PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The relationship between heavy metal exposure and type 2 diabetes: A large-scale retrospective cohort study using occupational health examinations
AUTHORS	Ji, Jun Ho; Jin, Mi Hyeon; Kang, Jung-Hun; Lee, Soon Il; Lee, Suee; Kim, Sung-Hyun; Oh, Sung Yong

VERSION 1 – REVIEW

REVIEWER	Kavita Singh Health Canada, Canada
REVIEW RETURNED	08-Jul-2020

GENERAL COMMENTS	The paper examines exposure to heavy metals from occupational exposures and association with type 2 diabetes and markers of diabetes. Environmental exposures are increasingly being recognized as potential factors in the development of chronic diseases such as diabetes. This is an important topic that is worthy of investigation. The paper, however, is unclear on several points and requires major revision. These are described point-by-point below. Abstract: • The Interventions section is just a repeat of the information provided in the Participant section. This should be replaced with an exposure section to provide more details of the measurement of exposure, and how exposed and unexposed were defined. What is meant by “within one year from exposure” and how was that established from the database. • Results: o The lead estimate is based on a univariate analysis and is not very informative due to small sample size of those diagnosed with diabetes and lead exposure (N=33) and other differences (confounders). Also, no units have been provided with the lead concentrations. o It is not clear what is meant by “Simple exposure to lead and cadmium…” • Conclusion: o Again, it is not clear what is meant by “simple occupational exposure to lead or cadmium…” o The conclusion indicates that lead and cadmium is not associated with prevalence of DM. However, based on the analysis, it appears that subjects with existing DM were excluded and therefore, new cases of DM were examined. Therefore, should this not be incidence of DM rather than prevalence? o It is not clear how the beginning of exposure was established from the database. Introduction:

	• For readability, the introduction needs to be split up into paragraphs. • Statements should be referenced • Line 42 indicates “natural exposures” and then goes on to describe exposures from disposal of toxic materials – this is not a natural exposure. • Of the heavy metals of environmental concern (i.e., mercury, arsenic, lead, cadmium), explain why lead and cadmium were chosen to be analyzed for this study. • Should provide more description of what types of occupations/industries are most concerned with lead and cadmium exposures Study Design (Materials and Methods): • Ferritin was an important factor in selecting which subjects were included in the analysis – it led to many exclusions and exclusion of all female subjects. Why was so much emphasis given to ferritin to select subjects? It is not clear why these subjects were excluded. • The database is described as containing data from the “general population of 403 253”. How does this represent occupational exposures? Were subjects with occupational exposures compared with general population exposures – this could introduce bias? • More details are required about how the diabetes outcomes were measured and by whom. E.g. self-reported vs. lab measured? What were the criteria to diagnose subjects with new diabetes? • How were subjects classified as having lead exposure or as having cadmium exposure, and all others in the control group? Did the control group have 0 lead or cadmium exposure, or below some limit of detection? This should be explained. • What was the limit of detection of the measurement method for lead and cadmium? How were values below the limit of detection handled in analyses? • It is not clear how the timing of exposure was established in the database. • More explanation is needed about how variables were selected into the statistical models • The number of subjects with diabetes and exposure to lead (N=33) or cadmium (N=11) is small – estimates based on these small numbers may be unstable Results: • Average follow-up time, or person-years follow-up, of the cohort should be provided • All concentrations should be provided with a unit of measurement • Table 2 – Sample size used in the Cox regression model should be provided. Variables that were adjusted for should be listed. • Figure 4 – There appears to be an outlier of lead concentration >20 µg/dL. If this point is removed, does that change the r? Other minor revisions • Title: Contains the word “diabetes” twice • Line 9: should be “type 2 diabetes mellitus”

REVIEWER	Shaowei Wu School of Public Health, Peking University, China
REVIEW RETURNED	12-Aug-2020

GENERAL COMMENTS	This paper investigated the association between heavy-metal exposure and serum ferritin, physical measurements, and risk of type 2 diabetes based on a retrospective cohort study with 34,814 subjects, and found that simple occupational exposure to lead or cadmium is not associated with prevalence of DM, but lead concentration at the beginning of exposure may be an indicator of DM and glucose elevation. I have the following comments to improve the present form of the manuscript. Title: it is rare to use the ing form of verb in titles, suggest revise the title as “The relationship between……” The study has some more limitations which have not been stated properly. For example, smoking, alcohol intake and other dietary factors (e.g., sugary beverages) are important risk factors for diabetes but were not included in the analysis. The follow-up time information (as shown in Figure 2/3) is not explained in the study methods. Although the authors stated in the study limitation that female subjects and young subjects with low incidence of DM were excluded from the analyses, there is no statement about this in the abstract, method and result sections. It is important to define the inclusion and exclusion standards clearly in the paper, and appropriate annotation should also be provided for Table 1. In statistical analysis section, the statement “The exposure levels of lead and cadmium in consecutive blood tests were set as dependent variables, and FBS and HbA1c were set as independent variables” was incorrectly specified, actually, lead and cadmium levels should be treated as independent variables whereas FBS and HbA1c should be treated as dependent variables. In addition, the definition of follow-up time calculation is also needed for the Cox regression models. Although the authors excluded female subjects because of the possibility of iron deficiency during menstruation, it would be interesting to investigate the question of interest in females as well, and the authors may discuss the potential reasons (including the iron deficiency during menstruation) for any gender-specific differences in the manuscript. Because the authors did not investigate iron directly, the issue may be less of concern for lead and cadmium in the manuscript. Table 2: need to explain if the RR values correspond to a unit increase in the adjusted variables, and write out the unit for each variable on the left side. Figure 1: the exclusion criteria on the right box do not have the category “young subjects” which was stated in the study limitation. Figure 2/3: need to provide the units for fasting blood glucose and HbA1c in the y-axis and right tables; the format of these figures is unusual, please consider split each original Figure into a separate figure and a separate table; also need to provide sample size for each follow-up visit in right tables; finally, need to specify the covariates adjusted in the mixed-models in the figure legend.

	Figure 4: need to specify the full name and unit for FBS in the figure legend, plus unit for the y-axis. It seems there is no statement about participants' consent to participate in the study. It would better include a separate conclusion paragraph after the paragraph for limitations. Suggest some language editing to improve the formulat

VERSION 1 – AUTHOR RESPONSE

Reviewers: 1

The paper examines exposure to heavy metals from occupational exposures and association with type 2 diabetes and markers of diabetes. Environmental exposures are increasingly being recognized as potential factors in the development of chronic diseases such as diabetes. This is an important topic that is worthy of investigation. The paper, however, is unclear on several points and requires major revision. These are described point-by-point below.

Abstract: • The Interventions section is just a repeat of the information provided in the Participant section. This should be replaced with an exposure section to provide more details of the measurement of exposure, and how exposed and unexposed were defined.

➔ We agreed this comment. Since this manuscript is a cohort study, the authors remove the intervention section in the abstract and the add the primary outcome measure. We added this at abstract. You can see this at the primary outcome measure in the abstract

What is meant by "within one year from exposure" and how was that established from the database.

➔ Thank you for the comment. The subjects of heavy metal exposure were in lead, those in charge of lead welding and mounting in shipyard, and in the case of cadmium, subjects who worked at battery manufacturing factories. The mentioned "within one year from exposure" refers to an occupational health checkup conducted within the first year of working at the above workplace.

• Results: o The lead estimate is based on a univariate analysis and is not very informative due to small sample size of those diagnosed with diabetes and lead exposure (N=33) and other differences (confounders). Also, no units have been provided with the lead concentrations. o It is not clear what is meant by "Simple exposure to lead and cadmium…"

➔ These comments are well taken. “simple exposure” refers to the fact that the subjects have worked on-site at the workplace regardless of the intensity of exposure. In this case, since the incidence of diabetes was low, univariate analysis was not significant. The unit for the heavy metals have been added to the abstract

• Conclusion: o Again, it is not clear what is meant by “simple occupational exposure to lead or cadmium…” o The conclusion indicates that lead and cadmium is not associated with prevalence of DM. However, based on the analysis, it appears that subjects with existing DM were excluded and therefore, new cases of DM were examined. Therefore, should this not be incidence of DM rather than prevalence?

➔ Thank you for the critical comments. The incidence, not the prevalence, is correct. We revised according to the comment.

o It is not clear how the beginning of exposure was established from the database.

➔ “The beginning of exposure” refers to the first health checkup conducted after starting work in the workplace related to heavy metal exposure.

Introduction: • For readability, the introduction needs to be split up into paragraphs. • Statements should be referenced • Line 42 indicates “natural exposures” and then goes on to describe exposures from disposal of toxic materials – this is not a natural exposure.

➔ Thank you for the comments. These comments are gladly taken.
For readability, the introduction has been divided into 4 parts.
1) About DM (P5 2nd – 7th line)
2) Examples of heavy metal exposure (P5 8th -24th line)
3) Few previously reported studies of occupational heavy metal exposure (P5 25th -P6 3rd)
4) About long term and low intensity heavy metal exposure related to the content of this study. (P6 4th – P6 13rd)

The “natural exposure” you commented has been changed to an unintended exposure. (Page 5, 20th line)

• Of the heavy metals of environmental concern (i.e., mercury, arsenic, lead, cadmium), explain why lead and cadmium were chosen to be analyzed for this study. • Should provide more description of what types of occupations/industries are most concerned with lead and cadmium exposures

➔ As mentioned in the text, Changwon, the city where the study was conducted, is the largest industrial city in Korea, with large shipyards, military defense industry companies and battery

manufacturers. DSME [daewoo Shipbuilding & marine Engineering], Samsung Electro-Mechanics, Hyundai wia, STX offshore & shipbuilding. The institution made contracts with the companies and conducted occupational health checkups yearly during the study period. The subjects of heavy metal exposure were in lead, those in charge of lead welding and mounting in shipyard, and in the case of cadmium, subjects who worked at battery manufacturing factories.

Study Design (Materials and Methods): • Ferritin was an important factor in selecting which subjects were included in the analysis – it led to many exclusions and exclusion of all female subjects. Why was so much emphasis given to ferritin to select subjects? It is not clear why these subjects were excluded.

➔ Thank you for the important comment.
This issue is also pointed out by other reviewers. The aurthors hypothesize that occupational heavy metal exposure is a chronic exposure, resulting in a chronic inflammatory reaction in the body, and then this inflammation may be associated with diabetes. And the percentage of female subjects is less than 10% (9.4%, 38,039/403,253), we thought that including female subjects in the analysis could confuse the results.

• The database is described as containing data from the "general population of 403 253". How does this represent occupational exposures? Were subjects with occupational exposures compared with general population exposures – this could introduce bias?

➔ "General population of 403,253 is all the numbers that carried out occupational health checkup at the Samsung Changwon Hospital from 2002 to 2018. This number is for all workers working in the area, and in case of occupational heavy metal exposure, it refers to those who work in direct contact with lead and cadmium such as Ni-Cd battery or welders. We added this at 5) Operational definitions in the Material and Methods

• More details are required about how the diabetes outcomes were measured and by whom. E.g. self-reported vs. lab measured? What were the criteria to diagnose subjects with new diabetes?

➔ The definition for newly diagnosed diabetes was described at 5) Operational definition in the "Material and Methods"
At the first occupational health checkup, the subjects with the following results,
1) No history of diabetes mellitus and

2) HbA1c < 6.5% and fasting plasma glucose < 100mg/dl

At a follow-up occupational health checkup conducted at least 1 year apart, diabetes was

newly diagnosed. (hbA1c ≥ 6.5% or fasting plasma glucose ≥ 126mg/dl)

- How were subjects classified as having lead exposure or as having cadmium exposure, and all others in the control group? Did the control group have 0 lead or cadmium exposure, or below some limit of detection? This should be explained.

➔ Thank you for the comment. In the case of lead exposure, a blood test was conducted by selecting those who worked with lead welding at the shipyard. Cadmium exposure refers to those involved in battery manufacturing. (You can this at 5) Operational definition in the Material and Methods") The control group selected and conducted screening subjects who were not exposed to heavy metals in the workplace. In the subject of the control group, the heavy metal concentration was not tested, so the result of lead/cadmium concentration is unknown. However, this study is not intended to compare heavy metal concentration, but rather to determine the risk of diabetes when heavy metal exposed and to find out the relationship between concentrations at the time of exposure and elevated blood glucose or HbA1c.

- What was the limit of detection of the measurement method for lead and cadmium? How were values below the limit of detection handled in analyses?

➔ Thank you for the critical comment. In this study, the minimum detectable limits of lead and cadmium are measured to the third decimal place. (0.001mg/dl), and below that, they were considered zero.

- It is not clear how the timing of exposure was established in the database.

➔ At Samsung Changwon Hospital, an institution where study is conducted, occupational examinations are continuously conducted every year through long-term contracts with various workplaces. Subjects who had been screened at least 2 times were included in the study. The occupational health checkup consists of questionnaire, blood sampling and imaging tests and the period of work at the workplace is recorded in the questionnaire. The subjects who took the heavy metal concentration measurement included only those who had a working period of heavy metal exposure within one year.

- More explanation is needed about how variables were selected into the statistical models

➔ Variables were determined as risk factors for diabetes based on the results of the questionnaire and laboratory results of occupational health checkup.

• The number of subjects with diabetes and exposure to lead (N=33) or cadmium (N=11) is small – estimates based on these small numbers may be unstable

➔ Thank you for the critical point, and the authors strongly agree.
It is also the biggest drawback of the study. Although it is a large-scale study, due to the characteristics of occupational health checkup, there are many younger populations and incidence rate of the diabetes in the younger population is inevitably low. Therefore, the highlights of this study are the relationship between heavy metal exposure and fasting glucose and HbA1c as shown in the graph, and changes in fasting glucose according to the concentration of lead exposure.

Results: • Average follow-up time, or person-years follow-up, of the cohort should be provided

➔ Thank you for the comment. We added this at Result section. (P10, 13th ~ 16th line)

• All concentrations should be provided with a unit of measurement

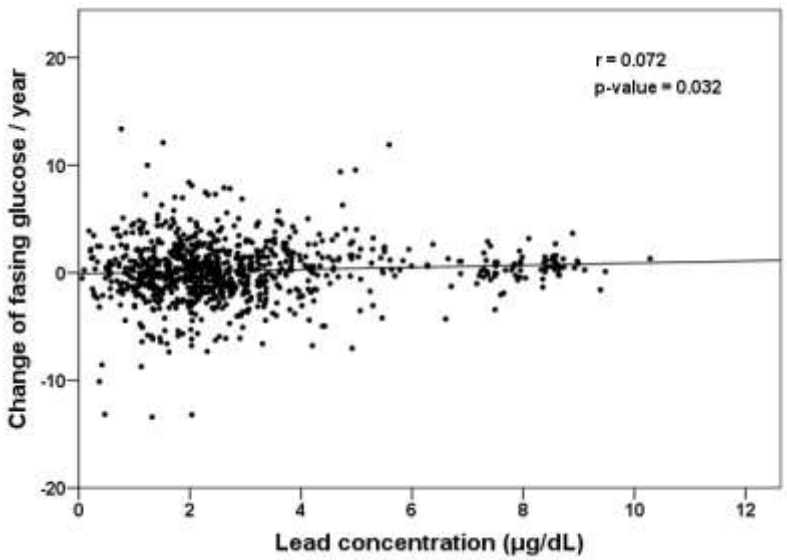
➔ We added the unit to the result of the text.

• Table 2 – Sample size used in the Cox regression model should be provided. Variables that were adjusted for should be listed.

➔ Thank you for the comment. We changed according to the comment. (Table 2)

• Figure 4 – There appears to be an outlier of lead concentration >20 μg/dL. If this point is removed, does that change the r?

➔ Thank you for the interesting comment.
The result was the same, except for subject exceeding 20 ug/dl of lead concentration. We added the figure made by the analysis excluding those subjects below.



Other minor revisions • Title: Contains the word “diabetes” twice • Line 9: should be “type 2 diabetes mellitus”

➔ Thank you for your meticulous comment. We modified it.

Reviewers: 2

This paper investigated the association between heavy-metal exposure and serum ferritin, physical measurements, and risk of type 2 diabetes based on a retrospective cohort study with 34,814 subjects, and found that simple occupational exposure to lead or cadmium is not associated with prevalence of DM, but lead concentration at the beginning of exposure may be an indicator of DM and glucose elevation. I have the following comments to improve the present form of the manuscript.

Title: it is rare to use the ing form of verb in titles, suggest revise the title as “The relationship between……”

➔ Thank you for the comment. The editorial comment also made the same point.
We will modify the title as follows according to the format of the journal.

“The relationship between heavy metal exposure and type 2 diabetes: a large-scale cohort study”

You can see this at page 1, 1~2nd line.

The study has some more limitations which have not been stated properly. For example, smoking, alcohol intake and other dietary factors (e.g., sugary beverages) are important risk factors for diabetes but were not included in the analysis. The follow-up time information (as shown in Figure 2/3) is not explained in the study methods.

➔ Thank you for the critical comment. As you commented, the results of the questionnaire on smoking and drinking were further analyzed and added to the results part and table

Although the authors stated in the study limitation that female subjects and young subjects with low incidence of DM were excluded from the analyses, there is no statement about this in the abstract, method and result sections. It is important to define the inclusion and exclusion standards clearly in the paper, and appropriate annotation should also be provided for Table 1.

➔ Thank you for the important comment.
This issue is also pointed out by other reviewers. The percentage of female subjects is less than 10% (9.4%, 38,039/403,253), we thought that including female subjects in the analysis could confuse the results.
We added this at abstract, method sections.

In statistical analysis section, the statement “The exposure levels of lead and cadmium in consecutive blood tests were set as dependent variables, and FBS and HbA1c were set as independent variables” was incorrectly specified, actually, lead and cadmium levels should be treated as independent variables whereas FBS and HbA1c should be treated as dependent variables.

➔ Thank you for the comment. We are sorry for the mistakes in statistics. We modified.

In addition, the definition of follow-up time calculation is also needed for the Cox regression models

➔ Thank you for the comment.
In the Cox regression model, the definition of follow-up time is the time period from the first examination (health checkup) to the time when diabetes was diagnosed in the subjects diagnosed with new diabetes, and the period form the first examination to the last examination in the subjects without diagnosed DM.

Although the authors excluded female subjects because of the possibility of iron deficiency during menstruation, it would be interesting to investigate the question of interest in females as well, and the authors may discuss the potential reasons (including the iron deficiency during menstruation) for any gender-specific differences in the manuscript. Because the authors did not investigate iron directly, the issue may be less of concern for lead and cadmium in the manuscript.

➔ We strongly agreed with the reviewer`s opinion. In this study, women were excluded because

of their relatively small number (9.4%, 38,039/403,253) and confounding variables due to iron deficiency, but we think the study of women`s occupational heavy metal exposure and diabetes incidence could be an interesting topic in the future. We added this in discussion section.

Table 2: need to explain if the RR values correspond to a unit increase in the adjusted variables, and write out the unit for each variable on the left side.

➔ As commented, we added units to the table 2.

Figure 1: the exclusion criteria on the right box do not have the category “young subjects” which was stated in the study limitation.

➔ We don`t know if we misunderstood the reviewer`s comment.
“Young subjects” stated in limitation is not subject to inclusion or exclusion criteria. The sentence refers to the fact that there were inevitably a large number of young people due to the nature of occupational health checkup.

Figure 2/3: need to provide the units for fasting blood glucose and HbA1c in the y-axis and right tables; the format of these figures is unusual, please consider split each original Figure into a separate figure and a separate table; also need to provide sample size for each follow-up visit in right tables; finally, need to specify the covariates adjusted in the mixed-models in the figure legend

➔ Thank you for the comment. As reviewer commented, we added the units provided in Figure 2/3. And We also divided the figure and table separately.

Figure 4: need to specify the full name and unit for FBS in the figure legend, plus unit for the y-axis.

➔ Thank you for the comment. We changed the figure 4 and figure legends.

It seems there is no statement about participants’ consent to participate in the study.

➔ Thank you for the comment. We added this at Material and Methods (P7 20th line)

It would better include a separate conclusion paragraph after the paragraph for limitations.

➔ Thank you for the comment. We modified the conclusion paragraph into a separate paragraph.

Suggest some language editing to improve the formulas

➔ We completely agreed and applied for the English language editing service.

<Additional request>

Thank you for submitting your manuscript entitled "The relationship between heavy metal exposure and type 2 diabetes: A large-scale cohort study" (manuscript ID bmjopen-2020-039541.R1) to BMJ Open. This has been returned to you to address the following issues before it can be assigned to the Editor.

- Patient and Public Involvement:

Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'.

This should provide a brief response to the following questions:

How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?

How did you involve patients in the design of this study?

Were patients involved in the recruitment to and conduct of the study?

How will the results be disseminated to study participants?

For randomised controlled trials, was the burden of the intervention assessed by patients themselves?

Patient advisers should also be thanked in the contributorship statement/acknowledgements.

If there is no patient involved in the study, please state "No patient involved" under the sub-heading 'Patient and public involvement'.

• Please provide a data availability statement in your main document. Kindly specify what unpublished data are available and where it can be accessed. If there are none then you can simply state "All data relevant to the study are included in the article or uploaded as supplementary information".

➔ Thank you for the comment. We additionally described end of “materials and method” section as below. And Acknowledgement is also added.

1) Patient and Public involvement

Patient and public were not involved in the development of the research question or the design of the study. No patient and public involved in the recruitment to and conduct of the study. As this study used de-identified results, the authors do not plan to disseminate the study results to study participants separately, but we plan to publish the paper with open access.

Acknowledgements: Thanks to all the patients who participated in this study.

Please note that the statement in the ScholarOne system and main document should be the same.

-> Thank you for the comment. We rechecked accordance of the statement in the ScholarOne system and main document.

● Figure citations should be in ascending order

You have cited ‘figure 2B’ right after ‘figure 2D’ and ‘figure 3B’ right after ‘figure 3D’ which makes your citations incorrect. Please review again the main document and ensure that all figures are cited in ascending order.

-> Thank you for the comment. We changed all of figure number as appearances sequence. Therefore, figure also changed sequence.

(Fig 2D->2B, 2B->2C, 2E->2D, 2C->2E and Fig 3D->3B, 3B->3C, 3E->3D, 3C->3E)

- I have checked that your Main document file is still with highlighted text or tracked changes. With this, please can you ensure to provide a clean copy of the main document file without highlighted text or tracked changes?

- Aside from the clean copy, please also provide a please also provide a marked copy of your manuscript with 'tracked changes' and upload it under the file designation ‘Main Document - marked copy’. This is to show all the changes you have made for your paper.

-> Thank you for the comment. We upload clean manuscript and blue marked copy.

VERSION 2 – REVIEW

REVIEWER	Kavita Singh Health Canada, Canada
REVIEW RETURNED	02-Oct-2020

GENERAL COMMENTS	Strengths and Limitations (p.3, Lines 6-9): Requires rewording to better place this point in context (e.g. explain that one of the main limitations of the study was that females were not included, why were they not included, and that further study in this population is needed) Material and Methods (p.6, Line 5): The use of term "general population" - The data was based on an occupational health checkup, and therefore excludes people not in occupations. So would be more accurate to describe it as the general workforce population or occupational population Material and Methods (p.7, Line 3). The limit of detection (LOD) for lead and cadmium should be specified here, along with statement that values below the LOD were considered to be zero. Materials and Methods (p.7, Line 11): The covariates that were inputted into the adjusted Cox proportional hazards model should be clearly listed in this section, and how these covariates were selected from the questionnaire (e.g. based on a priori theoretical knowledge, statistical thresholds?). Materials and Methods (p.8, Line 8): Were patients with lead and cadmium measurements provided their results? How were high lead and cadmium measurements communicated? Results (p.9, Lines 5-6): Currently confusing in the way that it is worded (i.e. states 1035 lead-exposed followed by 33 exposed to lead). Please reword to provided total number of participants in cohort A (i.e. 33 779 with no lead exposure + 1035 with lead

	exposure, of which a total of 1034 developed DM. Of the 1034 who developed DM, 33 were exposed to lead). Discussion (p.12, Line 18): Please revise use of term "normal Korean adults" - unclear what is meant by "normal" Other: Thank you for explaining what is meant by "simple" cadmium and lead exposures in your response. This explanation should also be included somewhere in the manuscript. Other: Thank you for explaining what is meant by "beginning of exposure" in your response. This should also be explained at the outset in the manuscript in the abstract.

REVIEWER	Shaowei Wu School of Public Health, Peking University, China
REVIEW RETURNED	05-Oct-2020

GENERAL COMMENTS	The reviewers have addressed the comments appropriately, and I have no more comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Kavita Singh
Institution and Country: Health Canada, Canada
Please state any competing interests or state 'None declared': None declared

➔ Thank you for providing this, we modified this p14, 1st line

Strengths and Limitations (p.3, Lines 6-9): Requires rewording to better place this point in context (e.g. explain that one of the main limitations of the study was that females were not included, why were they not included, and that further study in this population is needed)

➔ Thank you for your suggestion. We have reflected this comment by p3, 3-4th line

Material and Methods (p.6, Line 5): The use of term "general population" - The data was based on an occupational health checkup, and therefore excludes people not in occupations. So would be more accurate to describe it as the general workforce population or occupational population

➔ We agree with you. We have revised the text p6, 4-6th line.

Material and Methods (p.7, Line 3). The limit of detection (LOD) for lead and cadmium should be specified here, along with statement that values below the LOD were considered to be zero.

➔ Thank you for the suggestion. We added this at p7, 13-14th line.

Materials and Methods (p.7, Line 11): The covariates that were inputted into the adjusted Cox proportional hazards model should be clearly listed in this section, and how these covariates were selected from the questionnaire (e.g. based on a priori theoretical knowledge, statistical thresholds?).

➔ We agree with you. We have added this at p7, 20-23rd line.

Materials and Methods (p.8, Line 8): Were patients with lead and cadmium measurements provided their results? How were high lead and cadmium measurements communicated?

➔ Thank you for the comment. That is an interesting query.

Within a few weeks after the occupational health checkup, the results of all exam conducted, as well as the concentration of heavy metals are communicated to the subject through interviews and notified to the person and to the workplace by mail or e-mail.

Results (p.9, Lines 5-6): Currently confusing in the way that it is worded (i.e. states 1035 lead-exposed followed by 33 exposed to lead). Please reword to provided total number of participants in cohort A (i.e. 33 779 with no lead exposure + 1035 with lead exposure, of which a total of 1034 developed DM. Of the 1034 who developed DM, 33 were exposed to lead).

➔ Thank you for the comment. We agreed with you and we have reflected this comment by p9, 5th line.

Discussion (p.12, Line 18): Please revise use of term "normal Korean adults" - unclear what is meant by "normal"

➔ We totally agreed with you. We have modified this. Please see at p12, 17-19th line

Other: Thank you for explaining what is meant by "simple" cadmium and lead exposures in your response. This explanation should also be included somewhere in the manuscript.

➔ We have included this at “Material and Methods”. Please see at p8, 12-13th line

Other: Thank you for explaining what is meant by "beginning of exposure" in your response. This should also be explained at the outset in the manuscript in the abstract.

We agreed with you. This explaining could not be added to abstract because of the character limit. Instead, we added this in the Material and Methods section. Please see at p8, 14-15th line.

Reviewer: 2
Reviewer Name: Shaowei Wu
Institution and Country: School of Public Health, Peking University, China
Please state any competing interests or state ‘None declared’: None declared

➔ Thank you for providing this, we modified this p14, 1st line

The reviewers have addressed the comments appropriately, and I have no more comments.

VERSION 3 – REVIEW

REVIEWER	Kavita Singh Health Canada, Canada

REVIEW RETURNED	10-Dec-2020

GENERAL COMMENTS	Minor comments: - Materials and Methods p.6 Line 14: "only" word is repeated, please remove one - Materials and Methods p.7 Line 19-23: States that risk factors for DM (age, BMI, smoking, drinking, HbA1c, FBS, and ferritin) were entered into Cox models as dependent variables. In the Cox model, would these factors not have been entered as covariates along with the main independent variable of lead/cadmium exposure, with the dependent variable being type 2 DM? - Discussion, p.13, Line 16-17: Reference(s) should be provided for this statement "Although menstruation can cause iron deficiency, serum ferritin is associated with the risk of developing diabetes in fertile women."