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

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Association between Osteoarthritis and Cardiovascular Disease in Elderly in Japan: An Administrative Claims Database Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Uematsu, Takuya; Nojiri, Shuko; Ishijima, Muneaki; Nishizaki, Yuji</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Tsukada, Sachiyuki Iryo Hojin Shadan Hokusui Kinen Byoin, Orthopaedic Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>21-Nov-2023</td>
</tr>
</tbody>
</table>

| GENERAL COMMENTS | This study explored the potential link between osteoarthritis (OA) and cardiovascular disease (CVD) using data from Japanese health insurance claims. The findings revealed that, after adjusting for covariates, the odds of developing CVD with knee OA exposure were 1.184 (95% CI, 1.108–1.265). The authors concluded that there would be an association between knee OA and CVD. The study delves into a compelling topic, and the methodology used to arrive at the results is sound. The reviewer finds the manuscript, as it stands, deserving of acceptance. |

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Wen, Chunyi The Hong Kong Polytechnic University</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>22-Dec-2023</td>
</tr>
</tbody>
</table>

| GENERAL COMMENTS | This is a well conducted study to analyse the association between load-bearing joint osteoarthritis and cardiovascular diseases in Japanese database. The findings further strengthen the idea about an intimate relationship between these two major categories of age-related diseases. Even though hand osteoarthritis shows no statistical significance, better list the data in the table for comparison with knee and hip osteoarthritis. |

VERSION 1 – AUTHOR RESPONSE

Response to the reviewer #1:

Dear Dr. Tsukada M.D.,

【REVIEWER’S SPECIFIC COMMENTS】

This study explored the potential link between osteoarthritis (OA) and cardiovascular disease (CVD) using data from Japanese health insurance claims. The findings revealed that, after adjusting for
covariates, the odds of developing CVD with knee OA exposure were 1.184 (95% CI, 1.108–1.265). The authors concluded that there would be an association between knee OA and CVD. The study delves into a compelling topic, and the methodology used to arrive at the results is sound. The reviewer finds the manuscript, as it stands, deserving of acceptance.

【RESPONSE】
I am very pleased to hear that there is no issues in our manuscript. We were encouraged by your kind comment. It stimulates us to work hard. I look forward to working with you again in the future. Thank you.

Response to the reviewer #2:
Dear Dr. Wen M.D.,

【REVIEWER’S SPECIFIC COMMENTS】
This is a well conducted study to analyse the association between load-bearing joint osteoarthritis and cardiovascular diseases in Japanese database. The findings further strengthen the idea about an intimate relationship between these two major categories of age-related diseases.

Even though hand osteoarthritis shows no statistical significance, better list the data in the table for comparison with knee and hip osteoarthritis.

【RESPONSE】
I sincerely appreciate the valuable feedback provided by the reviewers. As accurately pointed out by the reviewers, we have conducted a reanalysis by incorporating the variable “hand osteoarthritis” into our study. The results of this analysis have been integrated into the table and appropriately added to the main text.

Furthermore, due to the reanalysis, we have reprocessed the matching, resulting in revised values for the Control group. We showed that there are no changes in the analysis results for KOA and HipOA concerning CVD (IHD, CHF, stroke). Also, we made a minor modification to the abstract to stay within word limit of 300. Therefore, there are no alterations to the main conclusions or findings.

【Change】
1. (P2 L39 Abstract)
Objective: To investigate whether osteoarthritis (OA) is a risk factor for cardiovascular disease (CVD); whether there are differences concerning ischemic heart disease (IHD), congestive heart failure (CHF), and stroke; and whether there are differences between OA sites (hips, knees, and hand) in predicting CVD onset
Design: Population-based matched case–control study
Setting: Health insurance claims data among Japanese patients
Participants: Japanese patients aged ≥65 years with newly diagnosed CVD and hospitalized between January 2015 and December 2020 (cases) and age- and sex-matched 1:1 individuals (controls)
Main outcome measures: A conditional logistic regression model was used to estimate the adjusted odds ratios (OR) and their 95% confidence intervals (CI) for CVD, IHD, CHF, and stroke risk, adjusting for covariates.
Results: A total of 79,296 patients were included, with respect to CVD (39648 patients with newly diagnosed CVD and 39648 controls). After adjustment for covariates, the exposure odds of knee OA (KOA), hip OA (HipOA), and hand OA (HandOA) for CVD were 1.192 (95% CI, 1.115–1.274), 1.057 (95% CI, 0.919–1.215), and 1.035 (95% CI, 0.684–1.568), respectively, showing an association only for KOA. The exposure odds of KOA, HipOA, and HandOA for IHD were 1.187 (95% CI, 1.086–1.297), 1.078 (95% CI, 0.891–1.306), and 1.099 (95% CI, 0.677–1.784), respectively. The exposure odds of KOA, HipOA, and HandOA for stroke were 1.221 (95% CI, 1.099–1.356), 0.918 (95% CI, 0.723–1.165), and 1.169 (95% CI, 0.635–2.151), respectively. Similar to CVD, only KOA was
associated with both. For CHF, neither KOA nor HipOA and HandOA were associated with CHF development.

Conclusion: This study confirms the association of KOA with CVD, particularly IHD and stroke, in the Japanese population. The finding that patients with KOA have a higher CVD risk can potentially assist in guiding future treatment strategies.

2. (P3 L110 INTRODUCTION)

Therefore, this study, using data with a high number of variables, such as Medical Data Vision (MDV) data, in Japan, which is experiencing super-aging, aimed to determine whether the presence of OA is a risk factor for CVD development, whether there are differences among IHD, CHF, and stroke, and whether there is any difference between CVD risk and OA sites (hips, knees, and hand).

3. (P4 L142 Definition of OA and covariates)

HipOA (M160–M169) and KOA (M170–M179) and hand OA (HandOA) (M180–M189) were defined as exposure factors.

4. (P8 L188 RESULTS CVD and osteoarthritis)

In the unadjusted analysis for CVD, the OR for KOA exposure in the case group compared with the control group was 1.204 (95% CI, 1.133–1.28). The ORs for HipOA and HandOA exposures were 1.14 (95% CI, 1.001–1.298) and 1.06 (95% CI, 0.72–1.56), respectively, indicating no significant association. After adjusting for covariates, the OR for KOA exposure was 1.192 (95% CI, 1.115–1.274), indicating a significant association with CVD occurrence. The ORs for HipOA and HandOA exposures were 1.057 (95% CI, 0.919–1.215) and 1.035 (95% CI, 0.684–1.566), respectively, indicating no significant association (Table 2). Similarly, in the unadjusted analysis for IHD, the OR for KOA exposure was 1.156 (95% CI, 1.067–1.253), while the ORs for HipOA and HandOA exposures were 1.016 (95% CI, 0.854–1.209) and 0.974 (95% CI, 0.623–1.523), respectively, with no significant association. After adjusting for covariates, the OR for KOA exposure was 1.187 (95% CI, 1.086–1.297), showing a significant association with IHD occurrence; however, the ORs for HipOA and HandOA exposures were 1.078 (95% CI, 0.891–1.306) and 1.099 (95% CI, 0.677–1.784), respectively, indicating no significant association (Appendix 3). For CHF, the unadjusted analysis showed ORs of 1.031 (95% CI, 0.962–1.104), 0.966 (95% CI, 0.834–1.12), and 0.911 (95% CI, 0.597–1.391) for KOA, HipOA, and HandOA exposures, respectively. After adjusting for covariates, the ORs for KOA, HipOA, and HandOA exposures were 1.027 (95% CI, 0.948–1.112), 0.968 (95% CI, 0.816–1.149), and 1.139 (95% CI, 0.705–1.841), respectively, indicating no significant association with CHF occurrence (Appendix 5). Finally, for stroke, the unadjusted analysis showed ORs of 1.26 (95% CI, 1.142–1.39), 1.013 (95% CI, 0.809–1.27), and 1.095 (95% CI, 0.606–1.979) for KOA, HipOA, and HandOA exposures, respectively. After adjusting for covariates, the OR for KOA exposure was 1.221 (95% CI, 1.099–1.356), indicating a significant association with stroke occurrence, while the ORs for HipOA and HandOA exposures were 0.918 (95% CI, 0.723–1.165) and 1.169 (95% CI, 0.635–2.151), respectively, showing no significant association (Appendix 7).

5. (P10 L257 Discussion)

In this study, no associations were observed in HipOA and HandOA. Macêdo et al. found that both HipOA and KOA increase the risk of subclinical atherosclerosis and CVD, whereas hand OA showed no association with CVD [30].

6. (P10 L262 Discussion)

In the present study, KOA showed a significant association; however, HipOA and HandOA did not. One possible reason is that the knee and hand are weight-bearing joints more than the hip, which may lead to excessive stress on the bones and cartilage because of biomechanical load caused by the body weight, increasing the risk for KOA development and leading to more significant inflammatory reactions and a more pronounced association with CVD.
7. (Table1, Table2, Appendix2~Appendix7)
Added variables to HandOA and revised values in the Control group through rematching. The modified sections are highlighted in red.

After reviewing it again, I have corrected the grammatical errors.

8. (P4 L130 Selection of cases and controls)
Each master code was defined based on the following ICD-10 diagnosis codes: IHD (I20–I25), CHF (I50), stroke (I60–I64), and CVD (I20–I25, I50, I60–I64) [10]. Cases were defined as patients aged ≥65 years that were first diagnosed with the target disease between January 2015 and December 2020, with the diagnosis date serving as the index date.

9. (P5 L158 Definition of OA and covariates)
Comorbidities with diagnosis dates before the index date and no end dates were registered until the index date was extracted.

I defined the abbreviation “ATC”.

10. (P5 L160 Definition of OA and covariates)
The explanatory variables included sex, age, comorbidities based on ICD-10 codes, and concomitant medications based on the Anatomical Classification of Pharmaceutical Products (ATC) codes.