

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Differential Associations of Physical Job Demands with Cognitive Impairment in Korean Workers Aged 45 and Older: A 14-Year Longitudinal Study Using the Korean Longitudinal Study of Aging (KLoSA)
<b>AUTHORS</b>	Ha, Jea Chul; Yoon, Jin-Ha

### VERSION 1 - REVIEW

<b>REVIEWER NAME</b>	<i>Wendsche, Johannes</i>
<b>REVIEWER AFFILIATION</b>	Federal Institute for Occupational Safety and Health
<b>REVIEWER CONFLICT OF INTEREST</b>	Na
<b>DATE REVIEW RETURNED</b>	02-May-2024

<b>GENERAL COMMENTS</b>	<p>Thank you so much for inviting me to review this well-prepared manuscript about physical activity and cognitive functioning using an impressive longitudinal data set.</p> <p>I think the paper needs no comprehensive revision because of its high quality preparation.</p> <p>However, I have one question. It seems that you have repeated measures of individuals over the waves but the data was analyzed focusing on cross-sectional relationships.</p> <p>From a methodological perspective a focus on variables changes would be more convincing. Thus, is a change in physical activity/demands related to changes in cognitive impairment.</p> <p>From my experience, there are models such as latent growth modeling or latent change score modeling that would allow to estimate lagged relationships, thus answering the question if an increase of physical demands between (two) waves (e.g. <math>w(t)-w(t+1)</math>) related to changes in cognitive impairment between the waves (parallel changes, <math>w(t)-w(t+1)</math>) or, which would be even better, following waves (e.g. <math>w(t+2)-w(t+3)</math>); thus, the change in working conditions related to time-lagged changes).</p> <p>What do you think about such an approach that would give credit to more causal relationships between variables?</p>
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<b>REVIEWER NAME</b>	<i>Zotcheva, Ekaterina</i>
<b>REVIEWER AFFILIATION</b>	Vestfold Hospital Trust, Norwegian National Centre for Ageing and Health

<b>REVIEWER CONFLICT OF INTEREST</b>	na
<b>DATE REVIEW RETURNED</b>	18-Jun-2024

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review this interesting, novel, and potentially important study. Identifying individuals and groups at increased risk of cognitive impairment later in life is crucial, given the shifting demographic distributions worldwide, with rapidly growing populations of older adults. This manuscript investigates the physical activity paradox by examining specific elements of occupational physical activity and their individual associations with cognitive impairment. This novel study contributes to a deeper understanding of the physical activity paradox using rich data from a large Korean population and enhances our comprehension of middle- and late-life risk factors for cognitive impairment. The manuscript is well-written and generally easy to follow. However, I have some comments that I hope the authors can address in a revised version of the manuscript:</p> <p>Overall comments</p> <ul style="list-style-type: none"> <li>• In my opinion, the risk of reverse causality and bias due to loss-to-follow-up needs further attention. It is likely that individuals who gained cognitive impairment were more likely to change job or stop working altogether, and to drop out of the study. Although the authors have used GLMM which is appropriate when data are missing at random, it is my opinion that these limitations mean that the authors need to be more cautious about the interpretation of the causal direction of the associations observed in this study.</li> </ul> <p>Other comments:</p> <ul style="list-style-type: none"> <li>• The first part of the introduction appears to be missing some references. For instance, this sentence on lines 57-58: "These abilities are not fixed but can change due to various factors such as physical health, mental stimulation, and social engagement, including work» needs references.</li> <li>• Lines 67-70: "In particular, recent population-based studies reported that orthostatic hypotension is associated with an increased risk of cognitive impairment, suggesting cerebral hypoperfusion might play a role in pathogenesis.<sup>4 5</sup> This suggests that physical job demands inducing cerebral hypoperfusion, such as lifting heavy objects, may contribute to cognitive impairment". It is not clear why the authors have chosen to include this in the introduction, as they are not looking at cerebral hypoperfusion, and cerebral hypoperfusion is merely a hypothesized (not an established) link between physical job demands and cognitive impairment. I suggest removing this from the introduction, or moving it to the discussion of potential mechanisms in the discussion section.</li> <li>• Have the authors read the following article in the Lancet Regional Health – Europe: doi: <a href="https://doi.org/10.1016/j.lanep.2023.100721">https://doi.org/10.1016/j.lanep.2023.100721</a>? It addresses a number of limitations of previous papers mentioned in the introduction, although not the limitation relating to various sub-elements of physical job demands.</li> <li>• Lines 82-86: In the following sentence, it is not clear what is meant by "the socioeconomic burden". What is the burden of? Cognitive impairment? "Exploring the risk of cognitive impairment by sub-elements of physical job demands and evaluating the presence of effect modification may help generate hypotheses about potential risk factors and mechanisms while contributing to policymaking and</li> </ul>
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	<p>implementing tailored interventions to reduce the socioeconomic burden”.</p> <ul style="list-style-type: none"> <li>• Lines 125-128 appear to be a repetition of the ethics statement provided on lines 108-112.</li> <li>• Could the authors provide an age range for the participants? How old was the oldest participant?</li> <li>• It would be useful to the reader if the authors could provide a rationale for using age 45 and above as cut-off (I suppose this was done to avoid including participants who were very unlikely to develop cognitive impairment during the follow-up due to young age?)</li> <li>• Choice of confounders: is it possible that physical job demands also could influence risk of diabetes and hypertension? I would think that there is a high possibility that these two variables also could serve as mediators in the physical job demands – cognitive impairment association. Perhaps the authors could elaborate on why they chose to treat these variables as potential confounders?</li> <li>• Lines 180-185 appear to be a rephrased repetition of lines 176-180 (parts of this information is also mentioned in lines 119-121).</li> <li>• Recent research suggests that cognitive ability early in life may be a much stronger predictor of cognitive abilities later in life than education or occupational characteristics (see, for instance Kremen et al., 2019 doi: 10.1073/pnas.1811537116; Huh et al., 2024 doi: 10.1002/alz.13739). Although multiple studies support findings regarding occupational physical activity and cognitive function later in life, I am missing a discussion on how early life cognitive ability may, at least in part, explain the associations observed here. Namely, that individuals with higher early life cognitive abilities are more prone to both choosing a more cognitively challenging occupation and that they are less likely to experience cognitive decline later in life.</li> </ul>
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### VERSION 1 – AUTHOR RESPONSE

Dear Dr. Johannes Wendsche,

Thank you very much for your insightful feedback and for recognizing the quality of our manuscript. We appreciate your suggestion to focus on changes in variables over time to better capture the relationships between physical job demands and cognitive impairment.

Initially, we analyzed the data with the dependent variable being the cognitive impairment status at the survey time point. For the independent variable, although the physical job demand assessment was conducted at each survey time point, it aimed to capture the overall physical job demand level of the participants' current job, not just at the specific survey moment. This approach aligns with our inclusion criterion of considering only those who had been in their jobs for at least three months at each survey wave, ensuring temporal precedence.

To address your suggestion of incorporating changes over time, we conducted a sensitivity analysis using a generalized linear mixed-effects model (GLMM) that incorporates time-lagged variables and changes. Specifically, we fitted a model with the following regression equation:

For the physical job demand change, we treated it as a continuous variable. We assumed equal intervals between the categories (never, sometimes, often, always) and calculated the change as the number of units increased or decreased from the previous wave.

We carefully considered your suggestion to use change scores for the dependent variable. However, we chose a different approach due to potential methodological issues. Recent literature, such as the work by Tennant PWG et al.,<sup>1</sup> suggests that analyses of 'change scores' may not accurately estimate causal effects in observational data. Additionally, including lagged dependent variables in GLMM can lead to severe bias, as noted in the literature.<sup>2</sup> To address these concerns while still capturing changes over time, we used the cognitive impairment status at time t+1 as the dependent variable, with physical job demands at time t and the change in physical job demands from t to t+1 as independent variables.

We have included the results of this sensitivity analysis in the manuscript's Sensitivity analysis section and presented them in Supplementary table 7. The findings were consistent with our original results, showing opposite directions of associations for physical strength (PS) and lifting heavy objects (LH) with cognitive impairment. Notably, when stratified by educational attainment, the dose-response relationship was maintained among low-educated people, while it disappeared among high-educated people. Furthermore, the associations of changes in PS and LH from t to t+1 with cognitive impairment were in the same direction as their respective physical job demands at time t.

We hope these revisions and additional analyses address your concerns and enhance the robustness of our findings. Thank you again for your valuable feedback.

Sincerely,

Authors

1 Tennant PWG, Arnold KF, Ellison GTH, Gilthorpe MS. Analyses of 'change scores' do not estimate causal effects in observational data. *Int J Epidemiol* 2022;51:1604-15. doi: 10.1093/ije/dyab050

2 Leszczensky L, Wolbring T. How to deal with reverse causality using panel data? Recommendations for researchers based on a simulation study. *Sociological Methods & Research* 2022;51:837-65. doi: 10.1177/0049124119882473

**Response to Reviewer 2 Comments:**

Reviewer:

2

Dr. Ekaterina Zotcheva, Vestfold Hospital Trust

Comments to the Author:

Thank you for the opportunity to review this interesting, novel, and potentially important study. Identifying individuals and groups at increased risk of cognitive impairment later in life is crucial, given the shifting demographic distributions worldwide, with rapidly growing populations of older adults. This manuscript investigates the physical activity paradox by examining specific elements of occupational physical activity and their individual associations with cognitive impairment. This novel study contributes to a deeper understanding of the physical activity paradox using rich data from a large Korean population and enhances our comprehension of middle- and late-life risk factors for cognitive impairment. The manuscript is well-written and generally easy to follow. However, I have some comments that I hope the authors can address in a revised version of the manuscript:

Dear Dr. Ekaterina Zotcheva,

Thank you for your thorough and thoughtful review of our manuscript. We greatly appreciate your recognition of the significance of our study in understanding the physical activity paradox and its implications for cognitive impairment in aging populations. Your comments are invaluable in enhancing the quality and clarity of our work.

Overall comments

- In my opinion, the risk of reverse causality and bias due to loss-to-follow-up needs further attention. It is likely that individuals who gained cognitive impairment were more likely to change job or stop working altogether, and to drop out of the study. Although the authors have used GLMM which is appropriate when data are missing at random, it is my opinion that these limitations mean that the authors need to be more cautious about the interpretation of the causal direction of the associations observed in this study.

We sincerely appreciate your insightful comments regarding the risk of reverse causality and bias due to loss-to-follow-up in our study. Your expertise has highlighted crucial aspects that warrant further attention, and we wholeheartedly agree with your assessment.

In response to your valuable feedback, we have thoroughly reviewed our entire manuscript to ensure a more cautious interpretation of the causal direction of the observed associations. We have made careful revisions throughout the text to reflect this more nuanced perspective, acknowledging the limitations inherent in inferring causality from our observational data.

Furthermore, we have incorporated your specific concerns about reverse causality and loss-to-follow-up bias into our limitations section. This addition provides a more comprehensive and detailed discussion of these potential issues, offering readers a clearer understanding of the constraints of our study design and findings.

We believe these revisions significantly enhance the clarity and scientific rigor of our manuscript. Your thoughtful comments have undoubtedly improved the quality of our work, and we are grateful for your contribution to strengthening our study.

Other comments:

- The first part of the introduction appears to be missing some references. For instance, this sentence on lines 57-58: "These abilities are not fixed but can change due to various factors such as physical health, mental stimulation, and social engagement, including work» needs references.

Thank you for your careful review and for pointing out the need for additional references in the introduction. We appreciate your attention to detail, as it helps strengthen the scientific foundation of our manuscript.

We have addressed your comment by adding citations for the relationships between cognitive ability and physical health, mental stimulation, and social engagement, including work.

- Lines 67-70: "In particular, recent population-based studies reported that orthostatic hypotension is associated with an increased risk of cognitive impairment, suggesting cerebral hypoperfusion might play a role in pathogenesis.<sup>4 5</sup> This suggests that physical job demands inducing cerebral hypoperfusion, such as lifting heavy objects, may contribute to cognitive impairment". It is not clear why the authors have chosen to include this in the introduction, as they are not looking at cerebral hypoperfusion, and cerebral hypoperfusion is merely a hypothesized (not an established) link between physical job demands and cognitive impairment. I suggest removing this from the introduction, or moving it to the discussion of potential mechanisms in the discussion section.

Thank you for your insightful comment regarding the content on cerebral hypoperfusion in our introduction. We appreciate your careful review and agree that this information was not directly relevant to our study's focus.

As per your suggestion, we have removed the following sentences from the introduction: "In particular, recent population-based studies reported that orthostatic hypotension is associated with an increased risk of cognitive impairment, suggesting cerebral hypoperfusion might play a role in pathogenesis.<sup>4 5</sup> This suggests that physical job demands inducing cerebral hypoperfusion, such as lifting heavy objects, may contribute to cognitive impairment."

Thank you again for bringing this to our attention. We believe this change improves the clarity and relevance of our introduction.

- Have the authors read the following article in the Lancet Regional Health – Europe: doi: <https://doi.org/10.1016/j.lanepe.2023.100721>? It addresses a number of limitations of previous papers mentioned in the introduction, although not the limitation relating to various sub-elements of physical job demands.

Thank you for bringing our attention to the article in the Lancet Regional Health – Europe. We appreciate your suggestion and have carefully reviewed the paper.

We agree that this article addresses several important limitations of previous studies in this field. In light of your recommendation, we have revised our introduction to incorporate these points. Specifically, we have added the following sentence to our discussion of previous studies' limitations:

"Many of these studies have relied on self-reported data and single-time point assessments, which can introduce recall bias and limit the ability to capture the dynamic nature of physical job demands over time"

We believe this addition strengthens our introduction by acknowledging these methodological challenges in the existing literature. While our study also uses self-reported measures, we feel it's important to recognize this limitation in the broader context of research in this area.

Thank you again for bringing this valuable resource to our attention. Your input has helped to enhance the comprehensiveness of our literature review and the overall quality of our manuscript.

- Lines 82-86: In the following sentence, it is not clear what is meant by "the socioeconomic burden". What is the burden of? Cognitive impairment? "Exploring the risk of cognitive impairment by sub-elements of physical job demands and evaluating the presence of effect modification may help generate hypotheses about potential risk factors and mechanisms while contributing to policymaking and implementing tailored interventions to reduce the socioeconomic burden".

Thank you for your valuable feedback regarding the clarity of the phrase "socioeconomic burden" in our introduction. We appreciate your attention to detail and have made the necessary revision to clarify this point.

We have revised the sentence to read:

"Exploring the risk of cognitive impairment by sub-elements of physical job demands and evaluating the presence of effect modification may help generate hypotheses about potential risk factors and mechanisms while contributing to policymaking and implementing tailored interventions to reduce the socioeconomic burden of cognitive impairment."

This revision ensures that it is clear the socioeconomic burden pertains specifically to cognitive impairment. Thank you for helping us improve the clarity and precision of our manuscript.

- Lines 125-128 appear to be a repetition of the ethics statement provided on lines 108-112.

Thank you for your careful review of our manuscript. Regarding your comment about the repetition of the ethics statement, we have carefully re-examined our manuscript and found that the ethics statement appears only once, between lines 119-121. It reads:

"This study was approved by the [blinded for peer review], and the need to obtain informed participant consent was waived due to the observational nature of the study."

We did not find any repetition of this statement elsewhere in the manuscript, including the lines 125-128 that you mentioned. We appreciate your attention to detail, and if you noticed something we might have overlooked, please let us know the specific content you found repetitive so we can address it appropriately.

- Could the authors provide an age range for the participants? How old was the oldest participant?

Thank you for your valuable feedback regarding the age range of the participants. We appreciate your suggestion and have incorporated this information into the "General characteristics of study participants" section of the Results.

We have revised the text to include the age range of the participants, which is from 45 to 83 years. The revised sentence now reads:

"Table 1 (see the detailed version in online supplementary table 1), presents the descriptive characteristics of study participants at baseline in 2006. The participants' age ranged from 45 to 83 years."

We believe this addition provides clarity on the age demographics of our study participants and enhances the comprehensiveness of our manuscript. Thank you for helping us improve the quality of our work.

- It would be useful to the reader if the authors could provide a rationale for using age 45 and above as cut-off (I suppose this was done to avoid including participants who were very unlikely to develop cognitive impairment during the follow-up due to young age?)

Thank you for your insightful comment regarding the age cutoff of 45 years and above used in our study. We appreciate your attention to this detail.



The age cutoff of 45 years and above was not arbitrarily chosen by us; rather, it is defined by the design of the Korean Longitudinal Study of Aging (KLoSA) survey. The KLoSA survey specifically targets individuals aged 45 and older, as mentioned in the Methods section of our manuscript:

"The KLoSA survey used a stratified two-stage cluster sampling technique to obtain a representative sample of the Korean population aged 45 years and older."

Therefore, the age range of our study participants is determined by the criteria established by the KLoSA survey, which aims to study the aging population in Korea. This design choice helps ensure that the survey captures relevant data on middle-aged and older individuals who are at a higher risk of developing cognitive impairment.

Thank you for allowing us to clarify this point. We hope this explanation addresses your concern.

• Choice of confounders: is it possible that physical job demands also could influence risk of diabetes and hypertension? I would think that there is a high possibility that these two variables also could serve as mediators in the physical job demands – cognitive impairment association. Perhaps the authors could elaborate on why they chose to treat these variables as potential confounders?

Thank you for your insightful comment regarding the choice of confounders, particularly concerning hypertension and diabetes. We appreciate your attention to this important methodological consideration.

We agree that physical job demands could potentially influence the risk of diabetes and hypertension, and that these variables could serve as mediators in the physical job demands-cognitive impairment association. Our approach to confounder selection was based on the modified disjunctive cause criterion proposed by VanderWeele (2019). This criterion suggests including variables that are causes of the exposure, the outcome, or both, especially useful when the causal relationship is uncertain.

In our study, the simultaneous measurement of potential confounders and physical job demands presented a challenge in definitively categorizing variables as confounders or mediators. Given this uncertainty, we opted for a more conservative approach by treating hypertension and diabetes as potential confounders. This decision was made to minimize the risk of biased estimates, as adjusting for a true confounder that has been incorrectly identified as a mediator could lead to more substantial bias than adjusting for a true mediator misidentified as a confounder.

To address your concern, we conducted an additional analysis without adjusting for hypertension and diabetes, treating them as potential mediators. The results of this analysis were largely consistent with our original findings, suggesting that the treatment of these variables did not substantially alter our main conclusions.

We appreciate your question as it has prompted us to further examine and validate our methodological choices. Thank you for contributing to the rigor of our study.

- Lines 180-185 appear to be a rephrased repetition of lines 176-180 (parts of this information is also mentioned in lines 119-121).

Thank you for your careful review and for pointing out the potential redundancy in our manuscript. We have reviewed the sections you mentioned and identified areas where information was repeated.

To address this, we have consolidated the repeated information to ensure clarity and conciseness. The revised text now reads:

"Since our research question focused on workers, which constituted a subpopulation of the complex survey data, we implemented subpopulation analysis instead of excluding non-workers from the original dataset to compute correct standard errors."

We believe this revision improves the readability of our manuscript and addresses your concern about redundancy. Thank you for helping us enhance the quality of our work.

- Recent research suggests that cognitive ability early in life may be a much stronger predictor of cognitive abilities later in life than education or occupational characteristics (see, for instance Kremen et al., 2019 doi: 10.1073/pnas.1811537116; Huh et al., 2024 doi: 10.1002/alz.13739). Although multiple studies support findings regarding occupational physical activity and cognitive function later in life, I am missing a discussion on how early life cognitive ability may, at least in part, explain the associations observed here. Namely, that individuals with higher early life cognitive abilities are more prone to both choosing a more cognitively challenging occupation and that they are less likely to experience cognitive decline later in life.

Thank you for your insightful comment regarding the role of early life cognitive ability in predicting cognitive abilities later in life. We appreciate your suggestion to discuss this factor as it may partially explain the associations observed in our study.

We agree that early life cognitive ability could be a significant predictor of cognitive abilities later in life and might influence the observed associations between physical job demands and cognitive impairment. Recent research, such as the studies by Kremen et al. (2019) and Huh et al. (2024), suggests that individuals with higher cognitive abilities early in life are more likely to choose cognitively challenging occupations and are less likely to experience cognitive decline.

In our study, we did not have data on early life cognitive ability, which is a limitation. To address this, we have added the following paragraph to the limitations section of our manuscript:

"Fifth, our study did not account for early life cognitive ability, which recent research suggests may be a stronger predictor of cognitive abilities later in life than education or occupational characteristics. Individuals with higher cognitive abilities early in life are more likely to choose cognitively challenging

occupations and are less likely to experience cognitive decline. This unmeasured confounding factor could partially explain the associations observed in our study. Future research should consider incorporating measures of early life cognitive ability to better understand its role in the relationship between physical job demands and cognitive impairment."

We believe this addition addresses your concern and enhances the comprehensiveness of our discussion on the study's limitations. Thank you for helping us improve the quality of our manuscript.

**VERSION 2 – REVIEW**

<b>REVIEWER NAME</b>	<i>Wendsche, Johannes</i>
<b>REVIEWER AFFILIATION</b>	Federal Institute for Occupational Safety and Health
<b>REVIEWER CONFLICT OF INTEREST</b>	Na
<b>DATE REVIEW RETURNED</b>	16-Aug-2024

<b>GENERAL COMMENTS</b>	Thank you very much for discussion my pints of concern from my earlier review and considering this issues in your manuscript which is, from my point of view, now ready to be published.
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<b>REVIEWER NAME</b>	<i>Zotcheva, Ekaterina</i>
<b>REVIEWER AFFILIATION</b>	Vestfold Hospital Trust, Norwegian National Centre for Ageing and Health
<b>REVIEWER CONFLICT OF INTEREST</b>	Na
<b>DATE REVIEW RETURNED</b>	21-Aug-2024

<b>GENERAL COMMENTS</b>	Thank you again for the chance to review this intriguing, innovative, and potentially significant study. Congratulations on a well-written manuscript. The authors have addressed the concerns raised in the previous review round appropriately, and I believe this manuscript can be accepted for publication in its present form.
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