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

TITLE (PROVISIONAL)	Risks of developing ulcerative colitis and Crohn's disease in relation to silica dust exposure in Sweden – a case-control study
AUTHORS	Wallden, Albin; Graff, Pål; Bryngelsson, Ing-Liss; Fornander, Louise; Wiebert, Pernilla; Vihlborg, Per

VERSION 1 – REVIEW

REVIEWER	Mirabella Zhao Gastro Unit, Copenhagen University Hospital Hvidovre, Denmark
REVIEW RETURNED	02-Nov-2019

GENERAL COMMENTS	The paper "Risks of developing ulcerative colitis and Crohn's disease in relation to silica dust exposure" reports on a case-control study which investigated the association between occupational exposure to silica dust and the development of inflammatory bowel disease. The study included 58.136 patients of inflammatory bowel disease diagnosed in the period between 2007 and 2016 identified using a national register in Sweden. For each case, two controls were matched on age, gender and county. Occupational exposure to silica dust was determined in cases and controls using a job exposure matrix. The study concluded that silica dust exposure significantly increased the risk of Crohn's disease in women and the risk of ulcerative colitis in men, the risk increases with duration of exposure. This is a very interesting study. Despite silica exposure being linked to several other inflammatory diseases, the role in IBD remains unknown. However, the study does not account for confounding factors including smoking history, socioeconomic status, family history of IBD which are known to influence the risk of IBD. Although this has been acknowledged by the authors, the lack of control for potential confounding factors weakens the robustness of the study and findings should be interpreted with caution. Specific questions: - Methods in abstract: please add the confidence intervals to the odds ratio estimates. - In the Methods section, please provide a brief description of how exposure to silica dust in relation to occupation is determined. Which occupation categories were linked to silica exposure? Did the categories differ in terms of the average quantity of exposure – e.g. if the effect is dose-dependent. - Cases are identified in the period between 2005 and 2016, however, I failed to find any information on the timing of exposure

	to silica dust in cases? How does the timing of exposure to silica dust relate to disease onset of CD and UC? - Please consider using a minimum of two with of the same diagnosis code for case ascertainment instead of only a single record to minimize the risk of including misdiagnosed cases - Please add data on causes of mortality (e.g. in table 2) if these are available

REVIEWER	Mitsuro Chiba Akita city Hospital
REVIEW RETURNED	13-Nov-2019

GENERAL COMMENTS	It is difficult to understand the content of study population. You state 58,136 cases in this study. You excluded 17,518 UC case and 10,557 CD cases (total 28,075) (Figure 1). You are handling 19,830 UC cases and 10,261 CD cases for statistical analysis in this study (total 30,091) (Table 1, Figure 1). It is difficult to follow why you include huge number of excluded cases. What a wash-out period means? If inclusion of excluded cases is necessary, plain explanation is desired. In Figure 1, my calculation for UC cases is not 19,830 but 19,800.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Please leave your comments for the authors below The paper “Risks of developing ulcerative colitis and Crohn’s disease in relation to silica dust exposure” reports on a case-control study which investigated the association between occupational exposure to silica dust and the development of inflammatory bowel disease. The study included 58.136 patients of inflammatory bowel disease diagnosed in the period between 2007 and 2016 identified using a national register in Sweden. For each case, two controls were matched on age, gender and county. Occupational exposure to silica dust was determined in cases and controls using a job exposure matrix. The study concluded that silica dust exposure significantly increased the risk of Crohn’s disease in women and the risk of ulcerative colitis in men, the risk increases with duration of exposure.
This is a very interesting study. Despite silica exposure being linked to several other inflammatory diseases, the role in IBD remains unknown. However, the study does not account for confounding factors including smoking history, socioeconomic status, family history of IBD which are known to influence the risk of IBD. Although this has been acknowledged by the authors, the lack of control for potential confounding factors weakens the robustness of the study and findings should be interpreted with caution.
• We have now more clearly mentioned that this is a limitation of the study in the discussion on page 13

Specific questions:
- Methods in abstract: please add the confidence intervals to the odds ratio estimates.
• This has now been added in the results part of the abstract

- In the Methods section, please provide a brief description of how exposure to silica dust in relation to occupation is determined. Which occupation categories were linked to silica exposure? Did the categories differ in terms of the average quantity of exposure – e.g. if the effect is dose-dependent.
• Examples of occupations denoted as exposed to silica are now included in the methods on page 7. The JEM also indicates an occupational exposure level to silica, and according to your suggestion we did a calculation on cumulative exposure which gave a dose-dependent response for UC. This is now

included in table 1, and mentioned in the results on page 10 and in the discussion on page

- Cases are identified in the period between 2005 and 2016, however, I failed to find any information on the timing of exposure to silica dust in cases? How does the timing of exposure to silica dust relate to disease onset of CD and UC?
• The cases had to be exposed to silica any time during the last 5 years before diagnosis to be included. This is mentioned I Figure 1, but we have now tried to make this more clear by also mentioning it in the methods on page 7.

- Please consider using a minimum of two with of the same diagnosis code for case ascertainment instead of only a single record to minimize the risk of including misdiagnosed cases
• The diagnostic is usually done by biopsy, so the risk of misdiagnosis is not that great. For approximately 75% of the cases there were more than one entry in the register. We have not done a recalculation, as we do believe that the risk of misclassifications is not so great that it merits a loss of 25% of the data.
- Please add data on causes of mortality (e.g. in table 2) if these are available
• Data on the main cause of mortality (Neoplasms) are now added to text on page 11

Reviewer: 2
Please leave your comments for the authors below It is difficult to understand the content of study population.
You state 58,136 cases in this study. You excluded 17,518 UC case and 10,557 CD cases (total 28,075) (Figure 1). You are handling 19,830 UC cases and 10,261 CD cases for statistical analysis in this study (total 30,091) (Table 1, Figure 1). It is difficult to follow why you include huge number of excluded cases.
• We have now tried to explain the resons for exlusion a bit more in the methods (page7)
What a wash-out period means?
• When the National Non-Primary Outpatient Care Register was established in 2005 there seem to be a higher rate of entries in the first 2 year, probably due to patients who had their diagnosis prior to the registry was established, but was entered into the register at a later date. As we do not know the date of the first diagnosis of these patients, we excluded data from the 2 first years.
• Below are a table showing the cases entered into the register pr year (for UC):

	Total	
	Controls	Cases
2005	21084	10542	31626
2006	9240	4620	13860
2007	5644	2822	8466
2008	5094	2547	7641
2009	4108	2054	6162
2010	3656	1828	5484
2011	3982	1991	5973
2012	3634	1817	5451
2013	3450	1725	5175
2014	3454	1727	5181
2015	3252	1626	4878
2016	3386	1693	5079
Total	69984	34992	104976

If inclusion of excluded cases is necessary, plain explanation is desired.
• All cases in Sweden of UC and CD in the relevant time period were included, however, some had to be excluded due to uncertainties about date of first diagnosis or that they had no silica exposure

within the last 5 years before diagnosis. We believe than in order to give an accurate account of the study design we have to first include all, and then exclude those who cannot be included in the study. In Figure 1, my calculation for UC cases is not 19,830 but 19,800.
• You are correct, there was an error in the flow-chart. This has now been corrected.

VERSION 2 – REVIEW

REVIEWER	Mirabella Zhao Gastro Unit, Hvidovre University Hospital, Denmark
REVIEW RETURNED	16-Dec-2019

GENERAL COMMENTS	Thank you for your responses to comments on the previous draft and for revising the manuscript accordingly. I have only few comment: 1. Based on results on SMR in table 2, the conclusion states that mortality risk is particularly increased among IBD patients exposed to silica dust - but the confidence intervals overlap each other, I would suggest to interpret the results with caution. 2. Page 14, lines 56-60: Maybe you mean to say smoking is a known strong risk factor for developing CD (and not UC)?

VERSION 2 – AUTHOR RESPONSE

Below are our answer to the comments from the reviewers for our manuscript- 2019-034752.R1: "Risks of developing ulcerative colitis and Crohn's disease in relation to silica dust exposure":

1. Based on results on SMR in table 2, the conclusion states that mortality risk is particularly increased among IBD patients exposed to silica dust - but the confidence intervals overlap each other, I would suggest to interpret the results with caution.
- We agree with this. We have now made changes on page 11, 13 and 15 to accommodate for this

2. Page 14, lines 56-60: Maybe you mean to say smoking is a known strong risk factor for developing CD (and not UC)?
- You are correct. We have corrected the manuscript on page 14