PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

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<tr>
<td>AUTHORS</td>
<td>Beidelschies, Michelle; Lopez, Rocio; Pizzorno, Joseph; Le, Phuc; Rothberg, Michael B.; Husni, ME; D'Adamo, Christopher</td>
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VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Andersson, Maria</th>
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<td>Spenshult R &amp; D center</td>
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<td>REVIEW RETURNED</td>
<td>24-Jan-2023</td>
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| GENERAL COMMENTS    | This manuscript with the title "Polycyclic aromatic hydrocarbons and risk of RA. A cross-sectional analysis of the national health and nutrition examination survey, 2007-2016", is very interesting. I have, however, some questions.
Method and results
• How were the participants included in the subsample analysis selected (inclusion criteria)?
• I can not find the exclusion criteria for the subsample analysis.
• Add information on the number of individuals included in the analysis of non-smokers.
Discussion
• Could the selection of individuals to the subsample affect the result? I can see that there are differences in for example creatinine levels between excluded and included in the analysis of PHA subset. Just selecting one-third of the available individuals should be able to affect the result, especially since the excluded individuals are a much larger group. Add as a limitation. |

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<th>REVIEWER</th>
<th>Hutchinson, David</th>
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<tr>
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<td>Royal Cornwall Hospitals NHS Trust, Rheumatology</td>
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<td>REVIEW RETURNED</td>
<td>31-Jan-2023</td>
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| GENERAL COMMENTS    | I think this is a well written paper, but there are significant limitations in both the introduction and discussion
As this is a paper about Polycyclic Aromatic Hydrocarbons and the risk of rheumatoid arthritis and the authors correctly state that Polycyclic Aromatic Hydrocarbon exposure can occur in the work place it is essential that given that RA is strongly linked to occupational insults this is mentioned in the introduction |
References

Occupational exposure to textile dust increases the risk of rheumatoid arthritis: results from a Malaysian population-based case–control study

Occupation and risk of developing rheumatoid arthritis: results from a population-based case–control study
A Ilar et al Arthritis care & research 70 (4), 499-509 (2018)

Occupational exposure to asbestos and silica and risk of developing rheumatoid arthritis: findings from a Swedish population-based case-control study

Occupational inhalable agents constitute major risk factors for rheumatoid arthritis, particularly in the context of genetic predisposition and smoking
B Tang et al Annals of the Rheumatic Diseases (2022)

This paper quantifies the risk of RA with polycyclic aromatic hydrocarbons

Is male rheumatoid arthritis an occupational disease? A review
D Murphy, D Hutchinson The open rheumatology journal 11 (1) (2017)

Vapour, gas, dust and fume occupational exposures in male patients with rheumatoid arthritis resident in Cornwall (UK) and their association with rheumatoid factor and anti …
D Murphy, K Bellis, D Hutchinson BMJ open 8 (5), e021754 (2018)

Also burn pits, a source of PAH have been associated with RA, five fold risk in study below

Association of agricultural, occupational, and military inhalants with autoantibodies and disease features in US veterans with rheumatoid arthritis
AV Ebel et al Arthritis & Rheumatology, 2021

Authors from Sudan have hypothesized that dukhan (smoke baths) practiced by Sudanese women might be a triggering factor for RA. Dukhan is a universal custom among married women in Sudan. The women sit covered by a blanket on a low footstool over a hollowing in the ground where talh wood is burned.
Active rheumatoid arthritis in Central Africa: a comparative study between Sudan and Sweden AI Elshafie et al Journal of rheumatology 2016

Additionally there has been a publication recently from NHANES demonstrating an increased risk of RA and OA with exposure to heavy metals polycyclic aromatic hydrocarbons
The combined effect of heavy metals and polycyclic aromatic hydrocarbons on arthritis, especially osteoarthritis, in the US adult population and Nutrition Examination Survey, 2007-2016
L Fang, H Zhao, Y Chen, Y Ma, S Xu, S Xu, G Pan… - Chemosphere, 2023

This study provided novel evidence that co-exposure to heavy metals and polycyclic aromatic hydrocarbons positively correlated with arthritis.

Therefore in the discussion it needs to be mentioned that a limitation of the study is that heavy metal have not been studied

This is important as

Smoking is strongly associated with heavy metal levels such as cadmium and given the potential interaction with PAHs to trigger RA it needs to be mentioned that Cd is associated with RA

Prevalence of rheumatoid arthritis in relation to serum cadmium concentrations: cross-sectional study using Korean National Health and Nutrition Examination Survey (KNHANES) data
SH Joo et al - BMJ open, 2019

Cadmium, one of the villains behind the curtain: has exposure to cadmium helped to pull the strings of seropositive rheumatoid arthritis pathogenesis all along?
D Hutchinson

Associations of blood and urinary heavy metals with rheumatoid arthritis risk among adults in NHANES, 1999–2018
L Chen et al… - Chemosphere, 2022

Therefore the author’s claim that the majority of the effect of smoking on RA risk is mediated through PAH needs to be tempered with an acknowledgement that other contents of cigarettes such as cadmium could equally have an effect on risk elevation of RA development and further studies are needed to see if there is an interaction or simply one or the other triggers RA

Additionally in discussion need to mention how PAHs may trigger RA, for example

Polycyclic aromatic hydrocarbons affect rheumatoid arthritis pathogenesis via aryl hydrocarbon receptor
X Xi, et al… - Frontiers in Immunol…, 2022

VERSION 1 – AUTHOR RESPONSE

Reviewer Reports:

Reviewer: 1

Comments to the Author:
This manuscript with the title “Polycyclic aromatic hydrocarbons and risk of RA. A cross-sectional analysis of the national health and nutrition examination survey, 2007-2016”, is very interesting. I have, however, some questions.

Method and results
• How were the participants included in the subsample analysis selected (inclusion criteria)?

In the methods section of the original manuscript, we stated:

"Eligible participants were organized into three subsample groups (PAH, PHTHTE and VOC). To be included in a group, a participant needed to have a subsample weight >0 and have at least one toxicant metabolite from that group of interest (eTable 2 in the supplement). The VOC subsample included only toluene as the other metabolites were below the lower limit of detection."

We have since edited this statement to be:

"Eligible participants were organized into three subsample groups (PAH, PHTHTE and VOC). To be included in a group, a participant needed to have participated in the NHANES subsample of interest (subsample weight >0) and have at least one measured toxicant metabolite from that group of interest (eTable 2 in the supplement). The VOC subsample included only toluene as the other metabolites were below the lower limit of detection."

• I cannot find the exclusion criteria for the subsample analysis.

The authors adjusted Figure 1 to include the exclusion criteria for the subsample analysis.

• Add information on the number of individuals included in the analysis of non-smokers.

This information was included in the text below eTable 7 in the supplement:

“PAH never smokers subset (n = 4,102) with PAH subsample weights used for analysis”.

Discussion
• Could the selection of individuals to the subsample affect the result? I can see that there are differences in for example creatinine levels between excluded and included in the analysis of PHA subset. Just selecting one-third of the available individuals should be able to affect the result, especially since the excluded individuals are a much larger group. Add as a limitation.

The authors agree that there may be potential for selection bias in the subsample and differences exist in specific characteristics (eg. creatinine). We have added the language below to the Limitations section to address this concern.

“Fourth, the authors cannot rule out the potential for selection bias in the toxicant subsamples, and differences exist in specific characteristics for those excluded versus included in the subsamples (eg.creatinine)."

Reviewer: 2

Comments to the Author:
I think this is a well written paper, but there are significant limitations in both the introduction and discussion.
As this is a paper about Polycyclic Aromatic Hydrocarbons and the risk of rheumatoid arthritis and the authors correctly state that Polycyclic Aromatic Hydrocarbon exposure can occur in the workplace it is essential that given that RA is strongly linked to occupational insults this is mentioned in the introduction.

References


This paper quantifies the risk of RA with polycyclic aromatic hydrocarbons.


- Vapour, gas, dust and fume occupational exposures in male patients with rheumatoid arthritis resident in Cornwall (UK) and their association with rheumatoid factor and anti … D Murphy, K Bellis, D Hutchinson. BMJ open 8 (5), e021754 (2018).

Also burn pits, a source of PAH have been associated with RA, five-fold risk in study below:


Authors from Sudan have hypothesized that dukhan (smoke baths) practiced by Sudanese women might be a triggering factor for RA. Dukhan is a universal custom among married women in Sudan. The women sit covered by a blanket on a low footstool over a hollowing in the ground where talh wood is burned. Active rheumatoid arthritis in Central Africa: a comparative study between Sudan and Sweden. Al Elshafie et al Journal of rheumatology 2016.

Additionally, there has been a publication recently from NHANES demonstrating an increased risk of RA and OA with exposure to heavy metals polycyclic aromatic hydrocarbons:

- The combined effect of heavy metals and polycyclic aromatic hydrocarbons on arthritis, especially osteoarthritis, in the US adult population and Nutrition Examination Survey, 2007-2016. L Fang, H Zhao, Y Chen, Y Ma, S Xu, S Xu, G Pan… - Chemosphere, 2023 -

- This study provided novel evidence that co-exposure to heavy metals and polycyclic aromatic hydrocarbons positively correlated with arthritis.

Therefore, in the discussion, it needs to be mentioned that a limitation of the study is that heavy metal
have not been studied. This is important as smoking is strongly associated with heavy metal levels such as cadmium and given the potential interaction with PAHs to trigger RA it needs to be mentioned that Cd is associated with RA.

Per the reviewer, the Introduction has been updated with the language below to speak to occupational insults and heavy metals and RA risk citing the references that the reviewer suggested.

“For example, occupational exposure to textile dust, asbestos or noxious airborne agents has been shown to be associated with increased risk of developing RA (18-22), especially in males with certain occupations (20,23). In military personnel, exposure to airborne agents from open-air burn pits has been shown to be associated with positivity for RA autoantibodies such as anti-cyclic citrullinated peptide (anti-CCP) independent of tobacco use (24). In addition, heavy metals such as cadmium have been shown to be independently associated with increased RA prevalence (25-27) and have a combined effect with other toxicants on arthritis, especially osteoarthritis (28).”

In addition, the authors recognize the relationship between heavy metals and RA, and agree that co-exposure (heavy metals and PAHs) is plausible and have mentioned this in Limitation section of the manuscript (see language below) along with references suggested by the reviewer.

“Sixth, previous research has demonstrated that heavy metals, such as cadmium, are associated with increased prevalence of RA (26). While the current study did not examine heavy metals, the authors recognize cigarettes as a major source of cadmium which can have a major effect on RA development.”


- Cadmium, one of the villains behind the curtain: has exposure to cadmium helped to pull the strings of seropositive rheumatoid arthritis pathogenesis all along? D Hutchinson. International journal of rheumatic diseases 18 (5), 570 (2015).

- Associations of blood and urinary heavy metals with rheumatoid arthritis risk among adults in NHANES, 1999–2018 L Chen et al… - Chemosphere, 2022 -

Therefore, the author’s claim that the majority of the effect of smoking on RA risk is mediated through PAH needs to be tempered with an acknowledgement that other contents of cigarettes such as cadmium could equally have an effect on risk elevation of RA development and further studies are needed to see if there is an interaction or simply one or the other triggers RA.

The authors agree that it is important to acknowledge that other toxicants, such as cadmium, contribute to risk. We have added language to the Introduction and Discussion that speaks to cadmium as noted above. We have also added the following language in the Conclusion that speaks to future studies addressing the association and interaction of toxicants such as PAHs and heavy metals:

“Future studies would evaluate the mechanisms underlying the etiology of RA while taking into consideration the interaction between environmental toxicants such as PAHs and heavy metals, and examine the relationship between socioeconomic status, PAHs and RA.”

Additionally, in the discussion, they need to mention how PAHs may trigger RA, for example:

The authors recognize the role of the Aryl Hydrocarbon Receptor (AHR) in PAH induced RA. This was referenced in the discussion; however, the AHR terminology wasn’t included in the sentence. This has been updated per below to acknowledge this specific pathophysiological mechanism.

“This is important as PAHs are ubiquitous in the environment, derived from various sources and are mechanistically linked by the aryl hydrocarbon receptor (AHR) to the underlying pathophysiology of RA (52).”

We hope the aforementioned revisions make the manuscript suitable for publication and look forward to your determination.

Sincerely,
Michelle Beidelschies, PhD

VERSION 2 – REVIEW

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<tr>
<th>REVIEWER</th>
<th>Andersson, Maria</th>
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