PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Psychosocial factors at work and inflammatory markers: protocol for a systematic review and meta-analysis
AUTHORS	Eguchi, Hisashi; Watanabe, Kazuhiro; Kawakami, Norito; Ando, Emiko; Arima, Hideaki; Asai, Yumi; Inoue, Akiomi; Inoue, Reiko; Iwanaga, Mai; Imamura, Kotaro; Kobayashi, Yuka; Nishida, Norimitsu; Otsuka, Yasumasa; Sakuraya, Asuka; Tsuno, Kanami; Shimazu, Akihito; Tsutsumi, Akizumi

VERSION 1 – REVIEW

REVIEWER	Neha John-Henderson Montana State University, United States
REVIEW RETURNED	19-Mar-2018

GENERAL COMMENTS	I think this meta-analysis will make a valuable contribution to the literature given the tendency to group finding together across multiple domains. I do hope that the authors are able to find enough studies that fit their criterion in order to produce statistically meaningful results and report these in line with meta-analytic guidelines.

REVIEWER	Johannes Siegrist Senior Professor of Work Stress Research, Faculty of Medicine, Heinrich-Heine-University Duesseldorf, Germany
REVIEW RETURNED	03-Apr-2018

GENERAL COMMENTS	This is a carefully prepared protocol paper for a systematic Review and meta-Analysis on an timely question of relevance to the field of occupational health research. The basic Quality requirements for systematic Reviews have been met by the authors, and the protocol has been registered. However, I wonder why authors do not propose GRADE instead of NOS as a tool of assessing study quality. They may have good reasons, but these might be briefly explained. Moreover, perhaps an additional sentence on searching electronic grey literature databases might be included into the paragraph on search strategy, just as a measure indicating the authors' striving for optimal representation of current state of research. Finally, I agree that at this stage it is not possible to make definite statements about adjustments in reporting effect sizes of the studies under review. However, at least a statement from authors would be desirable that they will try hard to present findings adjusted for age and gender, whenever possible. Without minimal comparable adjustment the significance of results may be limited.

REVIEWER	Linda L Magnusson Hanson

	Stockholm University, Sweden
REVIEW RETURNED	12-Apr-2018

GENERAL COMMENTS	This is a quite well written protocol addressing a highly relevant issue. I think the focus on prospective studies is a strength. However, I'd like to address the following points that might help to improve the manuscript. When motivating the study you argue that inflammation can be a mediator for cardiovascular disease. Although I understand the emphasis on CVD, inflammation is now acknowledged as a potential mediator for many other health outcomes such as metabolic diseases, psychotic and neurodegenerative disorders. I think it would be good to acknowledge that in the protocol. Abstract: The word effect usually imply causality, but even if prospective studies are used, potential associations may not represent causal associations. I would suggest that you avoid implying causality and accordingly rephrasing the aim somewhat. The last sentence in the methods and analysis section is not completely clear. If all investigators really will make searches and synthesize results, I suggest you explicitly state that and that inconsistencies/disagreements will resolved through discussion. I wonder if the term data collection is fully appropriate in this context, as people may believe that new data is collected. Introduction: Row 88 This is not an exhaustive list of psychosocial factors that may be of relevance. I therefore suggest you use e.g. or such as to indicate his. I also suggest that you add a may (or are thought to or something similar) in the next sentence since the evidence is not so clear on biological pathways. Siegrist and Li recently published a review on ERI and altered biomarkers which would be relevant to mention in the introduction. Although you comment on the selection of inflammatory markers in the method section, I think this could be better motivated in the introduction. The choice of markers may be of high relevance for the conclusions that can be drawn. Methods and analysis: The outcome definition is a little bit confusing. Are you really focusing simply on increased inflammatory markers? Some factors may be protective factors rather than risk factors and associated with decreased levels. I also guess the inflammatory markers is usually treated as continuous variables in many studies rather than dichotomous variables using a specific cutpoint indicating increased levels. The statement “increased inflammatory makers” seem to imply that only dichotomous measures are being studied. I suggest you clarify this in the protocol. If values should exceed a certain cutoff, then what are the suitable cutoffs that will be considered? On row 145 What do you mean by workplace interactions? Does it refer to social relationships in some way, or something else? Also it would be good to clarify if components from theoretical models such as the demand-control-support model and effort-reward imbalance

	model will be treated separately or combined. On row 154 I would add coefficients of associations Web of Science is also one of the major databases. Would it be valuable to add as an information source? How will you determine if meta-analysis is appropriate/possible? On row 187 perhaps the word discussion is better that the word consultation I agree that it would be highly relevant to summarize results adjusted for lifestyle factors. However, life style factors could also be potential mediators of associations meaning that part of the associations between work characteristics and inflammatory mediators is adjusted away by adjustment for life style factors. If possible, it would be of interest to illustrate results with and without adjustment for life style factors in some way. Why was NOS chosen for assessment of study quality? Is there any specific feature of NOS that is preferable as compared to other approaches? What is the reason for calculating log-transformed ORs etc? Strenghts and limitations: I do not fully agree with the statement "…show the strongest evidence for comprehensive associations…". What do you mean with comprehensive? Although you will focus on a range of work factors it is a selection of factors. Especially a smaller selection of inflammatory mediators will be studied. I think you should acknowledge that the results regard certain inflammatory markers. The results for these chosen markers will not necessarily give the full story of relationships between psychosocial work factors and inflammation. In the strengths and limitations section you also write that you will focus on inflammatory makers as an aggregated cluster. If I understand it correctly you will study each marker separately and not collectively. The above statement may thus be misleading. Appendix 1: The list of search terms include a lot of terms which is not directly related to the factors you mention in the method section. Why is that?

REVIEWER	Xavier Trudel Université Laval, Canada
REVIEW RETURNED	23-Apr-2018

GENERAL COMMENTS	It is an interesting protocol aiming to conduct a systematic review and meta-analysis of the effects of work-related psychosocial factors on inflammatory markers. The PRISMA –P checklist was completed and all requested information is available in the manuscript. However, there are some issues that should be clarified 1- Study selection process, data collection and assessment of study quality: The role of the 14 investigators should be clarified. What is the proportion of entries that will be double reviewed? How and

	when will the interrater reliability be assessed? 2- Additional information should be provided on the standardized forms used to assess eligibility for inclusion and for the data extraction. They could be presented in the Appendix. 3- In the main analyses, the definition of work-related exposures used for meta-estimates computation should be clarified. Will a different estimate be produced for each psychosocial work factor (job strain, ERI, organisational justice, shift work, etc?). Is there a sufficient number of prospective studies to use this strategy? I have the same concern for subgroup analyses. 4- P.4 line 45: main outcome is presented as an aggregated cluster of inflammatory markers. P. 7 line 125: study contribution is presented as showing which factor has the strongest association with specific markers. Examination of specific markers is however only presented in subgroup analyses, conditional to sufficient heterogeneity. Therefore, this should be clarified. Additional comments 5- The effort-reward imbalance model should be presented using original Siegrist's references in the introduction. 6- Search terms for psychosocial work factors: the list is extensive but also covers many other factors (e.g. moving and lifter patients, biomechanics, etc). If the search strategy is conducted for additional research investigation, it should be mentioned. 7- Search terms for study design: retained terms such as longitudinal, prospective follow-up are always combined with the term 'study/studies'. The search strategy will therefore miss prospective studies not using this specific wording.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers (bmjopen-2018-022612)

We are extremely grateful for the reviewers' considered comments about our study. We have carefully revised our manuscript and present our point-by-point responses to those comments below. In our responses, changes to the manuscript are indicated by underlined text; changes in the manuscript itself are indicated in red.

Reviewer: 1
Reviewer Name: Neha John-Henderson
Institution and Country: Montana State University, United States

I think this meta-analysis will make a valuable contribution to the literature given the tendency to group finding together across multiple domains. I do hope that the authors are able to find enough studies that fit their criterion in order to produce statistically meaningful results and report these in line with meta-analytic guidelines.

Reply. Thank you very much indeed for your positive evaluation. We hope that our meta-analysis will make an important contribution to occupational health.

Reviewer: 2
Reviewer Name: Johannes Siegrist
Institution and Country: Senior Professor of Work Stress Research, Faculty of Medicine, Heinrich-Heine-University Duesseldorf, Germany

This is a carefully prepared protocol paper for a systematic Review and meta-Analysis on a timely question of relevance to the field of occupational health research. The basic Quality requirements for systematic Reviews have been met by the authors, and the protocol has been registered.

Reply. Thank you very kindly for your confirmation of our protocol paper for our meta-analysis.

1. However, I wonder why authors do not propose GRADE instead of NOS as a tool of assessing study quality. They may have good reasons, but these might be briefly explained.

Reply. Thank you very much for your perceptive comment. In light of your comment, we have reconsidered which tools we should use for assessing risk of reporting biases in each study. As a result, we have decided to adopt Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) in our meta-analysis. We did so for the following reasons. GRADE was developed to address questions about alternative management strategies, interventions, or policies.1 It was not developed to deal with questions about risk or prognosis, and it has some domains of risk of bias that are irrelevant to observational studies (e.g., allocation concealment). However, evidence regarding risk or prognosis may be pertinent to estimating the magnitude of intervention effects or providing indirect evidence linking surrogates to patient-important outcomes. Therefore, we decided not to use GRADE in our meta-analysis. The NOS that we originally adopted was previously endorsed for use in nonrandomized studies, which is our focus in the meta-analysis, by the Cochrane Collaboration.2 Recently, however, that collaboration has proposed a modified risk-of-bias tool for nonrandomized studies.2 We suppose that the reason for the reviewer recommending GRADE rather than NOS is that there are fewer evaluation items with NOS than with GRADE. But we believe that the quality of the evaluation with RoBANS is superior to that with NOS: RoBANS can assess more domains of risk of bias (i.e., blinding outcomes, incomplete outcome data, and selective outcome reporting) than NOS.

Reference

1. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026.
2. Belisario JSM, Car LT, Reeves TJA, Gunn LH, Car J. Search strategies to identify observational studies in MEDLINE and EMBASE. Cochrane Database of Systematic Reviews 2013;12. http://cochranelibrary-wiley.com/doi/10.1002/14651858.MR000041/ful

P3, Line 62: The quality of studies will be evaluated using the Risk of Bias Assessment Tool for Nonrandomized Studies.

P8, Line 231: Fourteen investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT) will independently assess in pairs the quality of each included study using the internationally recognized Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS).36 37 The RoBANS was developed to determine the risk of bias of non-randomized studies; it comprises six domains: selection of participants; confounding variables; measurement of exposure; blinding of outcomes; incomplete outcome data; and selective outcome reporting. The risk of bias for each domain is classified as low, high, or unclear risk. The number of papers assessed by each investigator will depend on their capacity. Any discrepancies in quality assessment among the investigators will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached.

P9, Line 267: Results with and without adjustment for lifestyle variables will be compared in another sensitivity analysis. If trends are observed between pooled associations and any grouping

characteristics, meta-regression will be conducted using the “metareg” function of R. A sensitivity analysis may be conducted for included studies where the RoBANS is classified as low risk. All extracted data and analyzed results will be deposited by the corresponding author and made available for external reviewers and readers upon request.

2. Moreover, perhaps an additional sentence on searching electronic grey literature databases might be included into the paragraph on search strategy, just as a measure indicating the authors' striving for optimal representation of current state of research.

Reply. Thank you for your suggestion. We did not include electronic grey literature for the following reasons. As you mentioned, if we were to add electronic grey literature databases among our selected databases, low-quality papers would be included. We wanted to conduct our meta-analysis based on high-quality papers extracted from leading databases.

3. Finally, I agree that at this stage it is not possible to make definite statements about adjustments in reporting effect sizes of the studies under review. However, at least a statement from authors would be desirable that they will try hard to present findings adjusted for age and gender, whenever possible. Without minimal comparable adjustment the significance of results may be limited.

Reply. Thank you for your comment. We revised the data extraction section in line with your recommendation:

P8, Line 218: If the included studies report multiple measures of association, we will attempt to select measures of association adjusted by demographic variables (e.g., age, sex, education, and marital status).

Reviewer: 3
Reviewer Name: Linda L Magnusson Hanson
Institution and Country: Stockholm University, Sweden

This is a quite well written protocol addressing a highly relevant issue. I think the focus on prospective studies is a strength. However, I'd like to address the following points that might help to improve the manuscript.

Reply. Thank you very much indeed for your positive evaluation of our protocol paper for the meta-analysis. We have carefully revised our manuscript and present our point-by-point responses below.

4. When motivating the study you argue that inflammation can be a mediator for cardiovascular disease. Although I understand the emphasis on CVD, inflammation is now acknowledged as a potential mediator for many other health outcomes such as metabolic diseases, psychotic and neurodegenerative disorders. I think it would be good to acknowledge that in the protocol.

Reply. Thank you very much for this perceptive comment. We completely agree with you. We have now added “metabolic diseases and, psychotic and neurodegenerative disorders” as additional health outcomes to CVD:

P3, Line 40: Chronic inflammation may be a mediator for the development of cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders.

P3, Line 67: The findings may be useful for assessing risk factors for increased inflammatory markers in the workplace and determining future approaches for preventing CVD, metabolic diseases, and psychotic and neurodegenerative disorders.

P4, Line 85: The findings of this review may be useful for assessing chronic inflammation as a risk factor for cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders in the workplace as well as for determining future approaches for preventing CVD, metabolic diseases, and psychotic and neurodegenerative disorders.

P5, Line 99: These factors may affect cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders through such mechanisms as prolonged overactivation and dysregulation of the autonomic nervous system and the hypothalamus-pituitary-adrenal cortex axis.11-13

P5, Line 104: Chronic inflammation has been suggested as a potential mediator for the development of CVD, metabolic diseases, and psychotic and neurodegenerative disorders.14-18

5. Abstract:
The word effect usually imply causality, but even if prospective studies are used, potential associations may not represent causal associations. I would suggest that you avoid implying causality and accordingly rephrasing the aim somewhat.

Reply. Following your comment, we have changed “effect” to “association” in relevant parts of the manuscript:

P3, Line 47: Based on prospective studies, the present investigation will conduct a comprehensive systematic review and meta-analysis of the association between work-related psychosocial factors and inflammatory markers.

P4, Line 75: This systematic review and meta-analysis will offer comprehensive understanding of the association between work-related psychosocial factors and inflammatory markers.

P6, Line 131: Based on published prospective studies, the present investigation will conduct a comprehensive systematic review and meta-analysis of the associations between work-related psychosocial factors and inflammatory markers.

6. The last sentence in the methods and analysis section is not completely clear. If all investigators really will make searches and synthesize results, I suggest you explicitly state that and that inconsistencies/disagreements will resolved through discussion.

Reply. Thank you for your comment. We have revised that final sentence in the Methods and Analysis section as you suggest:

P3, Line 60: Study selection, data extraction, quality assessment, and statistical syntheses will be conducted by 14 investigators. Any inconsistencies or disagreements will be resolved through discussion.

7. I wonder if the term data collection is fully appropriate in this context, as people may believe that new data is collected.

Reply. Thank you for your comment. We have changed all instances of “data collection” to “data extraction.”

8. Introduction:
Row 88 This is not an exhaustive list of psychosocial factors that may be of relevance. I therefore suggest you use e.g. or such as to indicate his. I also suggest that you add a may (or are thought to or something similar) in the next sentence since the evidence is not so clear on biological pathways.

Reply. Following your comment, we have added “such as” and “may” as follows:

P5, Line 96: Increasing attention is being directed to work-related psychosocial factors such as job strain,1-5 effort-reward imbalance,6 organizational justice,7-9 and workplace social capital10; there is a major focus on work stress.2 These factors may affect cardiovascular disease (CVD) , metabolic diseases, and psychotic and neurodegenerative disorders through such mechanisms as prolonged overactivation and dysregulation of the autonomic nervous system and the hypothalamus-pituitary-adrenal cortex axis.11-13

9. Siegrist and Li recently published a review on ERI and altered biomarkers which would be relevant to mention in the introduction.

Reply. Thank you for this comment. We have added the following paper as reference 15:

Siegrist J, Li J. Work stress and the development of chronic diseases. Int J Environ Res Public Health 2018;15(3). pii: E536. doi: 10.3390/ijerph15030536.

10. Although you comment on the selection of inflammatory markers in the method section, I think this could be better motivated in the introduction. The choice of markers may be of high relevance for the conclusions that can be drawn.

Reply. In accordance with your perceptive comment, we have added a description about the selection of inflammatory markers in the Introduction:

P6, Line 131: Based on published prospective studies, the present investigation will conduct a comprehensive systematic review and meta-analysis of the effects of work-related psychosocial factors on inflammatory markers. Inflammatory markers will include those that were previously investigated in terms of associations with psychosocial factors at work, including CRP, IL-6, and TNF-α. Our hypothesis is that adverse work-related psychosocial factors would increase inflammatory markers. Moreover, we will identify the work-related psychological factors that have the strongest associations with specific inflammatory markers.

11. Methods and analysis: The outcome definition is a little bit confusing. Are you really focusing simply on increased inflammatory markers? Some factors may be protective factors rather than risk factors and associated with decreased levels. I also guess the inflammatory markers is usually treated as continuous variables in many studies rather than dichotomous variables using a specific cutpoint indicating increased levels. The statement “increased inflammatory makers” seem to imply that only dichotomous measures are being studied. I suggest you clarify this in the protocol. If values should exceed a certain cutoff, then what are the suitable cutoffs that will be considered?

Reply. Thank you very much for your comment. In this study, we will focus on CRP, IL-6, and TNF-α as the outcomes. With all these inflammatory markers, it is recognized that higher levels signify more adverse effects on health. In addition, we will focus on both continuous (i.e., specific values of the markers) and dichotomous (i.e., beyond or below cutoff points) variables. We explain in the “eligibility criteria” section that both types of studies will be eligible for our meta-analysis, which will provide

coefficients between adverse psychosocial factors at work and inflammatory markers in continuous (i.e., γ and β) and in dichotomous (i.e., ORs, RRs, and HRs) variables.

12. On row 145 What do you mean by workplace interactions? Does it refer to social relationships in some way, or something else? Also it would be good to clarify if components from theoretical models such as the demand-control-support model and effort-reward imbalance model will be treated separately or combined.

Reply. Apologies for the confusion. According to the cited paper, Semmer et al. (2006), workplace psychosocial factors that permit intervention are grouped into three categories: task characteristics, work conditions, and social conditions. The categories include specific concepts of the factors, such as in the JDS and ERI models. We have revised the sentence in question and added reference citations for each specific psychosocial factors:

P6, Line 157: The study exposures (adverse psychosocial factors at work) will include a range of task and organizational characteristics and work conditions,35 such as job strain,1-5 low social support, effort-reward imbalance,6 organizational injustice,7-9 and low workplace social capital.10

13. On row 154 I would add coefficients of associations.

Reply. Thank you for your comment. We have added the term in line with your recommendation:

P7, Line 168: (4) provided sufficient data for calculating coefficients of associations between psychosocial factors at work and inflammatory markers (γ, β), odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with standard errors (SEs) or 95% CIs;

14. Web of Science is also one of the major databases. Would it be valuable to add as an information source?

Reply. Thank you for your comment. We have now added Web of Science as an electronic database we will search:

P3, Line 50: The systematic review and meta-analysis will include published studies identified from electronic databases (PubMed, EMBASE, PsycINFO, PsycARTICLES, Web of Science and Japan Medical Abstracts Society) according to recommendations of the Meta-analysis of Observational Studies in Epidemiology guideline.

P7, Line 176: A systematic search of published studies will be conducted using electronic databases: PubMed (MEDLINE), EMBASE, PsycINFO, PsycARTICLES, Web of Science, and the Japan Medical Abstracts Society.

15. How will you determine if meta-analysis is appropriate/possible?

Reply. Thank you very much for your comment. We considered that meta-analysis would not be possible if too few studies were eligible. We have added a sentence to clarify this point:

P9, Line 255: The results will be presented in a narrative format if a meta-analysis is not appropriate or possible, e.g., if only two or fewer studies are eligible and included in the study.

16. On row 187 perhaps the word discussion is better that the word consultation.

Reply. Following your comment, we have changed “consultation” to “discussed”:

P8, Line 205: Any discrepancies or inconsistencies in the assessment will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached.

17. I agree that it would be highly relevant to summarize results adjusted for lifestyle factors. However, life style factors could also be potential mediators of associations meaning that part of the associations between work characteristics and inflammatory mediators is adjusted away by adjustment for life style factors. If possible, it would be of interest to illustrate results with and without adjustment for life style factors in some way.

Reply. Thank you for your comment. We have made revisions to the Methods and Analysis section, indicating that we will extract measures of association both with and without adjustment for lifestyle factors. We have also added one more sensitivity analysis:

P8, Line 218: If the included studies report multiple measures of association, we will attempt to select measures of association adjusted by demographic variables (e.g., age, sex, education, and marital status). If the studies report measures of association adjusted by lifestyle variables (e.g., smoking, physical activity, and sleep), we will as far as possible extract measures both with and without adjustment for lifestyle variables.

P9, Line 267: Results with and without adjustment for lifestyle variables will be compared in another sensitivity analysis.

18. Why was NOS chosen for assessment of study quality? Is there any specific feature of NOS that is preferable as compared to other approaches?

Reply. As we have already explained in comment 1 to Reviewer 2, we adopted RoBANS rather than NOS and GRADE based on our discussions.

19. What is the reason for calculating log-transformed ORs etc?

Reply. Thank you very much for your comment. Natural logarithms of the association measures and its standard errors will be necessary to examine publication bias using a funnel plot and the Egger's test. That is because it is a requirement of the statistical software we intend to use (i.e., R). We have clarified this point in the "data synthesis and statistical methods: section:

P9, Line 249: These parameters will be used in the meta-analysis and for examining publication bias by means of a funnel plot and Egger's test with statistical software, R version 3.4.1.38,39

20. Strenghts and limitations:
I do not fully agree with the statement "…show the strongest evidence for comprehensive associations…". What do you mean with comprehensive? Although you will focus on a range of work factors it is a selection of factors. Especially a smaller selection of inflammatory mediators will be studied. I think you should acknowledge that the results regard certain inflammatory markers. The results for these chosen markers will not necessarily give the full story of relationships between psychosocial work factors and inflammation.

Reply. Thank you very much for your comment. We have now omitted the word "comprehensive."

21. In the strengths and limitations section you also write that you will focus on inflammatory makers as an aggregated cluster. If I understand it correctly you will study each marker separately and not collectively. The above statement may thus be misleading.

Reply. Following your comment, we have now omitted “aggregated cluster.”

22. Appendix 1:
The list of search terms include a lot of terms which is not directly related to the factors you mention in the method section. Why is that?

Reply. Based on previous studies, we created the list of search terms to obtain a retrieval result while preventing retrieval failure. From the list of search terms, we obtained over 7000 papers. We believe that around 7000 papers are the limit for review by 14 investigators.

Reviewer: 4
Reviewer Name: Xavier Trudel
Institution and Country: Université Laval, Canada

It is an interesting protocol aiming to conduct a systematic review and meta-analysis of the effects of work-related psychosocial factors on inflammatory markers. The PRISMA –P checklist was completed and all requested information is available in the manuscript. However, there are some issues that should be clarified

23. Study selection process, data collection and assessment of study quality: The role of the 14 investigators should be clarified. What is the proportion of entries that will be double reviewed? How and when will the interrater reliability be assessed?

Reply. Thank you very much indeed for your very helpful comments. In light of your comments, we have clarified the role of the 14 investigators and assessed the inter-rater reliability. Accordingly, we made the following additions:

P7, Line 185: Study selection process
First, following the eligibility criteria, 14 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT) will independently conduct screening of identified titles and abstracts in pairs. Second, we will obtain full texts of all eligible studies. In the full-text review phase, the studies will be examined using a standardized form (Appendix 2) to assess eligibility for inclusion in this review. The number of papers examined by each investigator will depend on the investigator’s capacity. Any discrepancies in assessment will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached. We will directly contact the corresponding authors of eligible studies if the results of the publication are unclear and may be related to multiple interpretations or if the reported results did not show data relevant to our study analysis. The reasons for excluding studies will be recorded. A flow chart will be prepared showing the entire review process.

P8, Line 201: Data extraction
Data will be extracted independently from the included studies by 14 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT) working in pairs using a standardized data extraction form. The data will be distributed according to the investigators’ capacity. Any discrepancies or inconsistencies in the assessment will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached.

P8, Line 230: Assessment of study quality

Fourteen investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT) will independently assess in pairs the quality of each included study using the internationally recognized Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS).36 37 The RoBANS was developed to determine the risk of bias of non-randomized studies; it comprises six domains: selection of participants; confounding variables; measurement of exposure; blinding of outcomes; incomplete outcome data; and selective outcome reporting. The risk of bias for each domain is classified as low, high, or unclear risk. The number of papers assessed by each investigator will depend on their capacity. Any discrepancies in quality assessment among the investigators will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached.

24. Additional information should be provided on the standardized forms used to assess eligibility for inclusion and for the data extraction. They could be presented in the Appendix.

Reply. Thank you for your comment. We have added a reference to the standardized form we will use in this study in the “study selection process” as Appendix 2:

P7, Line 188: Second, we will obtain full texts of all eligible studies. In the full-text review phase, the studies will be examined using a standardized form (Appendix 2) to assess eligibility for inclusion in this review.

25. In the main analyses, the definition of work-related exposures used for meta-estimates computation should be clarified. Will a different estimate be produced for each psychosocial work factor (job strain, ERI, organisational justice, shift work, etc?). Is there a sufficient number of prospective studies to use this strategy? I have the same concern for subgroup analyses.

Reply. Thank you very much for your comment. We will combine all types of psychosocial factors at work in the main analysis. We have added a comment about this to the “data synthesis and statistical methods” section. For the subgroup analyses, it is not yet known how many studies will be included in the systematic review and meta-analysis. Therefore, we have just suggested possible sub-groupings in the study protocol. We have clarified this situation by using the word “possible” with regard to the subgroup analyses:

P9, Line 254: For the main analysis, we will synthesize all types of psychosocial factors at work in the random-effects model.

P9, Line 263: Major possible grouping characteristics will include types of exposure and outcome, participants’ demographic characteristics (e.g., sex, age, employment status, occupational groups), and study quality

26. P.4 line 45: main outcome is presented as an aggregated cluster of inflammatory markers. P. 7 line 125: study contribution is presented as showing which factor has the strongest association with specific markers. Examination of specific markers is however only presented in subgroup analyses, conditional to sufficient heterogeneity. Therefore, this should be clarified.

Reply. Following your comment, we have now deleted “as an aggregated cluster.”

27. The effort-reward imbalance model should be presented using original Siegrist’s references in the introduction.

Reply. In line with your comment, we have added the following reference (number 6):

Siegrist J. Adverse health effects of high-effort/low-reward conditions. J Occup Health Psychol 1996;1(1):27-41.

28. Search terms for psychosocial work factors: the list is extensive but also covers many other factors (e.g. moving and lifter patients, biomechanics, etc). If the search strategy is conducted for additional research investigation, it should be mentioned.

Reply. Based on previous studies, we originally created a list of search terms to obtain a retrieval result while preventing retrieval failure. We do not have any additional research plans for those search terms. From the list of search terms, we obtained over 7000 papers. We believe about 7000 papers to be the limit for review by 14 investigators.

29. Search terms for study design: retained terms such as longitudinal, prospective follow-up are always combined with the term 'study/studies'. The search strategy will therefore miss prospective studies not using this specific wording.

Reply. Thank you for your comment. In light of the comment, we have reconsidered the appropriateness of study design in our search strategy. We have reviewed the information about search filters for study design recommended by BMJ and the Cochrane Methodology Review Group.1,2 Accordingly, we have revised the search terms for study design by adding "(observational stud*) OR (case-control stud*) OR (cohort stud*) OR (epidemiologic stud*) OR (cohort analy*) OR (observ* stud*) OR (retrospective stud*)" to the previous list of terms related to study design.

Reference

1. Belisario JSM, Car LT, Reeves TJA, Gunn LH, Car J. Search strategies to identify observational studies in MEDLINE and EMBASE. Cochrane Database of Systematic Reviews 2013, Issue 12. http://cochranelibrary-wiley.com/doi/10.1002/14651858.MR000041/full
2. Study design search filters. http://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/

Appendix 1: Study design

(longitudinal stud*) OR (prospective cohort stud*) OR (prospective stud*) OR (follow-up stud*) OR (observational stud*) OR (case-control stud*) OR (cohort stud*) OR (epidemiologic stud*) OR (cohort analy*) OR (observ* stud*) OR (retrospective stud*)

We would like to thank the reviewers once again for their insightful comments. We hope that our manuscript now properly reflects the detailed comments of the reviewers and that BMJ will find it suitable for publication.

VERSION 2 – REVIEW

REVIEWER	Johannes Siegrist Senior Professor of Work Stress Research, Faculty of Medicine, Heinrich-Heine University Düsseldorf, Germany
REVIEW RETURNED	21-Jun-2018

GENERAL COMMENTS	This revised manuscript has addressed the multiple comments provided by the reviewers in much detail. By incorporating these changes the manuscript has been substantially improved. Particular strengths include the application of RoBAINS and of R version 3.4.1 (specifically to examine publication bias), as well as propositions for subgroup and sensitivity analyses (althouth this may strongly depend on the number and quality of studies to be included in meta-

	analysis). With regard to references Reference 15 has to be corrected. The quotation is: Siegrist J, Li J (2017) Work stress and altered biomarkers: A synthesis of findings based on the effort-reward imbalance model. International Journal of Environmental Research and Public Health 14, 1373.

REVIEWER	Linda Magnusson Hanson Stockholm University, Sweden
REVIEW RETURNED	26-Jun-2018

GENERAL COMMENTS	I think the authors have revised the manuscript well, adequately dealing with the comments, and think the manuscript is suitable for publication

REVIEWER	Xavier Trudel Université Laval, Quebec, Canada
REVIEW RETURNED	25-Jun-2018

GENERAL COMMENTS	The authors have addressed all of my comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Johannes Siegrist

Institution and Country: Senior Professor of Work Stress Research, Faculty of Medicine, Heinrich-Heine-University Duesseldorf, Germany

This revised manuscript has addressed the multiple comments provided by the reviewers in much detail. By incorporating these changes the manuscript has been substantially improved. Particular strengths include the application of RoBAINS and of R version 3.4.1 (specifically to examine publication bias), as well as propositions for subgroup and sensitivity analyses (although this may strongly depend on the number and quality of studies to be included in meta-analysis).

With regard to references Reference 15 has to be corrected. The quotation is: Siegrist J, Li J (2017) Work stress and altered biomarkers: A synthesis of findings based on the effort-reward imbalance model. International Journal of Environmental Research and Public Health 14, 1373.

Reply. Thank you very much indeed for your positive evaluation for our revised manuscript. According to your comment, we corrected the reference as follow:

P12, Line 360: 15. Siegrist J, Li J. Work stress and altered biomarkers: A synthesis of findings based on the effort-reward imbalance model. Int J Environ Res Public Health 2017;14:1373 doi: 10.3390/ijerph14111373.

Reviewer: 3

Reviewer Name: Linda L Magnusson Hanson

Institution and Country: Stockholm University, Sweden

I think the authors have revised the manuscript well, adequately dealing with the comments, and think the manuscript is suitable for publication

Reply. We wish to express our appreciation to you for their insightful comments on our paper. Your comments have helped us significantly improve the paper.

Reviewer: 4

Reviewer Name: Xavier Trudel

Institution and Country: Université Laval, Canada

The authors have addressed all of my comments.

Reply. We thank you for careful reading my manuscript and for your fruitful suggestions

We would like to thank the reviewers once again for their insightful comments. We hope that our manuscript now properly reflects the detailed comments of the reviewers and that BMJ will find it suitable for publication.