22 %) has not been commented upon in the discussion: "In the results section the authors report 78 % hypertension, which must be an inverse

typo since the proportion in Table 1 is 22 %. Anyway, 22 % is still a very high accounting for the young age of the subjects at baseline. Since the authors use the argument of low prevalence of non-smoking risk factors as a rationale for their study they should comment on the high proportion of hypertensive subjects."

Response: Thank you, however when we checked table 1 again, the prevalence of hypertension was 15.7 in nonsmokers, 15.1 for ex-smokers, 14.5, 15.6, 15.7, respectively for current smokers by cigarettes per day.

We will once again submit the latest version of Table 1.

And we think 15.4% is not a high prevalence for the young age at baseline.

\* May I ask the authors to clarify their reply to the following question? Do the authors mean that analyses in subjects that quit smoking is the subject of an upcoming study?

Response: Korea's adult smoking rate is currently around 40%. The subjects of this study received a medical examination every two years. In 2002, 10 years later, the smoking rate dropped to 36%. As of 1992, a systematic analysis of smokers after 10 years in smokers will be needed in the next study."

Response: Korea's adult smoking rate is currently around 40%. The subjects of this study received a medical examination every two years. In 2002, 10 years later, the smoking rate dropped to 36%. We have considered that analyses in subjects that quit smoking is the subject of an upcoming study.

\*The added section in the discussion about former smokers is important, however the authors may try to improve the language in order to be more clear what they mean here.

Response: We have edited as reviewer's comments:

"In this study, the non-significant risk of CVD among ex-smokers can be interpreted in two ways.

First, this result may simply reflect the effect of smoking cessation. Most previous studies have shown that the effects of smoking cessation are immediate in CVD (most of the excess risk of vascular mortality due to smoking may be eliminated rapidly upon cessation), while lung cancer occurs within 20 years<sup>25</sup>. In particular, most of the excess risk of vascular mortality due to smoking in women may be eliminated rapidly upon cessation and within 20 years for lung diseases.<sup>26</sup>

Secondly, even if a number of young adult ex-smokers, aged 20-29 years, may have smoked continuously from adolescence, it is still a short term of smoking, compared to adults. Previous studies shown that reducing adult smoking pays more immediate dividends, both in terms of health improvements and cost savings.<sup>27</sup> While this study lacks information on smoking duration of ex-smokers, current smokers who continued to smoke seem to have increased risk of CVD by 40%. Therefore, while the smoking duration of ex-smokers is unknown, it may be reasonable to consider the results were mainly affected by the smoking cessation. Further research on the effects of smoking cessation among young adults is necessary."

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Viktor Hamrefors Dept of clinical sciences, Lund University, Malmö, Sweden
<b>REVIEW RETURNED</b>	12-Dec-2018

<b>GENERAL COMMENTS</b>	The authors have responded well to my questions and corrected an error regarding hypertension prevalence in the cohort.
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	However, please just clarify in the manuscript that the follow-up time reported (23 years) is the mean follow-up time (if this is the case).
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### VERSION 3 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Viktor Hamrefors

Institution and Country: Dept of clinical sciences, Lund University, Malmö, Sweden

Please state any competing interests or state 'None declared': None declared

Response: Thank you for confirming. We double checked the statement you mentioned, and we confirmed that we wrote as 'None declared'

Please leave your comments for the authors below

The authors have responded well to my questions and corrected an error regarding hypertension prevalence in the cohort. However, please just clarify in the manuscript that the follow-up time reported (23 years) is the mean follow-up time (if this is the case).

Response: Thank you for your comment. We agree that should use more accurate statement. Therefore we clarified our sentences as follows: "followed up for an average of 23 years"